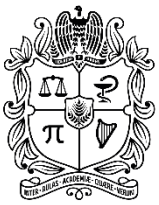

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Seguridad y Efectividad de la reducción o retiro de la terapia antihipertensiva en gestantes con enfermedad vascular hipertensiva crónica

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“Seguridad y Efectividad de la reducción o retiro de la terapia antihipertensiva en gestantes con enfermedad vascular hipertensiva crónica”

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2021

A nuestros padres, y a la Gloriosa Universidad Nacional de Colombia, motor y motivo de nuestros sueños realizados.

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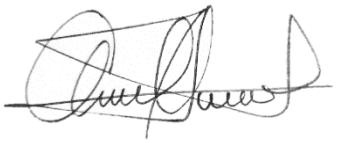

Catalina Hamon Pinilla

Andrea Milena Salamanca Téllez

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Resumen

Objetivo: Estimar la seguridad y efectividad de la reducción o retiro de la medicación antihipertensiva en mujeres embarazadas con hipertensión crónica.

Métodos: Se incluyeron ensayos controlados aleatorios que compararon el tratamiento con fármacos antihipertensivos versus ningún antihipertensivo, suspensión del fármaco, placebo u otras intervenciones. Se realizaron búsquedas en CENTRAL, MEDLINE, LILACS y ClinicalTrials. También se realizaron búsquedas manuales en las actas de congresos (ACOG, FIGO, RCOG, FECOLSOG). Dos autores de la revisión evaluaron de forma independiente los ensayos para su inclusión, extrajeron los datos y evaluaron el riesgo de sesgo. Los desacuerdos fueron resultos por consenso. Utilizamos el enfoque GRADE para evaluar la calidad de la evidencia.

Resultados: La búsqueda no encontró ningún ensayo clínico controlado que evaluara la reducción o el retiro de la terapia antihipertensiva. Cuando se comparó el tratamiento antihipertensivo con placebo o ningún antihipertensivo, encontramos que el tratamiento antihipertensivo se asoció con una reducción de la probabilidad de desarrollar hipertensión grave en mujeres embarazadas con hipertensión crónica (OR 0,43; IC del 95%: 0,26 a 0,70) y una mayor probabilidad de efectos adversos. asociado al tratamiento antihipertensivo (ORa 8,52; IC del 95%: 1,05 a 69). No encontramos diferencias en la probabilidad de desarrollar preeclampsia superpuesta, parto prematuro, desprendimiento de placenta, pequeño para la edad gestacional, pérdida del embarazo, muerte neonatal, ingreso en la unidad de cuidados intensivos neonatales o APGAR bajo al nacer. No encontramos diferencias en la edad gestacional al nacer. La calidad de la evidencia fue muy baja debido a la presencia de un riesgo grave de sesgo, las limitaciones en la aplicabilidad de los resultados y el intervalo de confianza.

Conclusión: La evidencia de muy baja calidad sugiere que probablemente la terapia antihipertensiva reduce la incidencia de hipertensión severa en mujeres embarazadas con hipertensión crónica en comparación con placebo o ningún antihipertensivo.

Palabras clave: Embarazo, Hipertensión, Antihipertensivos, Privación de Tratamiento

Abstract

Safety and effectiveness of the reduction or withdrawal of antihypertensive therapy in pregnant women with chronic hypertensive vascular disease

Objective: To estimate the security and effectivity of the reduction or retirement of antihypertensive medication in pregnant women with chronic hypertension. Methods: Randomized controlled trials that compared management with antihypertensive drugs vs. no antihypertensive, discontinuation of the drug, placebo, or other interventions were included. We searched CENTRAL, MEDLINE, LILACS, and ClinicalTrials. We also hand-searched conference proceedings (ACOG, FIGO, RCOG, FECOLSOG) and reference lists of retrieved studies. Two review authors independently assessed trials for inclusion, extracted data and assessed risk of bias. We resolved disagreements through consensus. We used the GRADE approach to assess the quality of evidence. Results: The search did not find any controlled clinical trial evaluating the reduction or withdrawal of antihypertensive therapy. When antihypertensive management was compared with placebo or no antihypertensive, we found that antihypertensive treatment was associated with reduction of probability of developing severe hypertension in pregnant women with chronic hypertension (OR 0,43 95% CI 0.26 to 0.70) and increased probability of adverse effects associated to antihypertensive management (aOR 8.52; 95% CI 1.05 to 69). We did not found differences in the probability of developing superimposed pre-eclampsia, preterm birth, placental abruption, small for gestational age, pregnancy loss, neonatal death, admission to the neonatal intensive care unit or low APGAR at birth. We did not found differences in gestational age at birth. Quality of the evidence was very low due to the presence of serious risk of bias, limitations in the applicability of results and the confidence interval.

Conclusion: Very low-quality evidence suggest that probably antihypertensive therapy reduces the incidence of severe hypertension in pregnant women with chronic hypertension when compared with placebo or no antihypertensive.

Keywords: Pregnancy, Hypertension, Antihypertensive Agents, Withholding Treatment

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Introduction

Condition description:

Different prospective studies have shown that there is a relationship between the sustained increase in blood pressure values and the occurrence of cardiovascular events. A meta-analysis performed by Lewington et. al in 2002 showed that the risk of cardiovascular disease increased with systolic (SBP) and diastolic (DBP) blood pressure levels greater than 115 and 75 mmHg, respectively and that levels of systolic blood pressure 20 mmHg higher or diastolic blood pressure 10 mmHg higher, increase twice the risk of cardiovascular disease (1). Based on this, the American College of Cardiology (ACC) and the American Heart Association (AHA) in their latest recommendations changed the criteria for the diagnosis of hypertension in adults (2,3). According to these recommendations, blood pressure values can be divided into four categories: 1) normal (SBP less than 120 mm Hg and DBP less than 80 mm Hg); 2) elevated (SBP from 120 to 129 mm Hg and DBP less than 80 mm Hg); 3) first stage of hypertension (SBP from 130 to 139 mm Hg or DBP from 80 to 89 mm Hg); and 4) second stage of hypertension (SBP equal to or greater than 140 mm Hg or DBP equal to or greater than 90 mm Hg)(2,3).

Chronic arterial hypertension is present in 0.9 to 1.5% of pregnant women and according to the American College of Obstetricians and Gynecologists (ACOG) it is defined as the finding before pregnancy or before 20 weeks' gestation of SBP equal to or greater than 140 mm Hg and DBP equal to or greater than 90 mm Hg, on at least two occasions each four hours apart, (4). In turn, those patients who are diagnosed with hypertensive disorders for the first time after week 20 of gestation and who do not resolve during the postpartum period are also considered chronic hypertensive (5). Considering the values proposed by AHA / ACC for the diagnosis of chronic arterial hypertension, an increase in the prevalence of this condition in women of reproductive age is expected. However, it should be taken into account that patients without a previous diagnosis of chronic arterial hypertension who present SBP between 130 and 139 mm Hg or DBP between 80 and 89 mm Hg before 20 weeks of gestation would be considered to be hypertensive by AHA / ACC but normotensive during pregnancy according to ACOG. Anyhow, ACOG recommends that a greater degree of observation should be carried out in this type of patients (4).

Pregnant women with preexisting chronic hypertension have been shown to have a 5 to 6 times higher risk of stroke, pulmonary edema, kidney failure, and death than normotensive women (6). Additionally, there is an increased risk of developing pre-eclampsia and gestational diabetes, possibly as a consequence of common risk factors such as obesity, increased insulin resistance, chronic inflammation, and endothelial dysfunction (7). Different observational studies indicate that chronic arterial hypertension in pregnancy is associated with poor perinatal outcomes. The perinatal mortality rate associated with maternal chronic arterial hypertension has been shown to be two to four times higher than that of the general population (8). The systematic review carried out by Panaitescu et al. showed that the incidence of low birth weight was approximately 17% and of preterm birth 28% (9). Women with severe hypertension, target organ damage or secondary hypertension represent the highest risk category, in which the risk of intrauterine growth restriction increases to 25 to 40%, preterm delivery to 67%, placental abruption to 8 to 20% and perinatal death 11% (10).

Description of the intervention

Given that elevated blood pressure is associated with an increased risk of adverse cardiovascular events, any treatment that has the ability to lower SBP or DBP is desirable. The meta-analysis carried out by Ettehad et al. showed that for every 10 mm Hg reduced in SBP there is a significantly reduction on the risk of major cardiovascular events, coronary heart disease and stroke, which in addition leads to a decrease in the risk of mortality (11). These effects vary according to the patient's risk category and the blood pressure value, which is why different guidelines establish that antihypertensive therapy reduces the risk of cardiovascular events among people at high risk of atherosclerotic cardiovascular disease at 10 years (equal to or greater than 10%) and blood pressure greater than or equal to 140/90 mm Hg, but there is no agreement regarding the value of using antihypertensive treatment for patients with lower risk (12).

The options for treating high blood pressure are pharmacological and non-pharmacological interventions. Non-pharmacological interventions are based on healthy lifestyle changes or measures such as low-salt diet, regular exercise, weight loss, moderation in alcohol consumption, avoiding excessive caffeine consumption and stopping tobacco use (2). Lifestyle interventions were studied in a systematic review with the purpose of quantifying

the effectiveness of the measures, finding that improving the low-salt diet decreases 5.0 mmHg in SBP and 3.7 mmHg in DBP and the performance of regular exercise decreases SBP by 4.6 mmHg and DBP 2.4 mmHg (13). Pharmacological management includes multiple classes of antihypertensive drugs that can be used alone or in combination, such as angiotensin II receptor antagonists (ARBs), angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, diuretics, beta blockers, alpha 1 antagonists or alpha 2 agonists, among others. Antihypertensive therapy may be combined since the use of two or more antihypertensive drugs of different pharmacological classes has shown up to five times more effectiveness than doubling the dose of a single antihypertensive (14).

A Cochrane systematic review evaluating the effects of the use of antihypertensive drugs in preventing mortality in adults aged 18 to 59 years with mild to moderate primary hypertension, showed that the use of antihypertensive drug therapy decreased cardiovascular mortality and morbidity mainly due to reduction in mortality and cerebrovascular morbidity but had no effect on mortality from other causes or coronary disease (15). Another systematic review sought to establish whether it was possible to withdraw antihypertensive medications in patients aged 58 to 82 years who were consuming them and to look for the effects of suspending this type of medication found that discontinuation showed no effect on mortality, acute myocardial infarctions or strokes compared to continuing antihypertensive medications (16).

It is controversial which are the benefits and harms of treating chronic arterial hypertension during pregnancy, regarding physiologic adaptations during pregnancy as well as certain fetal aspects (4) and there is currently a lack of agreement on which patients with chronic arterial hypertension should be treated during pregnancy. According to the results of the Cochrane systematic review published by Abalos et al. in 2018 and the CHIPS trial, ACOG recommends the initiation of antihypertensive therapy for persistent chronic arterial hypertension when SBP is equal to or greater than 160 mm Hg and DBP is equal to or greater than 110 mm Hg (4). On the other hand, the NICE guideline recommends offering antihypertensive treatment to pregnant women with a diagnosis of arterial hypertension if they have a SBP greater than or equal to 140 mmHg or DBP greater than 90 mmHg in a sustained manner (17). A wide variety of drugs can be used to lower blood pressure in pregnant women with hypertension but some pharmacological groups have different potential for and also known adverse side effects as described below:

Thiazide diuretics: The initial action of thiazide diuretics is to decrease extracellular volume by interacting with the sodium chloride transporter expressed in the distal convoluted tubule of the kidney, which increases the excretion of sodium in the urine and leads to decreased cardiac output (18). Antihypertensive effects can be achieved in patients with as little as 12.5 mg per day of chlorthalidone or hydrochlorothiazide. When used as monotherapy, the maximum daily dose cannot exceed 25 mg of hydrochlorothiazide. The potassium depletion produced by thiazide diuretics is dose dependent and variable among individuals, thus a group of patients may present a substantial potassium depletion when using this type of medication.

Angiotensin-converting enzyme (ACE) inhibitors: this group of drugs inhibits angiotensin-converting enzyme, kinase II and peptidyl dipeptidase, causes a reduction in angiotensin II and aldosterone levels and an increase in endogenous vasodilators of the family of kinins. As an adverse effect, it generates cough in up to 30% of patients. They cause major kidney damage in the fetus and are contraindicated in pregnancy (19).

Angiotensin receptor antagonists: competitively inhibit angiotensin II at the AT1 receptor. There are just as effective as ACE inhibitors in lowering blood pressure and have the advantage of generating a lower incidence of cough, although they cause hyperkalemia. They cause major kidney damage in the fetus and are contraindicated in pregnancy (19).

Alpha agonists: inhibit vasoconstriction through a central effect, reduce arteriolar resistance and increase venous capacitance, which, as a sympathetically mediated reflex, causes an increase in the frequency and activity of plasma renin. During long-term therapy, vasodilation persists, but output, heart rate, and plasma renin activity return to normal (19). Methyldopa is the most commonly used alpha agonist during pregnancy in chronic high blood pressure. Clonidine is also an alpha agonist but has the disadvantage that sudden withdrawal of the drug can cause hypertensive crisis (18). Some side effects of methyldopa include blurred vision, dizziness, headache, nasal congestion, and weakness, especially after starting the medications and when the dose is increased (18).

Beta blockers: They block beta adrenergic receptors in the heart, peripheral vessels, airways, pancreas and liver, leading to a reduction in vasomotor tone and associated with a reduction in plasma renin (20). Labetalol has an additional vasodilator action that lowers

peripheral resistance. Some side effects of beta-blockers include edema, postural hypotension, bradycardia, cold or cyanotic extremities, masking of the response to hypoglycemia, nausea, dyspepsia, vomiting, difficulty in urination, headache, vertigo and paresthesia (20). Different controlled clinical trials have documented various unwanted fetal effects depending on the time of exposure to beta-blockers and the type of beta-blocker used, some outcomes are: small for gestational age fetus, mild neonatal hypoglycemia and bradyarrhythmia (21,22).

Calcium antagonists: includes amlodipine, nifedipine, nicardipine, nimodipine, and verapamil. These drugs block the functioning of calcium channels that are involved in the depolarization of vascular smooth muscle, cardiac myocytes, and the cardiac node (23). Common side effects of calcium channel blockers include dizziness, headache, feeling hot, weakness, facial flushing, palpitations, transient hypotension, nausea, dyspnea, nasal congestion, and muscle cramps (23).

Peripheral vasodilators: hydralazine is a vasodilator with a relaxing effect on the smooth muscle of the blood vessels, predominantly in the arterioles. Although multiple changes in cell signaling pathways influenced by hydralazine have been described, the precise molecular targets that explain its ability to dilate arteries remain uncertain. Potential mechanisms include inositol triphosphate-mediated inhibition of calcium release from cellular deposits, opening of high-conductance calcium channels, activation of potassium channels in smooth muscle, and activation of the arachidonic acid pathway cyclooxygenase and prostacyclin (24). Commonly reported side effects are palpitations and tachycardia, in addition to facial flushing, hypotension, nausea, vomiting, and diarrhea (24).

How the intervention can work

Treatment of chronic high blood pressure during pregnancy is believed to improve vascular perfusion and fetal growth, reduce the incidence of pre-eclampsia and associated organ compromise, and may also reduce the risk of long-term cardiovascular disease (25). However, the Cochrane review conducted by Abalos et al. in 2014 that included 29 trials comparing the use of any antihypertensive drug with no medication or placebo in women with mild to moderate hypertension during pregnancy and evaluated the benefits, risks and adverse effects of drug therapy, found that there is a reduction in the risk of developing

severe hypertension associated with the use of antihypertensive medications compared to placebo but that there is no clear evidence of a difference in the risk of developing pre-eclampsia, fetal or neonatal death, preterm delivery, small for gestational age fetuses or placental abruption (25).

The International Study of Control of Hypertension in Pregnancy, or CHIPS, evaluated the differences in maternal and perinatal outcomes according to a less strict control of blood pressure levels with a DBP of 100 mm Hg or less, compared to strict control target DBP of 85 mm Hg or less in pregnant women with non-severe hypertension and without proteinuria. Women were included if they had a live fetus between 14 to 33 weeks 6 days of gestation, had non-severe pre-existing arterial hypertension without proteinuria or gestational hypertension, a DBP between 90 and 105 mm Hg if they did not receive antihypertensive therapy or 85 to 105 mm Hg if they were receiving this treatment. It was found that the number of pregnancy losses, the requirement for high-level neonatal care for more than 48 hours, and the rate of maternal complications did not differ significantly between groups, although less strict control was associated with a higher frequency of severe hypertensive episodes (26).

Randomized multicenter studies have been carried out in pregnant women with chronic hypertension exposed to different pharmacological treatments compared to non pharmacological intervention. The results are contradictory since in one study there was no direct relationship with the incidence of pre-eclampsia / eclampsia, other studies found a moderate association with this outcome, and uncertain association with the ocurrence of acute renal failure and placental abruption (27–29).

Taking into account these contradictory previous results, withdrawal of antihypertensive medications could also be a part of the management of chronic arterial hypertension during pregnancy, since no differences have been demonstrated between replacing or suspending antihypertensive medications (unless a clear maternal/fetal contraindication exists for a given antihypertensive drug used) and it could reduce costs and maternal and perinatal risks of the use of this type of therapy, without losing the benefits of therapy in those patients who really need them.

Why this review is important

There is evidence showing that antihypertensive management in pregnancy increases the risk of low birth weight and preterm delivery (30) and, as mentioned previously, there is controversy regarding the incidence of maternal complications. Bearing this in mind, it is important to synthesize the results of studies investigating the advisability of reducing or withdrawing antihypertensive drugs in pregnant women with chronic arterial hypertension. That is why we propose the evaluation of the evidence related to the safety and efficacy of reduction or withdraw antihypertensive drugs during pregnancy of chronic hypertensive women in order to make informed clinical decisions and support future research.

Objective

To estimate the safety and effectiveness of reducing or withdrawing antihypertensive therapy in pregnant women with chronic hypertensive vascular disease.

Methods

Criteria for including studies in this review

Randomized controlled trials or non-randomized controlled trials, published, unpublished and ongoing.

Types of participants

Pregnant women with a diagnosis of chronic hypertensive vascular disease defined as: systolic blood pressure greater than 130 mm Hg or diastolic pressure greater than 80 mm Hg (2,3) on at least two occasions 4 hours apart, before pregnancy or before 20 weeks of pregnancy (4).

Type of intervention

Withdrawal of antihypertensive drugs defined as abrupt suspension of drug use, de-staging of the drug until the withdrawal is complete, or decrease in current drug dose (16); versus:

1. Continue usual antihypertensive therapy with one or more medications of the type: alpha 2 agonists, calcium antagonists, alpha and beta blockers, alpha adrenergic antagonists, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, vasodilators, and diuretics.
2. Placebo.
3. Other interventions.

Types of outcomes

Primary Outcomes

Maternal:

Maternal death: Defined as the death of a woman due to direct or indirect obstetric causes during pregnancy or up to 42 days after its termination, regardless of the place in which it occurred or its duration (31).

Severe preeclampsia: Defined as finding after week 20 of gestation up to 6 weeks postpartum of systolic blood pressure values greater than or equal to 160 mm Hg or diastolic blood pressure values greater than or equal to 110 mm Hg on two occasions separated by a short interval of time (5-15 minutes), or the finding of systolic blood pressure values greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg on at least two occasions separated by four hours and associated with: thrombocytopenia (platelet count less than 100 x 10^9 / L); impaired liver function indicated by abnormal serum levels of liver enzymes (twice the higher level of reference); persistent severe pain in epigastrium or right upper quadrant not due to other diagnoses; renal failure (serum creatinine greater than 1.1 mg / dL or twice the baseline serum creatinine concentration in the absence of other kidney disease); pulmonary edema; recent-onset headache that does not respond to analgesic management and is not related to alternative diagnoses; hyperreflexia; visual disturbances such as photophobia, blurred vision, photopsia, scotomas, or blindness that are not related to alternative diagnoses (32); eclampsia defined as the sudden onset of focal or multifocal tonic-clonic seizures in the absence of other conditions that cause it such as epilepsy, cerebral ischemia or infarction, intracranial hemorrhage or use of medications; or HELLP syndrome defined as elevated lactic acid dehydrogenase (LDH) greater than or equal to 600 IU / L, aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) greater than twice the upper limit of normality and platelets less than 100 x 10^9 / L (4).

Admission to the Intensive Care Unit: defined as the requirement for care in intermediate or intensive care units (33).

Adverse reactions: defined as adverse events caused by the withdrawal or use of antihypertensive medications, including palpitations, headache, joint pain, lower limb edema, orthostatic hypotension or rebound hypertension, in addition to changes in serum biochemistry, heart rate, pulse rate, kidney function, and left ventricular parameters (34).

Fetal:

Loss of pregnancy: Defined as abortion (death of the fruit of conception before week 20 or less than 500 g) or death (death of a fetus in utero after week 20 and greater than 500 g) (26).

Neonatal Mortality: defined as those newborns who die before reaching 28 days of life (35).

APGAR less than or equal to 5 at minute 5: defined by the Apgar scale that assesses the viability of a newborn according to five simple physio-anatomical parameters: muscle tone, respiratory effort, heart rate, reflexes and skin color, each parameter is assigned a score between 0 and 2 (36).

Neonatal intensive care unit admission: defined as admission of a neonate to a neonatal intensive care unit for some neonatal condition that requires surveillance or monitoring (37). Among the causes of admission are: prematurity or birth weight less than 1500 g, gestational age less than 32 weeks, respiratory distress that requires ventilatory support (continuous positive pressure in the airway, mechanical ventilation), seizure syndrome; congenital abnormalities or inborn errors of metabolism, congenital heart disease or cardiac arrhythmias requiring cardiac management, hypoxic-ischemic encephalopathy, other conditions requiring neonatological consultation (severe hyperbilirubinemia, severe

intrauterine growth restriction, birth weight between 1000 g 2000 g and gestational age between 32 and 36 weeks (38).

Secondary outcomes

Maternal

Severe arterial hypertension: Defined as the finding of systolic blood pressure values greater than or equal to 160 mm Hg or diastolic blood pressure greater than or equal to 110 mm Hg on two occasions separated by a short time interval (minutes) (4).

Gestational age at delivery: Defined as weeks from conception to the date of delivery. It will be calculated taking into account the gestational age reported in the first trimester ultrasound (up to week 13 6/7) or that of the subsequent trimesters if the first trimester is not provided. If the date of the last menstruation agrees with the gestational age obtained through the ultrasound of the first trimester or of the subsequent trimesters, it can be used (39).

Hospitalization During Pregnancy: Defined as admission to a hospital during pregnancy (40)

Renal compromise: Defined as serum creatinine greater than or equal to 1.1 mg / dL (4).

Placental abruption: Defined as a process consisting of premature detachment of the placenta characterized by vaginal bleeding, uterine hypertonicity or unsatisfactory fetal status associated with direct visualization of retroplacental hemorrhage or hematoma (41).

Fetal:

Small for gestational age fetus: defined as a newborn whose weight is less than the 10th percentile for gestational age (42).

Preterm delivery: Defined as delivery before 37 weeks of gestation (43).

Hypoxic / Ischemic Encephalopathy: defined as the presence of neurological dysfunction in the form of neonatal encephalopathy, associated with depression of the level of consciousness, respiratory depression, alteration of muscle tone and seizures, associated with suggestive findings on brain MRI (44).

Search methods for identification of studies

Electronic searches

A comprehensive search was conducted to identify as many relevant studies as possible in the electronic databases. A combination of controlled vocabulary was used (MeSH, Emtree terms, Health Sciences, and descriptors (DeCS). The following electronic databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL).

- MEDLINE, PubMed

- EMBASE Ovid

- LILACS (Health Sciences of Latin America and the Caribbean).

Search for other resources

The following resources were sought for additional studies:

• International Clinical Trials Registry Platform (ICTRP) https://apps.who.int/trialsearch/AdvSearch.aspx

• Gray literature: a search was carried out in the information system for gray literature in Europe “OpenGrey”.

Manual search

Abstracts of the following conferences were hand searched:

- International Federation of Gynecology and Obstetrics (FIGO) (www.figo.org).

- American College of Obstetricians and Gynecologists (ACOG) (www.acog.org).

- Royal College of Obstetricians and Gynecologists (RCOG) (www.rcog.org.uk).

- Colombian Federation of Obstetrics and Gynecology. (https://www.fecolsog.org/)

Data extraction and analysis

The following methods were used when the reports were identified:

Study selection

Two reviewers independently assessed the inclusion of all potential studies that were identified as a result of the search strategy. Relevance and adherence to the inclusion criteria were evaluated. If studies did not meet the inclusion criteria, they were not included and the reasons for exclusion were wrote. Any disagreement was resolved through discussion or, if necessary, a third reviewer was consulted.

Data extraction and management

A form for data extraction was designed. For chosen studies, two reviewers extracted data using the agreed form. Discrepancies were resolved through discussion or, if necessary, a third reviewer was consulted. The data was entered into the RevMan 2019 software and verified for accuracy. When the information on any of the previous points was not clear, an attempt was made to contact the authors and editors of the original studies and the journals where they were published to provide more details.

Assessment of risk of bias in included studies

The risk of bias from randomized clinical trials was assessed using the criteria described in RoB 2.0 bias assessment tool (45). Any disagreement was resolved by discussion or involving a third reviewer.

RoB 2.0 risk assessment of biases

Biases created from the randomization process

1.1 Was the allocation process randomized?
Low risk of bias: Yes, or probably yes
High risk: No or probably not
Other: No information

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
Low risk of bias: Yes, or probably yes
High risk: No or probably not
Other: No information

1.3 Do the baseline differences between the intervention groups suggest a problem with the randomization process?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information

Biases due to deviations from planned interventions

2.1 Were the participants aware of the assigned intervention during the trial?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information

2.2 Were the caregivers and the people who carried out the interventions aware of the patients assigned to the intervention during the trial?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information

2.3 If yes, probably yes or no information to 2.1 or 2.2 Were there any deviations from the planned intervention that arose from the trial context?
Low risk of bias: No or probably not
High risk: Yes, or probably yes

Other: No information or does not apply

2.4 If yes, probably yes or no information was answered at 2.3 Did these deviations probably affect the outcome?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information or does not apply

2.5 If yes or probably yes to 2.4 Were the deviations from the planned intervention balanced between groups?
Low risk of bias: Yes, or probably yes
High risk: No or probably not
Other: No information or does not apply

2.6 Was an appropriate analysis used to estimate the effect of the allocation to the intervention?
Low risk of bias: Yes, or probably yes
High risk: No or probably not
Other: No information

2.7 If no, probably no, or no information at 2.6 Was their potential for a substantial impact (on the outcome) of the failure to analyze participants in the group to which they were randomized?

Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information or does not apply

Biases due to missing data

3.1. Was information for this outcome available to all or almost all randomized participants?
Low risk of bias: Yes, or probably yes
High risk: No or probably not
Other: No information

3.2. If no, probably no or no information was answered at 3.1 Was their evidence that the results are not biased due to lack of data on the outcomes?
Low risk of bias: Yes, or probably yes
High risk: No or probably not
Other: Does not apply

3.3 If the answer was no or probably not to 3.2, could the lack in the outcome depend on its true value?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information or does not apply

Biases in the measurement of outcome

4.1 Was the method for measuring the outcome inadequate?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information

4.2 Could the measurement or finding of the gap have differed between the intervention groups?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information

4.3 If no, probably no or no information was answered at 4.1 and 4.2 Were the outcome assessors aware of the intervention received by the study participants?
Low risk of bias: No or probably not
High risk: Yes, or probably yes
Other: No information

4.4 If yes, probably yes or no information was answered to 4.3 Could the outcome evaluation have been influenced by knowledge of the intervention received?

Low risk of bias: No or probably not

High risk: Yes, or probably yes

Other: No information

4.5 If yes, probably yes or no information was answered to 4.4 Is it likely that the outcome assessment was influenced by knowledge of the intervention received?

Low risk of bias: No or probably not

High risk: Yes, or probably

Other: No information

Bias in the selection of reported results

5.1 Were the data that produced this outcome analyzed in accordance with a pre-specified analysis plan that was finalized before the non-hidden outcome data was available for analysis?

Low risk of bias: Yes, or probably yes

High risk: No or probably not

Other: No information

The numerical result being evaluated was probably selected, based on the results, from:

5.2… multiple eligible outcome measures (eg, scales, definitions, time points) across the outcome domain?

5.3… multiple eligible analyzes of the information?

Risk of bias in general

- Low
- High
- Some concerns

Assessment of the risks of ROBINS-2 biases1.

1.1 Is there a potential risk to confound the effect of the intervention in this study?

No: the study can be considered to have a low risk of bias due to confounding factors; no other questions need to be considered.

Yes: Determine if you need to assess the risk of confusion that varies over time.

1.2 Was the analysis based on dividing the participants' follow-up time according to the intervention received?

No: answer questions 1.4 to 1.6.
Yes: go to question 1.3.

1.3 Are interruptions or changes to the intervention likely to be related to factors that are prognostic for the outcome?

No: answer questions 1.4 to 1.6.
Yes: answer the questions related to baseline and confounders that vary over time (1.7 and 1.8)

Questions related to confusing baseline only.

1.4 Did the authors use an appropriate analysis method that controlled for all important confounding domains?

1.5 Yes to question 1.4: Were the confounding domains controlled validly and reliably by the variables available in this study evaluated?

1.6 Did the authors control for post-intervention variables that might have been affected by the intervention?

Baseline questions and confusion that varies over time.

1.7 Did the authors use a suitable analysis method that controlled for all important confounding domains and confounding for variation over time?

1.8 Yes to question 1.7: Were the confounding domains controlled validly and reliably by the variables available in the study measured?

Risk of bias judgment: What is the predicted orientation of bias due to confounding?

Bias in the selection of study participants

2.1 Was the selection of participants in the study (or in the analysis) based on the characteristics of the participants observed after the start of the intervention?

No: go to 2.4

2.2 Yes: Yes to 2.1: Were the post-intervention variables that influenced the selection likely associated with the intervention?

2.3 Yes to 2.2: Would the post-intervention variables that influenced the selection likely be affected by the outcome or a cause of the outcome?

2.4. Do the start of follow-up and the start of the intervention coincide for most of the participants?

2.5 Yes to 2.2 and 2.3 or no to 2.4: Were adjustment techniques used that can correct the presence of selection biases?

Judgment of risk of bias: What is the predicted direction of bias due to the selection of study participants?

Bias in the classification of interventions

3.1 Were the intervention groups clearly defined?

3.2 Was the information used to define the intervention groups at the beginning of the intervention?

3.3 Could the classification of the intervention state be affected by knowledge of the outcome or the risk of the outcome?

Judgment of risk of bias: What is the predicted direction of bias due to the classification of the interventions?

Bias due to deviations from planned interventions

Assessment of the effect of the intervention allocation, answer questions 4.1 and 4.2

4.1. Were there deviations from the intended intervention beyond what would be expected in routine practice?

4.2. Yes to 4.1: Were these deviations from the intended intervention an imbalance between the groups and are they likely to have affected the outcome?

Evaluation of the effect of starting and adhering to the intervention, answer questions 4.3 to 4.6

4.3. Were the major co-interventions balanced between the intervention groups?

4.4. Was the intervention successfully implemented for the majority of participants?

4.5. Did the study participants adhere to the assigned intervention regimen?

4.6. No to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of initiating and adhering to the intervention?

Judgment of risk of bias: What is the predicted direction of bias due to the classification of the interventions?

5. Missing data bias

5.1 Were outcome data available for all or almost all participants?

5.2 Were participants excluded due to lack of data on intervention status?

5.3 Were participants excluded due to lack of data on other variables required for analysis?

5.4 No to 5.1, or yes to 5.2 or 5.3: Are the proportion of participants and the reasons for missing data similar across all interventions?

5.5 No to 5.1, or yes to 5.2 or 5.3: Is there evidence that the results were robust in the presence of missing data?

Risk of bias judgment: What is the predicted direction of bias due to missing data?

6. Bias in the measurement of results

6.1 Could the outcome measure have been influenced by knowledge of the intervention received?

6.2 Were the outcome assessors aware of the intervention received by the study participants?

6.3 Were the outcome assessment methods comparable between the intervention groups?

6.4 Were the systematic errors in the measurement of outcomes related to the intervention received?

Judgment risk of bias What is the predicted direction of bias due to the outcome measurement?

7. Bias in the selection of reported results

The reported effect estimate is likely to be selected, based on the results, from:

7.1 .... multiple outcome measurements within the outcome domain?

7.2 ... multiple analyzes of the intervention-outcome relationship?

7.3 ... different subgroups?

Judgment risk of bias

Interpretation of risk of bias by domains and global

- Low risk of bias: when the study was judged as low risk in all domains
- Moderate risk of bias: when the study was judged as low or moderate risk in all domains

- Serious risk of bias: when the study was judged as serious risk of bias in some domain, but none was critical.
- Critical risk of bias: when the study was judged as critical risk of bias in at least one domain.

Assessment of the quality of evidence using the GRADE system

The quality of evidence was evaluated using the GRADE system as specified in the GRADE manual so as to assess the quality of evidence related to the outcomes of the main comparison. Antihypertensive withdrawal was defined as abrupt discontinuation of drug use, de-escalation of the drug until complete withdrawal or tapering of the drug dose compared to continuing established antihypertensive therapy, Placebo and Other interventions. A summary of the effect of the intervention and of the quality measurement for each of the next outcomes was developed using the GRADE system (Annexed tables 1 and 2).

Maternal

- Maternal death
- Severe preeclampsia
- Admission to intensive care unit
- Adverse effects

Fetal

- Loss of pregnancy
- Neonatal Mortality
- APGAR less than or equal to 5 at minute 5
- Admission to the neonatal intensive care unit

Secondary outcomes

Maternal

- Severe hypertension

- Gestational age at delivery
- Placental abruption

Fetal

- Fetus small for gestational age
- Preterm delivery

The GRADEpro tool was used to import information from RevMan 2019, so that summary tables of findings were created. The GRADE approach System uses five considerations; study limitations, consistency of effect, imprecision, uncertainty about whether the evidence is direct, and publication bias. Evidence was downgraded from high quality by one or two levels if it had serious or very serious limitations respectively, depending on the assessment of risk of bias, uncertainty about whether the evidence was direct, presence of serious inconsistencies, imprecision of effect, or bias of publication.

Measurement of treatment effect

Dichotomous data

The results were reported as a probability ratio (OR) with a 95% confidence interval (CI).

Continuous data

The mean difference (MD) was used if the results are measured in the same way within the included studies and the standardized mean difference (SMD) was used to combine trials measuring the same outcome, but with different methods.

Assessment of missing data

An intention-to-treat analysis was performed, that is, an attempt was made to include all participants assigned to each analysis group and all participants who were analyzed in the group to which they were assigned, regardless of whether or not they received the assigned

intervention. The impact of including studies with high levels of missing data in the overall evaluation of treatment effects was explored using a sensitivity analysis.

Assessment of heterogeneity

Statistical heterogeneity was assessed using I2 values and Chi square test values. Heterogeneity was considered substantial if the I2 statistical value was greater than 40% or if there was a low p-value (less than 0.10) in the Chi-square test.

Assessment of reporting bias

Publication bias was assessed when ten or more studies were retrieved through the evaluation of the asymmetry of the funnel plot and the formal tests. For continuous variables, the test proposed by Egger was used (46), and for dichotomous results the test proposed by Harbord was used (47).

Subgroup analysis and investigation of heterogeneity

We explored the following potential sources of heterogeneity where it was considered that the effect size may have changed based on their results using subgroup analysis.

1. Definition of chronic arterial hypertension. Chronic arterial hypertension defined as SBP greater than or equal to 130 and DBP greater than or equal to 80 vs. defined as SBP greater than or equal to 140 and DBP greater than or equal to 90.

2. Subgroup of type of antihypertensive. alpha 2 agonists, calcium antagonists, alpha blockers, beta blockers, alpha adrenergic antagonists, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, vasodilators, and diuretics.

3. Etiology of hypertension. Primary hypertension vs. secondary hypertension.

Data analysis

Statistical analysis was performed using RevMan 2019, a fixed-effect meta-analysis was used to pool the data when it was reasonable to assume that the studies estimated the same underlying treatment effect, that is, when the studies examined the same intervention, and the populations and study methods were sufficiently similar. When there was sufficient clinical heterogeneity to have expected underlying treatment effects differed between studies or substantial statistical heterogeneity, a random effects meta-analysis was performed.

The average effect of the random effects was assessed as the average range of possible treatment effects and the clinical implications of treatment effects that differed between trials was discussed. If the average effect was not clinically significant, the trials were not combined. If random effects analysis was used, the results were presented as the mean treatment effect and 95% confidence intervals and I2 estimates.

Sensitivity analysis

A sensitivity analysis was performed by type of studies and based on other aspects of the review that may had have an effect on the results, a sensitivity analysis was also performed to explore the inclusion of the effects of fixed or random effects analysis for the results with statistical heterogeneity.

Ethical considerations

The Ministry of Social Protection through Resolution 8430 of 1993 establishes that research for health must include the development of actions that contribute to the knowledge of biological and / or psychological processes in human beings, as well as the knowledge of the links between the causes of the disease, medical practice, and social structure (Ministry of Health, 1993). This project marks one of the guidelines in which scientific research in health is developed through the safety and effectiveness of the reduction or withdrawal of pharmacological antihypertensive therapy in pregnant women with chronic hypertensive vascular disease. To do this, we used the available bibliographic evidence from a systematic search of the literature; we did not include the participation of individuals or use

of direct data from information collected from patients. For this reason, this systematic review constitutes a Risk-Free Research, and did not require the use of informed consent. This study is classified according to Resolution 8430 of 1993, as a risk-free investigation since it uses retrospective documentary investigation techniques and methods. The protocol was approved by the Ethics Committee of the Faculty of Medicine of the National University of Colombia in the evaluation report N° 019-218 of November 26, 2020, Regarding the Declaration of conflict of interest of the authors, all declared not having any conflict of interest for the development of this systematic review.

Results

Results of the search

We searched the available literature up to May 30, 2021. We retrieved references, of which we screened 2975 after we removed duplicates. Of these, we screened the full-text of 37 references. Eleven published trials met our inclusion criteria (Arias 1979; Welt 1981; Weitz 1987; Sibai 1984; Sibai 1990; Redman 1976; Mutch 1977; Butters 1990; Hirsch 1996; Vigil de Gracia 2013; Steyn 1997). We present a PRISMA diagram in Figure 1 to illustrate the study selection process.

The eleven included trials had 1632 participants with a sample size ranging from 20 to 491 people. Five trials were from United States (Arias 1979; Welt 1981; Weitz 1987; Sibai 1984; Sibai 1990), three from the United Kingdom (Redman 1976; Mutch 1977; Butters 1990), one trial each from Israel (Hirsch 1996), Panama (Vigil de Gracia 2013), and South Africa (Steyn 1997). Three trials were multicentric (Mutch 1977; Butters 1990; Hirsch 1996), without using a method for sample size calculation. Two studies were sponsored by academic institutions with industry support (Redman 1976, Steyn 1997), two were sponsored by the pharmaceutical industry without mentioning academic support (Weitz 1987; Butters 1990), one had academic support without mentioning assistance from the industry (Mutch 1977), five did not made a clear allusion to this aspect (Arias 1979; Welt 1981; Sibai 1984; Sibai 1990; Hirsch 1996) and only one declared not having conflicts of interest (Vigil de Gracia 2013). All trials were published in English.

Population

Included studies recruited pregnant women with a mean age from 24 to 35 years, whose mean gestational age at enrollment ranged from 7 to 26 weeks. Eight studies included only singleton pregnancies (Redman 1976; Mutch 1977; Arias 1979; Welt 1981; Sibai 1984; Weitz 1987; Sibai 1990; Steyn 1997). Duration of chronic hypertension before pregnancy was described in two studies (Sibai 1984; Sibai 1990) and varied between 3.5 and 4.8 years Five studies included women with chronic hypertension documented before 20 weeks of pregnancy (Arias 1979; Kahale 1985; Sibai 1990; Steyn 1997; Vigil de Gracia 2013).

Five trials enrolled patients with either systolic or diastolic pressure that equaled or exceeded 140 or 90 mm Hg. Three of them (Redman 1976; Mutch 1977; Butters 1990) before 28 weeks and two before 35 weeks (Weitz 1987, Hirsch 1996). Furthermore, (Redman 1976) recruited patients from 28 to 32 weeks who had either systolic or diastolic pressure equal to or greater than 150 or 95 mm Hg, respectively. Two studies (Welt 1981, Steyn 1997) selected patients with either systolic or diastolic pressure that exceeded 130 or 80 mm Hg, respectively, at rest during the first two trimesters of pregnancy. One study (Sibai 1984) only included women with history of chronic hypertension who received management with diuretics before pregnancy. All trials included outpatients.

Interventions

In six studies the intervention group received methyldopa, whose dose varied from 25 mg to 4 g per day (Redman 1976; Mutch 1977; Arias 1979; Weitz 1987; Sibai 1990; Welt 1981). Methyldopa was compared to labetalol with a dose that ranged from 300 mg to 2400 mg per day (Sibai 1990), hydralazine 25 mg three times per day and hydrochlorothiazide (Welt 1981). One study (Arias 1979) divided the intervention arbitrarily into a group assigned to methyldopa plus hydrochlorothiazide 50 mg per day, another to hydralazine from 75 mg to 250 mg per day plus hydrochlorothiazide in the same previous dose and the last one to methyldopa plus hydralazine plus hydrochlorothiazide, In two trials (Sibai 1984; Vigil de Gracia 2013) the intervention group received management with diuretics. In the trial done by Sibai in 1984, methyldopa was added when necessary to keep blood pressure at < 160 mm Hg systolic and/ or < 110 mm Hg diastolic levels and the patients received a daily diet containing approximately 2 grams of sodium. In the study by Vigil de Gracia in 2013 one

group received furosemide 20 mg each day, the second group received amlodipine 5 mg each day and a third group aspirin 75 mg each day (without antihypertensive).

In Butters 1990 the intervention was atenolol from 50 mg to 20 mg daily and in and Kahale 1985 and Hirsch 1996 treatment was pindolol from 10 mg to 40 mg daily, Ketanserin from 40 mg to 80 mg daily was used by Steyn 1997 that additionally gave patients aspirin (Steyn 1997).

Three of the studies defined that elevation of DBP greater than 90 to 100 mm Hg on two occasions, at least 6 hours apart, was considered treatment failure and indicated therapy with methyldopa (Sibai 1984) or hydralazine up to 50 mg (Hirsch 1996) or 300 mg/day (Sibai 1990). Three trials indicated that if severe hypertension developed, hydralazine or labetalol was used to treat hypertension and magnesium sulfate was administered (Arias 1979; Weitz 1987; Vigil de Gracia 2013).

Comparisons

The search did not find any controlled clinical trial evaluating the reduction or withdrawal of antihypertensive therapy. Overall, 12 trials with a total of 1.732 women compared an antihypertensive drug with placebo or no antihypertensive drug.

Five studies used placebo as comparison (Welt 1981; Weitz 1987; Butters 1990; Hirsch 1996; Steyn 1997). Five studies used no treatment as comparison (Redman 1976; Mutch 1977; Arias 1979 ; Sibai 1984; Sibai 1990). One study prescribed aspirin 75 mg orally daily as comparison (Vigil de Gracia 2013).

Outcomes

Severe hypertension was reported by seven studies (Mutch 1977; Arias 1979; Welt 1981; Sibai 1990; Hirsch 1996; Steyn 1997; Vigil de gracia 2013) and was defined as systolic blood pressure that varies between 160 to 170 mmHg and diastolic that varied between 100 and 120 mmHg.

Superimposed preeclampsia was assessed by ten studies (Redman 1976; Mutch 1977; Arias 1979; Welt 1981; Kahale 1985; Weitz 1987; Sibai 1984; Sibai 1990; Steyn 1997; Vigil de Gracia 2013) but there were differences in reporting and definition of this outcome between the studies. Those differencies included: appearance of proteinuria, defined between a range from 300 mg / ml to 1 g / 24 h (Redman 1976; Mutch 1977; Arias 1979; Kahale 1985; Weitz 1987; Sibai 1984; Sibai 1990; Steyn 1997; Vigil de Gracia 2013), edema (Redman 1976; Mutch 1977; Welt 1981), uric acid greater than 6 mg/dl (Redman 1976; Mutch 1977; Sibai 1990), weight gain greater than 2 pounds (Weitz 1987) and / or increased blood pressure, which was either defined as increase in SBP 30 mmHg or more or DBP greater than 15 mmHg (Weitz 1987) or DBP greater than 100 or 110 mmHg (Arias 1979; Kahale 1985; Steyn 1997; Vigil de Gracia 2013), or symptoms suggesting organ damage, such as headache, visual disturbances, epigastric pain, or tinnitus (Vigil de Gracia 2013).

Ten studies reported small for gestational age, defined as weight at birth under the tenth percentile for gestational age (Mutch 1977; Arias 1979; Welt 1981; Weitz 1987; Sibai 1984; Sibai 1990; Butters 1990; Hirsch 1996; Steyn 1997; Vigil de Gracia 2013). Nine trials reported weeks of pregnancy at birth (Redman 1976; Mutch 1977; Arias 1979; Weitz 1987; Sibai 1984; Sibai 1990; Hirsch 1996; Steyn 1997; Vigil de Gracia 2013).

Four trials documented the frequency of Apgar < 7 at 5 minutes (Mutch 1977; Sibai 1984; Sibai 1990; Hirsch 1996). Preterm birth, defined as birth under 37 weeks of gestation, was described in four studies (Arias 1979; Sibai 1984; Sibai 1990; Vigil de Gracia 2013). Abruptio placentae defined as diagnosis of retroplacental hematoma at the time of delivery was assessed in three studies (Sibai 1990; Vigil de Gracia 2013; Steyn 1997). Neonatal mortality was informed in eight studies (Redman 1976; Mutch 1977; Arias 1979; Kahale 1985; Weitz 1987; Sibai 1984; Sibai 1990; Steyn 1997) and neonatal admission to intensive care unit was assessed in one study (Mutch 1977). Miscarriage was documented in four studies (Redman 1976; Mutch 1977; Kahale 1985; Hirsch 1996) and stillbirth in nine studies (Redman 1976; Mutch 1977; Arias 1979; Sibai 1984; Kahale 1985; Sibai 1990; Butters 1990; Steyn 1997; Vigil de Gracia 2013).

Excluded studies

We excluded 17 studies for the following reasons: nine were not randomized clinical trials (Lip 1977; Mabie 1986; Freire 1988; Lydakis 1999; Bayliss 2002; Niegowska 2004; Chen 2018; Nzelu 2018; Mito 2019), two included only women beyond 24 weeks of pregnancy (Cruickshank 1991; Lunell 1991), one only reported fetal hemodynamic outcomes (Vasconcellos 2000) and three due to differences from the included population; the first included only women with gestational hypertension (Blake1991), the second women without hypertension (Flowers 1962) and the third excluded patients with previous antihypertensive treatment (Parazzini 1988). Two studies carried out in Egypt, that showed the same design and results, were excluded due to methodological concerns (Resk 2019; Salama 2019) (see Characteristics of excluded studies table).

Risk of bias in included studies

We summarized the risk of bias assessment in *Figure 2* and *Figure 3*

Bias arising from the randomization process

Three trials adequately reported the random sequence generation method by using a computer-generated randomization list (Sibai 1990, Steyn 1997, Vigil de Gracia 2013). The remaining included trials did not report the random sequence generation method. Two studies adequately implemented a valid concealment of allocation method, using sequentially numbered sealed envelopes (Steyn 1997, Vigil de Gracia 2013), making selection bias at entry unlikely. The remaining included trials did not report the method of allocation concealment, so they have unclear risk of selection bias.

Bias due to deviations from intended interventions

Six studies did not report the implemented methodology to blind study participants, outcome assessors and personnel from knowledge of which intervention a participant received (Arias 1979, Kahale 1985, Butters 1990, Hirsch 1996, Steyn 1997, Vigil de Gracia 2013). However, we considered the studies at low risk for deviations from intended interventions because the outcomes were objectively assessed, so the lack of blinding would be unlikely

to affect results. Six studies did not report the methodology to blind study participants outcome assessors and personnel appropriately and so were at unclear risk for performance and detection bias because lack of blinding would be unlikely to affect results (Redman 1976, Mutch 1977, Welt 1981, Sibai 1984, Weitz 1987, Sibai 1990).

Bias due to missing outcome data

Eight trials appropriately stated the attrition and exclusions at each stage; the reasons were balanced across groups and the level of missing data was not over 20%, making bias due to missing data unlikely (Redman 1976, Mutch 1977, Arias 1979, Welt 1981, Sibai 1984, Hirsch 1996, Steyn 1997, Vigil de Gracia 2013). Four studies were at high risk of bias because the level of missing data was over 20% or because they used an 'as treated' analysis with substantial departure of intervention received from that assigned at randomization (Kahale 1985, Weitz 1987, Butters 1990, Sibai 1990).

Bias in measurement of the outcome

Six trials had an appropriate method of measuring outcomes and despite outcome assessors were aware of intervention, assessment was not influenced by knowledge of intervention (Arias 1979, Kahale 1985, Butters 1990, Hirsch 1996, Steyn 1997, Vigil de Gracia 2013). Six trials had an appropriate method of measuring outcomes and despite outcome assessors were aware of intervention it is unlikely that assessment was influenced by knowledge of intervention (Redman 1976, Mutch 1977, Welt 1981, Sibai 1984, Weitz 1987, Sibai 1990).

Bias in selection of the reported result

The trial protocol was not available for all the included trials and it was unclear if the published reports included all the expected outcomes, including those that were prespecified. The report had insufficient information to permit judgement of 'yes' or 'no' (rated as unclear risk of bias).

Overall risk of bias

Because of some limitations on bias assessment arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selective reporting domains included studies were classified as unclear (Redman 1976, Mutch 1977, Arias 1979, Welt 1981, Sibai 1984, Hirsch 1996, Steyn 1997, Vigil de Gracia 2013) or high risk of bias (Kahale 1985, Weitz 1987, Butters 1990, Sibai 1990).

Selective reporting

The trial protocol was not available for all the included trials and it was unclear if the published reports included all the expected outcomes, including those that were prespecified. The report had insufficient information to permit judgement of 'yes' or 'no' (rated as unclear risk of bias).

Effects of interventions

Primary outcomes

Maternal death: None of the included studies reported maternal death *Analysis 1*

Superimposed preeclampsia: Ten trials including 1103 women suggest that there may be little or no difference in the risk of developing proteinuria/pre-eclampsia (average Odds ratio (aOR) 0.73, 95% CI 0.50 to 1.07 $I^2 = 0\%$), *Analysis 2*. The quality of the evidence was very low due to limitations on risk of bias.

Subgroup Analyses: There is a reduction in the risk of developing proteinuria/pre-eclampsia in women treated with 5-HT2A receptor antagonist versus no antihypertensive drugs/placebo (one trial, 69 women; OR 0.13; 95% CI 0.03 to 0.59). There is no difference with other type of pharmacological groups.

Admission to intensive care unit None of the included studies reported maternal admission to intensive care unit.

Adverse effects: Low-certainty evidence suggests that there may be difference in the risk of developing adverse effects, that were reported by four trials with 527 women (aOR 8.52; 95% CI 1.05 to 69,19 I^2 =0%) *Analysis 3.* No evidence of differences was found between any of the pharmacological subgroups. The quality of the evidence was very low due to limitations on precision, and risk of bias.

Loss of pregnancy Thirteen trials reported the loss of pregnancy. The information obtained is divided according to gestational age in abortions and stillbirths.

Nine trials including 1084 women reported stillbirths. There was no evidence of difference between antihypertensive therapy and placebo or not treatment (OR 0.72, 95% CI 0.27 to 1.93; I2 = 0%; *Analysis 4*). There were no evidence of differences between any of the pharmacological subgroups. The quality of the evidence was very low due to limitations on precision, heterogeneity, and risk of bias.

Four trials reported miscarriage. There was no evidence of difference between antihypertensive therapy and placebo or not treatment (OR 0.43, 95% CI 0.15 to 1.19; I2 = 23%; *Analysis 5*). At the subgroup analysis there is reduction in the risk of developing abortions in women treated with Alpha 2 adrenergic agonist, two trials with 421 women (OR 0.11, 95% CI 0.01 to 0.88; I2 = 0%). The quality of the evidence was very low due to limitations on precision, heterogeneity, and risk of bias.

Neonatal Mortality Eight trials reported neonatal deaths. There was no evidence of a difference between antihypertensive therapy and placebo or not treatment (OR 0.43, 95% CI 0.15 to 1.19; 10 studies 1011 patients I2 = 23%; *Analysis 6*). No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision and risk of bias

Low APGAR at minute 5: Four trials including 510 patients reported APGAR less 7 in the fifth minute of life. There was no evidence of difference between antihypertensive therapy and placebo or not treatment (OR 1.52, 95% CI 0.59 to 3.92; I2 = 0%; *Analysis 7*). No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision and risk of bias.

Admission to the neonatal intensive care unit: One study that included 202 patients reported the outcome. There was no evidence of a difference between antihypertensive

therapy and not treatment (OR 1.54, 95% CI 0.63 to 3.79; heterogeneity analysis was not applicable; *Analysis 8*). No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision, heterogeneity and risk of bias.

Secondary outcomes

Severe hypertension There is probably a halving in the risk of developing severe hypertension associated with the use of antihypertensive drug/s (OR 0,43 95% CI 0.26 to 0.70; 7 studies, 773 participants; I2 = 0%; *Analysis 9).* No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations by risk of bias.

Gestational age at delivery: Nine trials including 1007 patients reported this outcome. There was no evidence of difference between antihypertensive therapy and placebo or not treatment (Mean Difference in weeks -0.09 , 95% CI - 0.25 to 0,06 I2 = 44%; *Analysis 10)*. No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision and risk of bias.

Placental abruption: Three studies reported the outcome. There was no evidence of a difference between antihypertensive therapy and placebo or not treatment (OR 0.55, 95% CI 0.20 to 1.54; 5 studies, 462 women, I2 0%, *Analysis 11*). No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision, heterogeneity and risk of bias.

Preterm delivery Four trials including 402 patients reported the outcome. The frequency of the event was similar between the comparison groups: antihypertensive therapy and placebo or not treatment (OR 1,28, 95% CI 0.66 to 2.49; I2 = 0%; *Analysis 13*). No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision and risk of bias.

None of the included studies reported hospitalization during pregnancy or renal compromise as a quantitative or qualitative outcome.

Fetus small for gestational age Ten trials including 900 patients reported small for gestational age. The frequency of the event was similar between the comparison groups: antihypertensive therapy and placebo or not treatment (OR 0,86, 95% CI 0.53 to 1.40; I2 = 0%; *Analysis 12*). No differences were documented between pharmacological subgroups. The quality of the evidence was very low due to limitations on precision and risk of bias.

None of the included studies reported hypoxic ischemic encephalopathy as a quantitative or qualitative outcome.

Discussion

Very low certainty evidence suggests that antihypertensive drugs rather than placebo or no treatment, may probably decrease the risk that pregnant women with chronic hypertension will develop severe hypertension during the course of pregnancy.

Furthermore, very low certainty evidence suggests that the risk of presentation of maternal adverse effects such as altered liver function, hemolytic anemia, congenital abnormalities, intrauterine growth retardation, hypoglycemia or neonatal morbidity, may probably increase when antihypertensive drugs are used in pregnant women with chronic hypertension. This finding differs from the results reported by Abalos et al (48) who found no apparent differences for this outcome.

According to the results of the present review, antihypertensive treatment during pregnancy in women with chronic hypertension compared to no antihypertensive drug or the use of placebo does not modify the appearance of adverse outcomes such as superimposed pre-eclampsia, preterm delivery, placental abruption, small for gestational age fetus, stillbirth, miscarriage, neonatal death, admission to the neonatal intensive care unit or low APGAR at birth. Gestational age at birth was similar for both groups of women. However, none of the studies included in the present review reported maternal mortality, as in the review by Webster et al. in 2017 (49)

The studies included in this systematic review differ from those included in the review by Abalos et al. in 2018. The present review included trials with women with chronic arterial hypertension only, without severe hypertension on admission. On the other hand, the review by Abalos et al. included women with mild to moderate hypertension during any time of pregnancy, which means that patients with chronic hypertension, gestational hypertension or pre-eclampsia were incorporated, therefore a greater number of studies were included but analyzing the behavior of maternal and fetal outcomes such as severe hypertension, superimposed preeclampsia, gestational age at birth, small for gestational age fetus, neonatal death or death not exclusively in the population with chronic arterial hypertension. Furthermore, unlike the meta-analysis by Abalos et al., this review included the randomized clinical trial by Sibai 1984, which allows to analyze the safety profile of diuretics during pregnancy.

The systematic review carried out by Webster et al, included clinical trials carried out up to 1998, while the present study integrates the clinical trial carried out by Vigil de Gracia 2013. Webster's review excluded this trial because the use of calcium channel blockers and diuretics was compared with the use of aspirin. It is important to bear in mind that although aspirin does not have an antihypertensive effect, it is a common co-intervention during prenatal care for high risk pregnancies since it has been found that aspirin decreases the risk of early onset pre-eclampsia (50). The inclusion of this study might modify the results towards favoring the null hypothesis of no benefits from hypertensive therapy during pregnancy for chronic vascular disease.

When performing the analysis by pharmacological subgroups, regarding the decrease in the frequency of severe hypertension, it was found that the use of methyldopa and ketanserin is associated with a lower probability of presenting severe hypertension. It should be noted that the number of patients who received treatment with alpha 2 adrenergic agonists was greater than that of patients who received calcium antagonists, diuretics, and direct-acting vasodilators altogether.

There were no apparent differences in the subgroup analysis for adverse events associated with treatment. It is important to note that this outcome was not reported for alpha 2 adrenergic agonists. Abalos et al. (48)reported that that the use of antihypertensive medications during pregnancy may have little or no effect on the number of women

who must modify their antihypertensive medication due to side effects, with no significant differences found between subgroups. However, as in the present review, there was an absence of reports of this type of events in most of the included studies.

Integrity and general applicability of the evidence

In the present review, an exhaustive search of the literature was carried out to date to find clinical trials in which the effectiveness of antihypertensive drugs was evaluated against placebo or the absence of antihypertensive drugs during pregnancy of chronic hypertensive women. There was no language restriction in the search and selection of studies. In the included studies population comprised exclusively pregnant women with chronic hypertension, excluding women with pregnancy associated hypertension or non-pregnant women with chronic hypertension in childbearing age.

There are limitations in the applicability given the heterogeneity in the populations, the interventions, and the definition of the outcomes. There were significant variations in the definition of chronic arterial hypertension between the different studies, so that patients with systolic blood pressure that varied between 140 and 170 mmHg and diastolic between 90 and 110 mmHg were included, from before pregnancy to up to week 34 of pregnancy. Only one of the included studies (Weitz 1987) reported proteinuria on admission and excluded women with proteinuria > 100 mg/24 h prior to admission. A variety of definitions were also found for severe hypertension and superimposed pre-eclampsia; the first was defined as systolic blood pressure with a variation between 160 to 170 mmHg and the diastolic varied between 100 and 120 mmHg, and the second had multiple definitions among which the appearance of proteinuria is commonly found (between 300 mg / ml and 1 g / 24 h), edema, increased uric acid and / or increased blood pressure (DBP greater than 100 or 110 mmHg).

Only three of the studies were conducted in low- and middle-income countries and it must be highlighted that seven studies included in the meta-analysis evaluated agents that are no longer used for the routine management of hypertension in pregnancy (atenolol, pindolol, hydrochlorothiazide, furosemide, ketanserin, oral labetalol and oral hydralazine).

Quality of evidence

The quality of the individual outcomes was mostly graded as very low according to the recommendations of the GRADE Working Group, mainly due to design limitations that generated a serious risk of bias, indirect evidence, and imprecision of the point estimates of the effect. Most of the studies have unclear concealment of the intervention and are reported as randomized without providing further details about the randomization process, in addition to being described as double blind without further information on the matter. Likewise, included studies with small sample sizes and low frequencies of outcomes are imprecise. The heterogeneity found for the main outcomes evaluated was low (I2 <40%), and a low risk of publication bias was estimated given the symmetry found in the funnel plot. *(See Table 1 Quality of Evidence)*

Possible biases in the review process

This systematic review has some strengths as we adhered to the predefined objectives and study eligibility criteria. Our search included an appropriate range of databases and sources, including additional methods to identify eligible studies. We assessed all studies for risk of bias and graded the quality of evidence using the GRADE approach. There is a low risk of publication bias given the symmetry of in the funnel plot. It is important to remember that two studies were sponsored by academic institutions with industry support (Redman 1976, Steyn 1997) and two were sponsored by the pharmaceutical industry without mentioning academic support (Weitz 1987; Butters 1990).

Agreements and disagreements with other studies or reviews

The Cochrane review conducted by Abalos et al. on the use of antihypertensive treatment for “mild to moderate” hypertension in pregnancy versus placebo/no antihypertensive drug found that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension and has little or no effect on other outcomes such as proteinuria or pre-eclampsia, small-for-gestational-age babies, preterm

birth, reported fetal and neonatal death (including miscarriage) and admission to neonatal or intensive care nursery, which is in agreement with our findings.

This review also showed that there may be little or no effect on the risk of changed or stopped drugs due to maternal side-effects. As stated, this finding may be related to the fact that most of the studies did not report this outcome and should be judged carefully. It also found a possible but still uncertain effect of antihypertensive drugs on the risk of severe pre-eclampsia, or eclampsia, impaired long-term growth and development of the baby in infancy and childhood due to very low certainty of evidence. There may be little or no effect on the, or admission to neonatal or intensive care nursery (low-certainty evidence). The meta-analysis done by Webster et al. concluded that antihypertensive treatment reduces the risk of severe hypertension in pregnant women with chronic hypertension but there is no effect in other outcomes such, superimposed preeclampsia, cesarean section delivery, abruption, stillbirth, neonatal death, birth weight, small for gestational age, gestation at delivery, preterm birth and apgar score <7 at 5 min.

Authors 'conclusions

Implications for practice.

The use of antihypertensive therapy reduces the incidence of severe hypertension in pregnant women with chronic hypertensive vascular disease, without sufficient evidence to support its effectiveness in reducing the incidence of other maternal or perinatal adverse outcomes.

All the results of this review should be viewed with caution as they are based on low values and very low-quality evidence.

Implications for research

More clinical trials are required to analyze the impact of the intervention in populations with target organ involvement, and to evaluate the safety and effectiveness of several commonly used antihypertensives. Evidence of critical outcomes for decision-making is lacking. Studies should evaluate the long-term impact of antihypertensive therapy in the mother,

fetus, and neonate. Furthermore, studies are required to compare head-to-head antihypertensive management in women with chronic arterial hypertension.

Author contributions

Each author actively participated in conceptual development, title selection, study quality assessment, data extraction and analysis, and writing of the first draft of the systematic review and subsequent amendments.

Figure 1 Study flow diagram

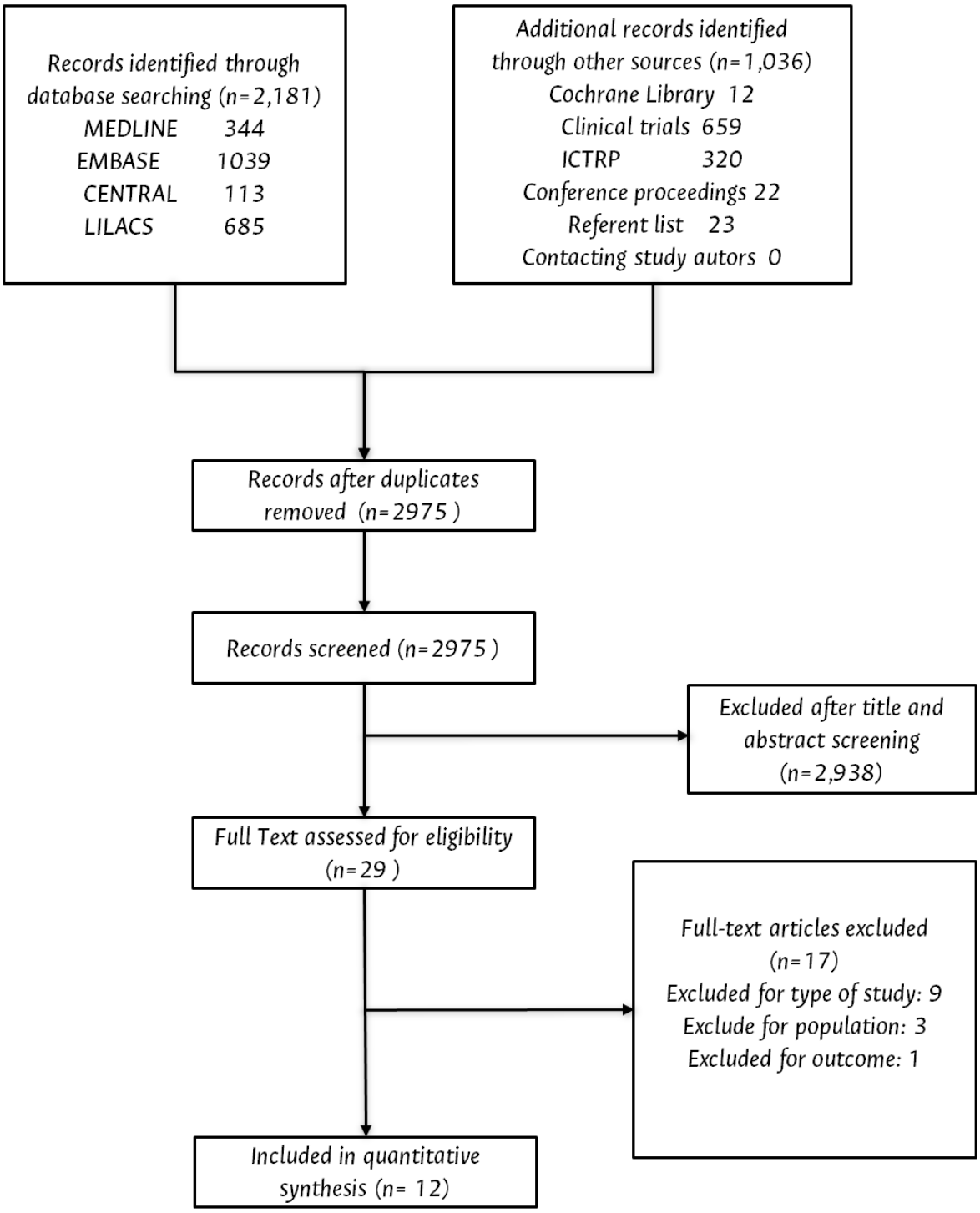


Figure 2 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

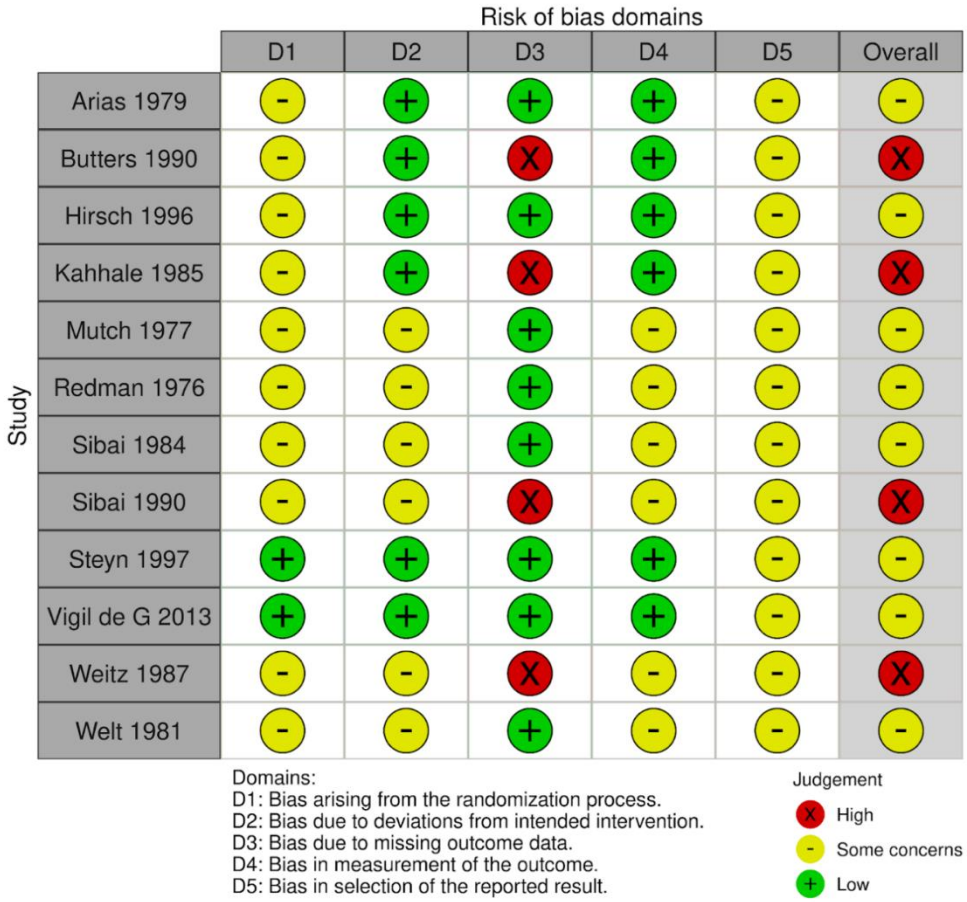


Figure 3 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

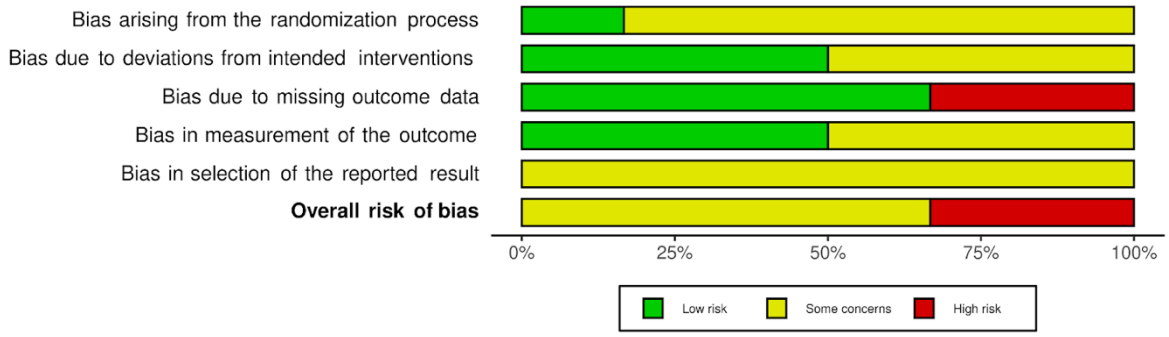
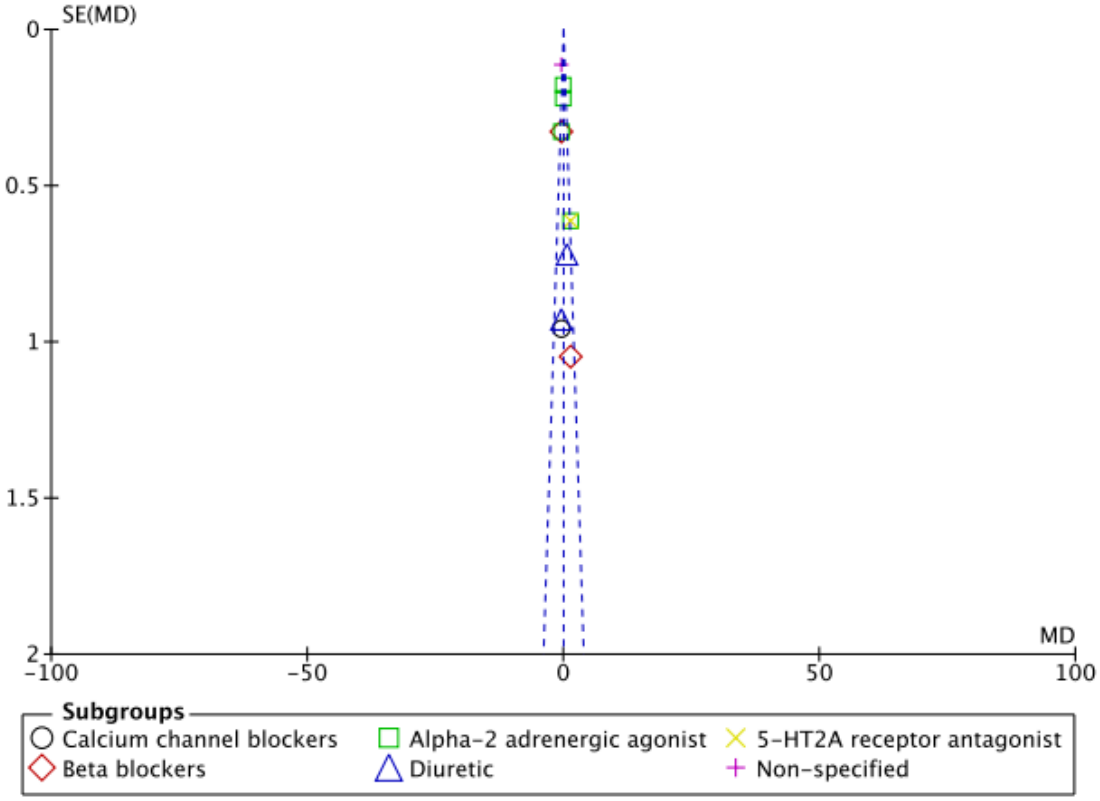
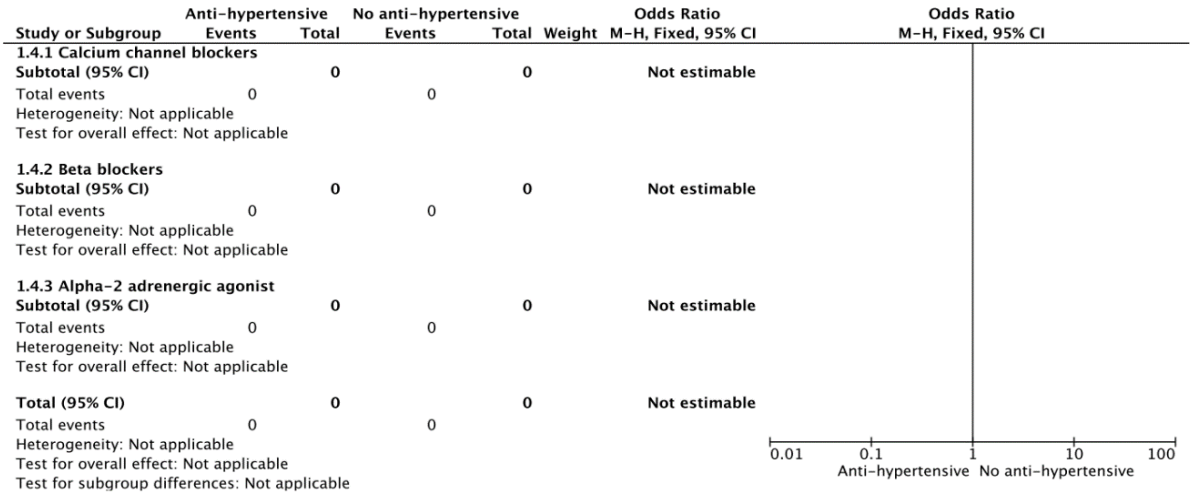


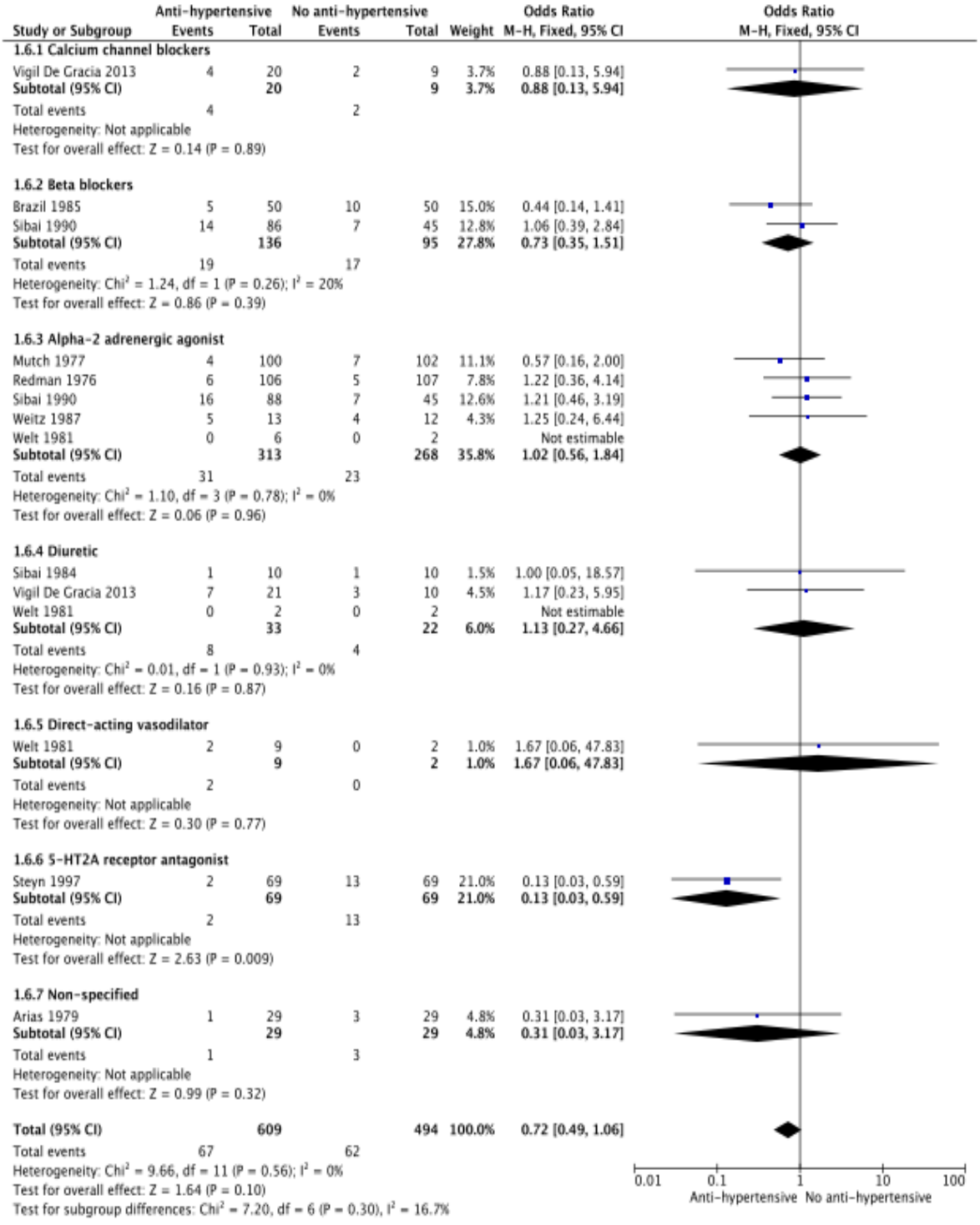
Figure 4 Funnel plot of comparison: 1 Any antihypertensive drug versus no antihypertensive drugs/placebo



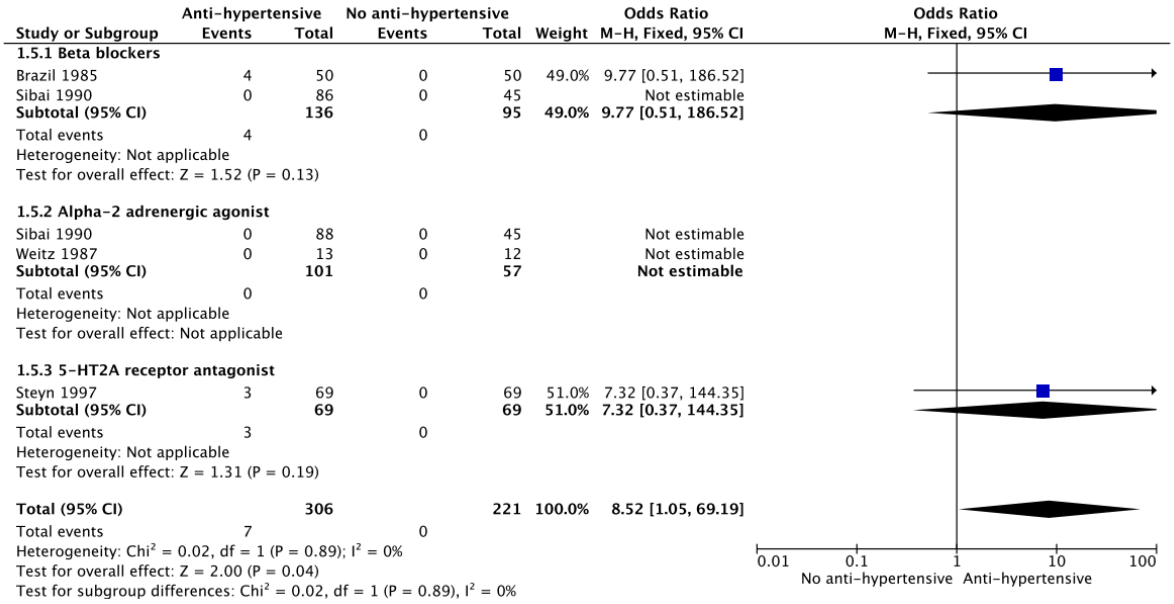
Analysis 1 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome 1 Maternal Death



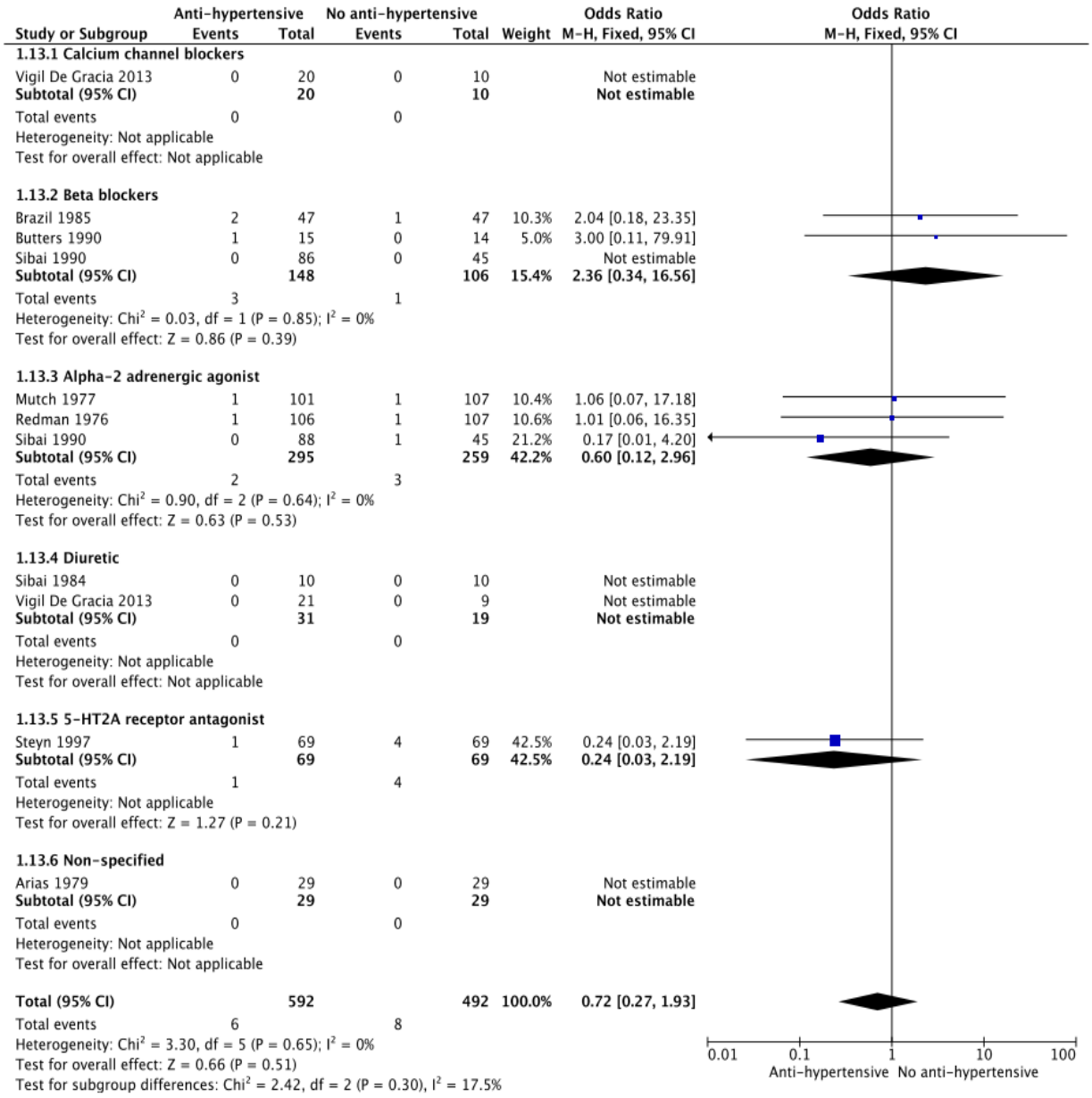
Analysis 2 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome 2 Superimposed preeclampsia



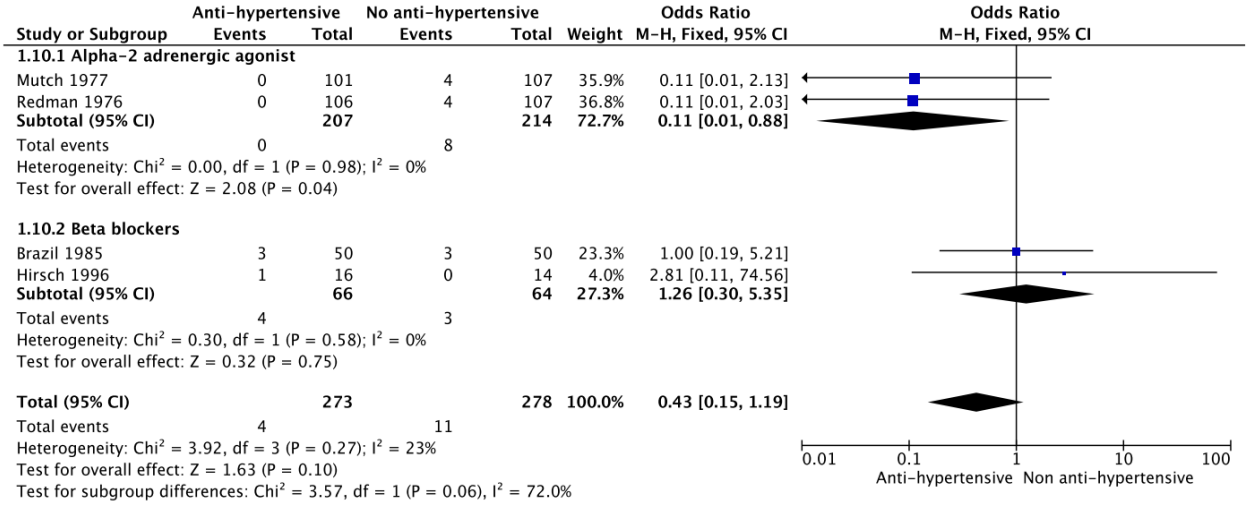
Analysis 3 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome Adverse Effects or drug therapy



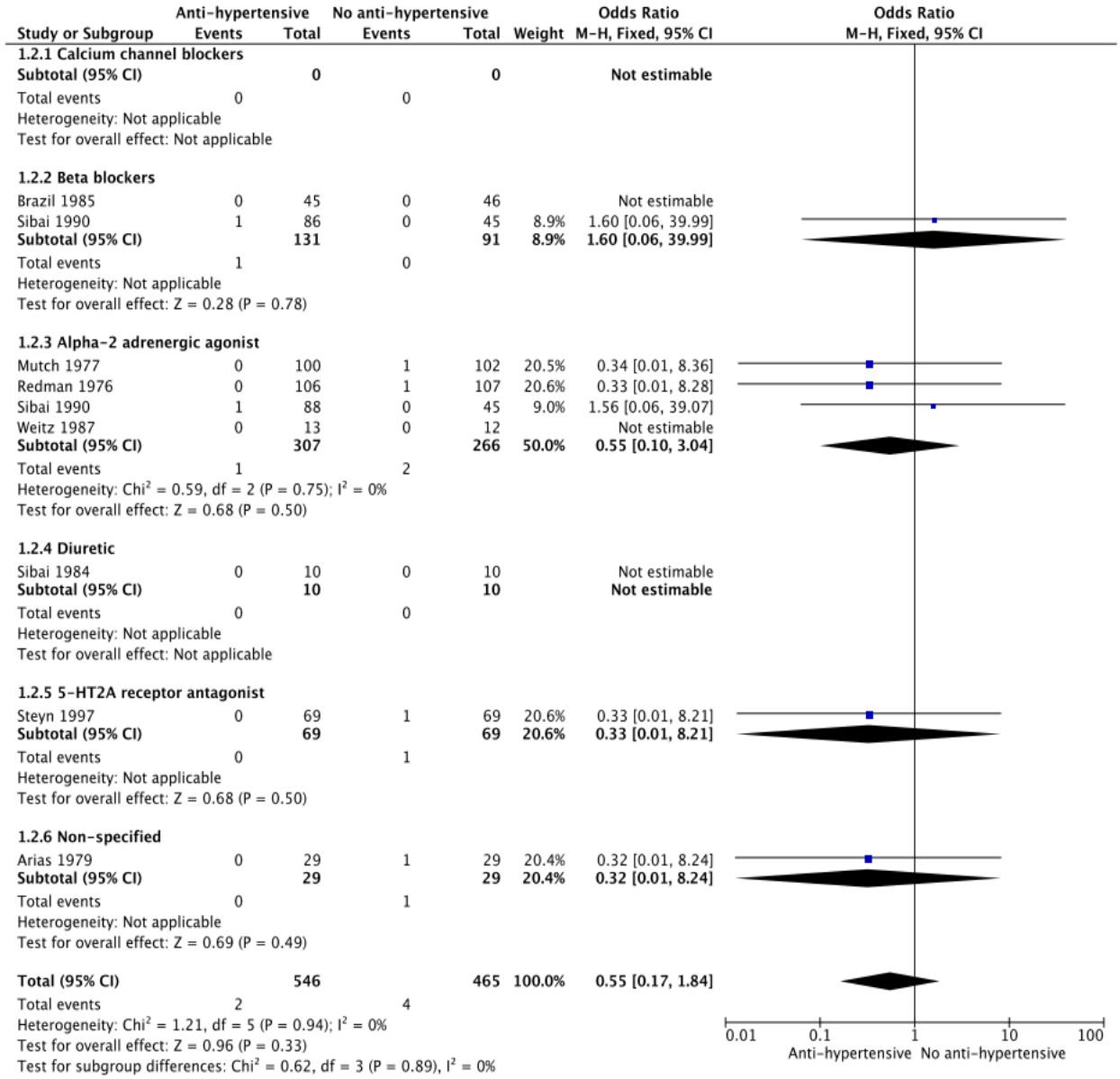
Analysis 4 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome Stillbirth



Analysis 5 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome Miscarriage



Analysis 6 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Neonatal Death



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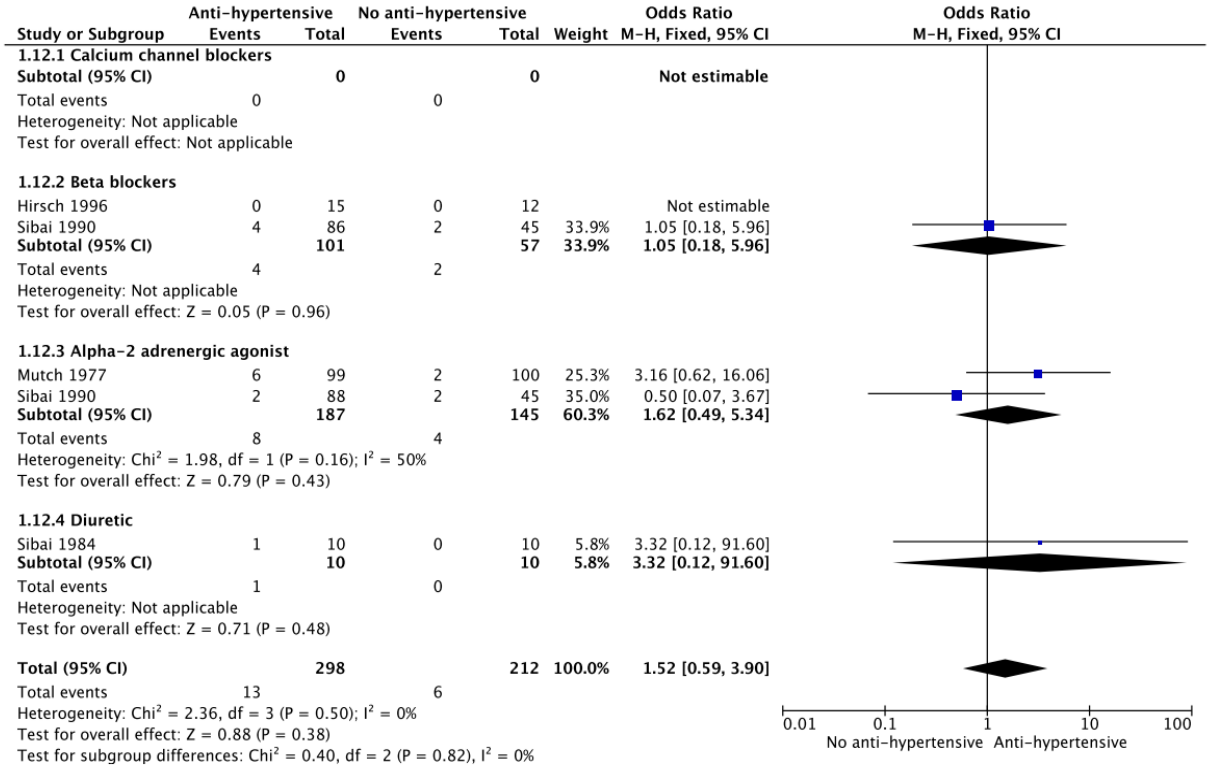
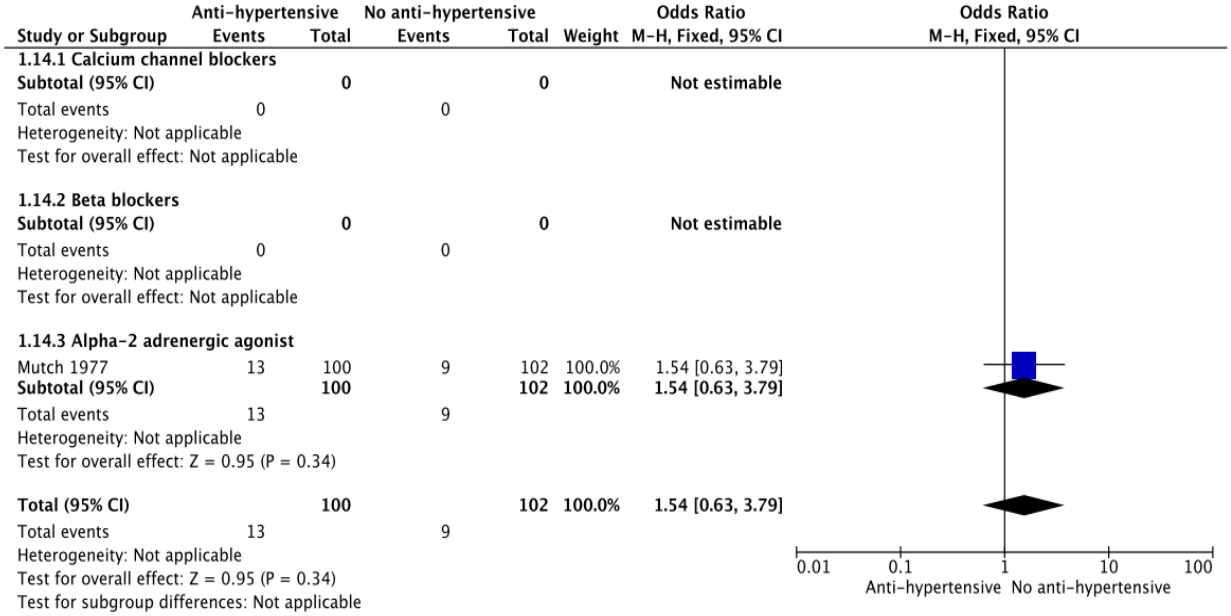
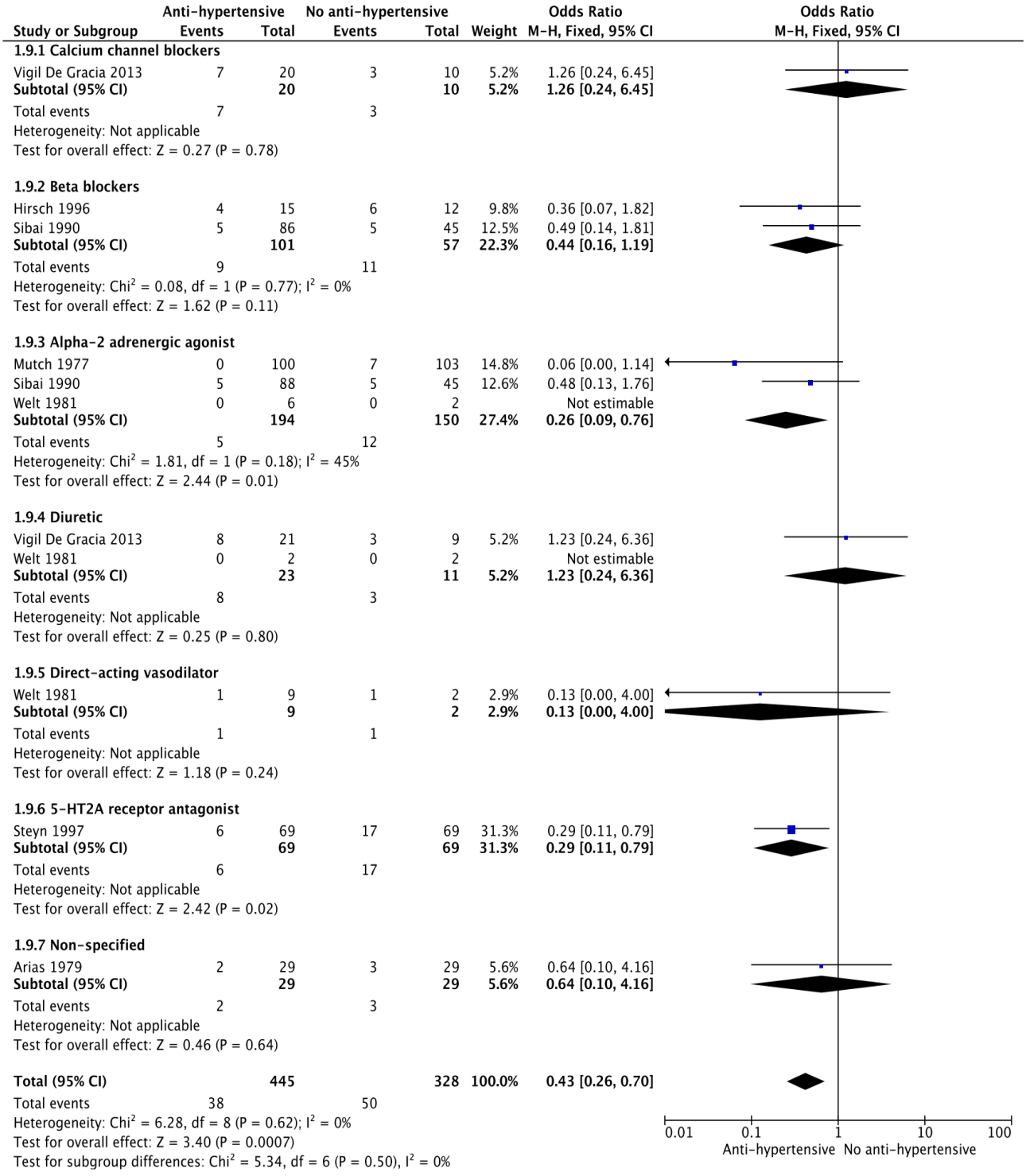
Analysis 7 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Low APGAR score at fifth minute



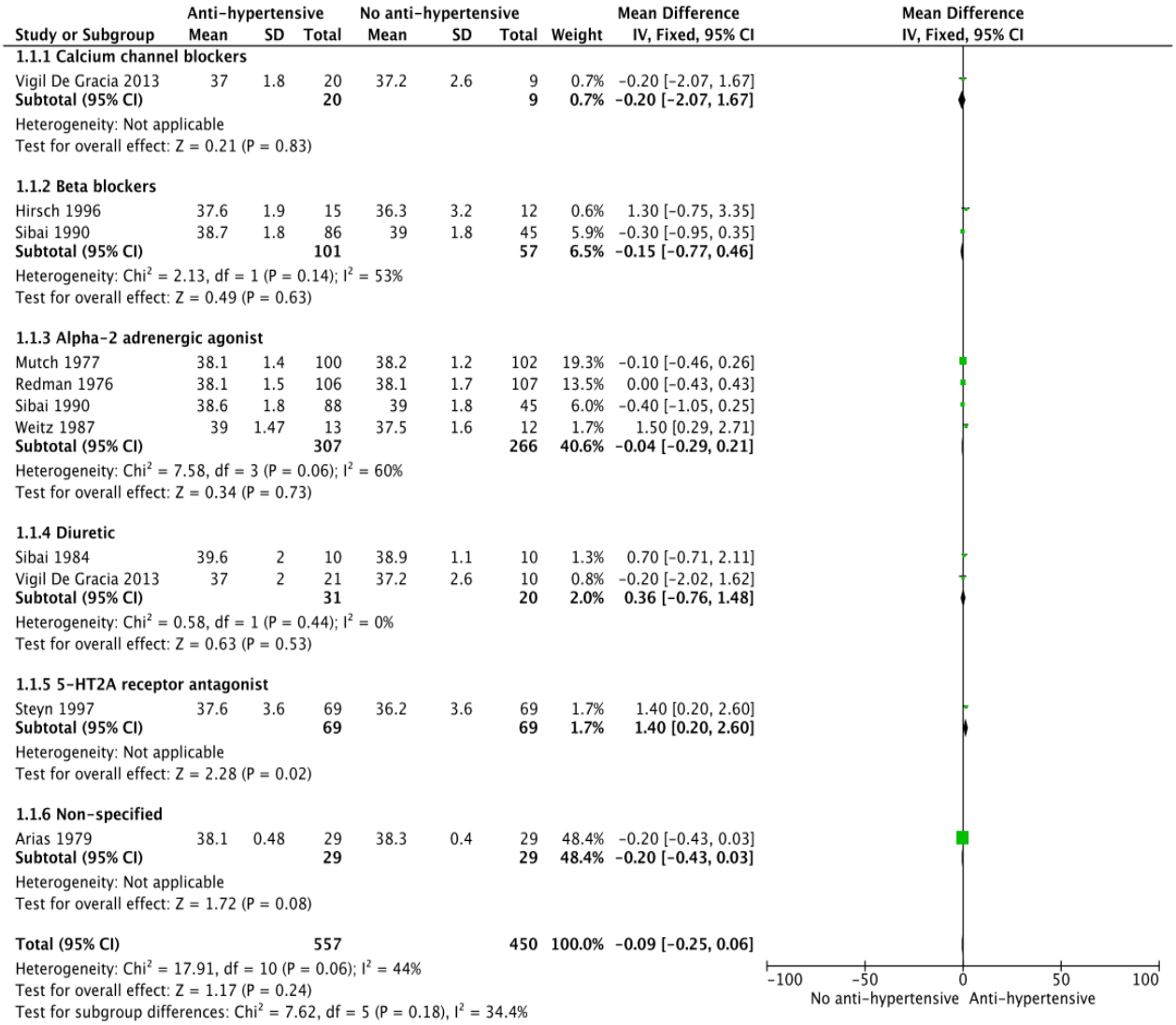
Analysis 8 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Admission neonatal intensive care unit



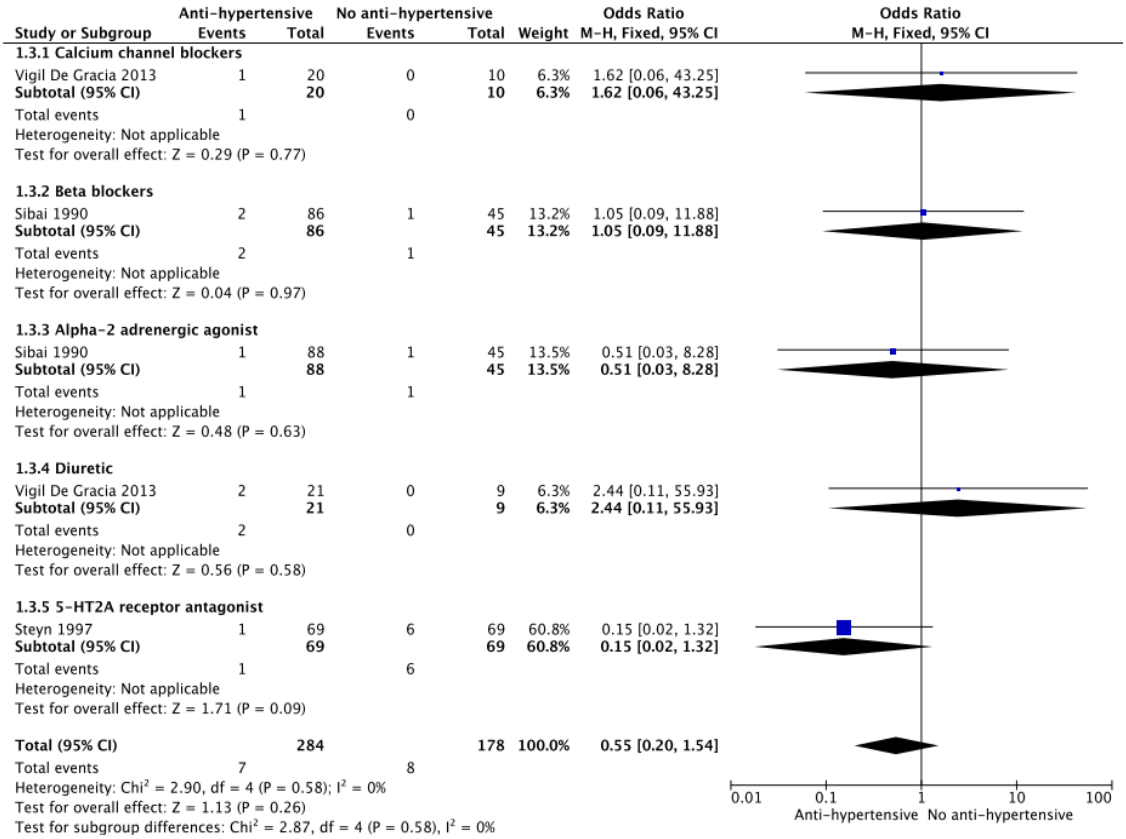
Analysis 9 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Severe hypertension



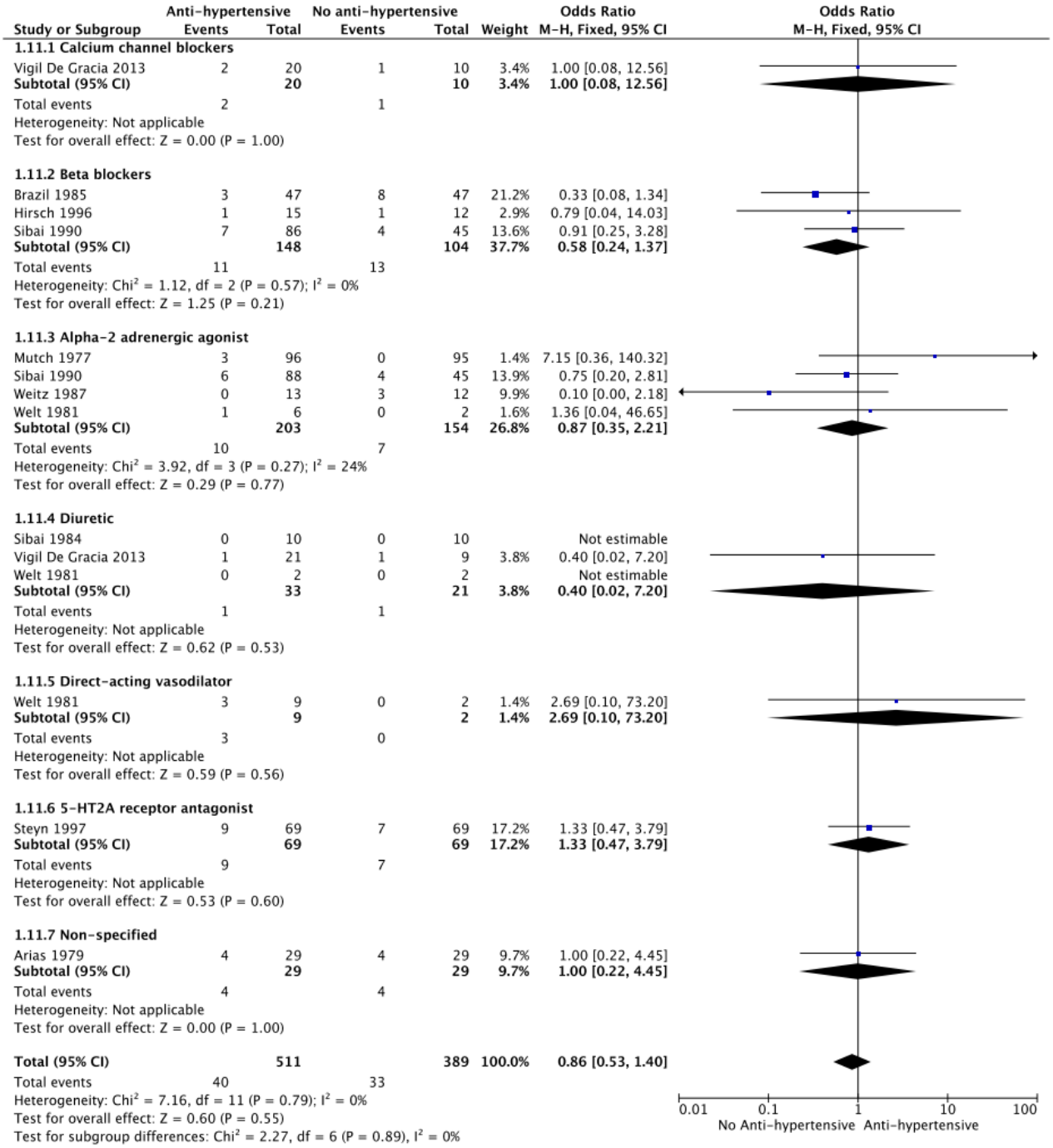
Analysis 10 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Gestational age at delivery



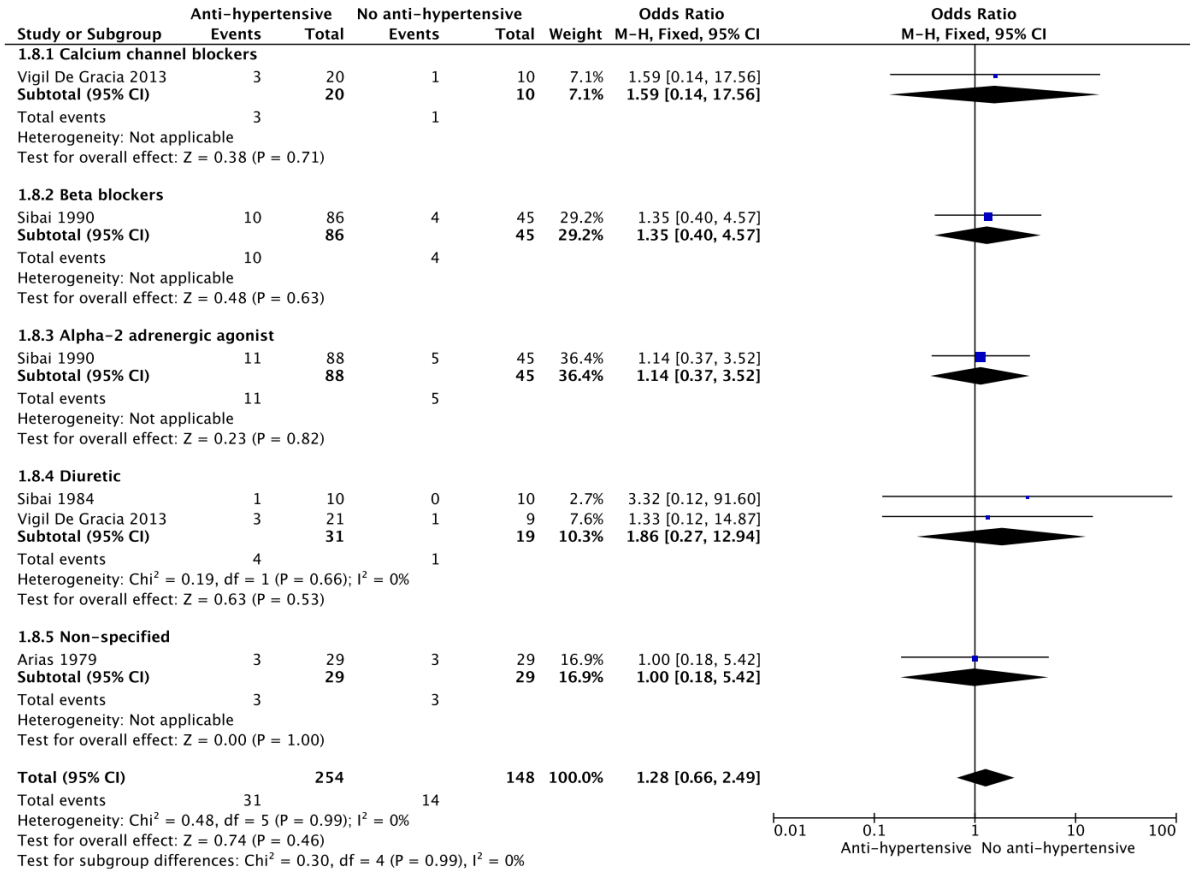
Analysis 11 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Placental Abruption



Analysis 12 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Small for gestational age



Analysis 13 Forest plot of comparison: Any antihypertensive drug versus no antihypertensive drugs/placebo (subgrouped by class of drug), Outcome: Preterm Delivery



Characteristics of studies

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Characteristics of included studies

Arias 1979

Methods	**Setting: USA** **Trial design:** Allocation concealment: not stated. Authors state: "allocated randomly to treatment or no treatment". Two arms **Funding sources:** Not mentioned **Ethical issues:** Not Mentioned **Withdrawals:** not mentioned
Participants	**Included Criteria**: women with HT before pregnancy or BP >/= 140/90 mmHg x 2 more than 24 hrs apart before 20 weeks' gestation. **Excluded Criteria**: DBP > 100 mmHg, nulliparous, other major medical or obstetric problem **Age:** 32, 7 yr **Number:** 58 patients **Baseline characteristics:** Average parity was 4,75 gestations, average gestational age at admission was 15,5 weeks. The moment of diagnosis of hypertension and the mean duration of hypertension was not reported. The mean blood pressure at admission was 98.25 mmHg, average serum creatinine at admission, mean serum uric acid at admission, proteinuria at admission or use of antihypertensive prior to study was not mentioned

Interventions	**Intervention 1:** oral methyldopa 750 mg/day to 2000 mg/day, oral hydrochlorothiazide 50 mg/day, oral hydralazine 75 mg/day to 250 mg/day. (29 women) **Control:** no antihypertensive. (29 women) **Cointerventions:** All patients had clinic visits were scheduled every 2 weeks until 32 weeks of gestation and every week thereafter, fetal growth was followed by serial ultrasonic measurements of the biparietal diameter, plasma free estriol, and human placental lactogen, destinations were performed at each clinic visit after 32 weeks of gestation
Outcomes	Women: severe HT, proteinuria (> 1+ or > 300 mg/L in 24 hrs), caesarean section. Babies: perinatal death, gestation at delivery, birthweight < 2500 g, fetal distress, SGA (undefined)
Notes	No information about how BP was measured. In exp group, 11 women had methyldopa + hydrochlorothiazide, 10 hydralazine + hydrochlorothiazide, 8 had all 3 drugs.

Butters 1990

Methods	**Setting:** Glasgow United Kingdom **Trial design:** single center, randomized, double blind, placebo-controlled study. 2 arms. **Funding sources:** Supported by a grant from ICI Pharmaceuticals. LB and PCR were supported by the Welcome Trust **Ethical issues:** approved by the research and ethical committee of Greater Glasgow Health Board Northern District. **Withdrawals:** 4 (12%), 1 exp (changed her mind), 3 control (2 severe HT, 1 breathlessness). Two arms
Participants	**Included Criteria**: mild essential hypertension (systolic blood pressure 140-170 mm Hg or diastolic pressure 90-110 mm Hg on two occasions at least 24 hours apart). Recruitment took place at between 12- and 24-weeks' gestation **Excluded Criteria**: if 'usual' contraindications to beta blockers **Age:** information not provided **Number:** 33 Women **Baseline characteristics:** Average parity at admission not specific, Average Gestational age at entry was 15,8 weeks. The moment of diagnosis of hypertension (prior vs during pregnancy) was not specified, The mean duration of hypertension was not specified, average blood pressure at entry was 146/88. Average serum creatinine at admission was not specified. Mean serum uric acid at admission was not specified, Proteinuria at admission was not specified. Use of antihypertensive prior to study was not specified
Interventions	**Intervention 1:** oral atenolol 50 mg/day to 200 mg/day (14 women) **Control:** oral placebo (character not stated) (15 women) **Cointerventions:** All patients were seen at intervals of four weeks until they were 28 weeks pregnant, then every two weeks until they were 36 weeks pregnant, and then weekly until delivery. Babies were assessed at

	birth and at 12 months of age. Authors do not mention the use of antihypertensive medications prior to the study
Outcomes	Women: mean BP, Babies: stillbirth, birthweight, SGA (< 5th centile), placental weight, gestation at delivery (mean)
Notes	Korotkoff phase V used for DBP. Additional data provided by authors.

Hirsch 1996

Methods	**Setting:** Israel **Trial design:** Allocation concealment: trial drug supplied by pharmacy in packs with serial numbers, in blocks of 6. Two arms **Funding sources:** no information about funding source. **Ethical issues:** The study was approved by the ethics committee of Beilinson Medical Center. All participating patients provided written consent prior to their inclusion in the study. **Withdrawals:** 4 patients (1 of pindolol group, 3 placebo group)
Participants	**Included Criteria**: women < 35 weeks' gestation with DBP 85-99 mmHg x 2, 12 hrs apart, and no treatment for HT during this pregnancy. **Excluded Criteria**: multiple pregnancy, contraindication to beta blockers or insulin-dependent diabetes. **Age:** 33 yr **Number:** 30 **Baseline characteristics:** The parity of the participants was between 0,7 and 3.5, Average Gestational age at admission was 24,4 weeks. The moment of diagnosis of hypertension or the mean duration of hypertension was not reported. The mean blood pressure at admission was 105 mmHg, Average serum creatinine, mean serum uric acid, or proteinuria at admission was not mentioned. Use of antihypertensive prior to study was not reported
Interventions	**Intervention 1:** oral pindolol 5 mg x 2/day. If DBP still >/= 85 mmHg on day 3, increased to 5 mg x 3/day, if no response next day, increased to 10 mg x 2/day. (16 women) **Control:** oral identical placebo. (14 women) If DBP 100-109 mmHg x 2 or > 110 mmHg x 1, hydralazine added for pindolol group. In placebo group, pindolol given first, followed by hydralazine if DBP > 100 mmHg. **Cointerventions:** Platelet function testing was performed for each patient on admission to the study, 7 to 10 days after initiation of the treatment protocol, and 6 weeks after the delivery date.
Outcomes	Women: mean BP, platelet aggregation Babies: stillbirth, birthweight, SGA (< 5th centile), placental weight, gestation at delivery (mean)
Notes	Korotkoff phase V used for DBP. Additional data provided by authors.

Kahhale 1985

Methods	Allocation concealment: not stated. Authors state: "...patients were randomly divided into two groups...". Two arms

Participants	100 women with chronic HT diagnosed before 20th week, BP >/= 140/90 mmHg x 2, 5 mins apart. With no proteinuria and no contraindication to beta blockers.
Interventions	Exp: oral pindolol 10 mg/day to 30 mg/day. (50 women) Control: no treatment. (50 women)
Outcomes	Women: MAP, severe PE, side-effects. Babies: abortions, fetal deaths, neonatal deaths, gestational age, birthweight, IUGR, Apgar score, congenital malformations, hypoglycaemia.
Notes	Methods for measuring BP not mentioned. Main paper in Portuguese. Funding: no information about funding source. Declaration of interests not described

Mutch 1977

Methods	**Setting:** United Kingdom multicentric **Trial design:** Authors state: "randomly allocated" **Funding sources:** not mentioned **Ethical issues: not mentioned** **Withdrawals:** 8 (5.3%) women
Participants	**Included Criteria**: If systolic or the diastolic pressure equaled or exceeded 140- or 90-mm Hg, respectively on two occasions more than 24 h apart, and before 28 wk gestation **Excluded Criteria**: blood pressures at the time of assessment were systolic or diastolic pressures of 170 or 110 mm Hg or more, or there were other complications already present such as multiple pregnancy, rhesus incompatibility, or severe associated maternal diseases **Age:** 28, 9 yr **Number:** 202 **Baseline characteristics:** Average parity was 43% nulliparous, Only 4% had a history of 4 or more pregnancies. Average Gestational age at admission was not reported, The moment of diagnosis of hypertension (prior vs during pregnancy) was not mentioned, The mean duration of hypertension was not reported, The mean blood pressure at admission was not mentioned. Average serum creatinine, mean serum uric acid, or proteinuria at admission were not reported Use of antihypertensive prior to study was not mentioned
Interventions	**Intervention 1:** Methyldopa—dosing regimen not specified **Control:** No treatment **Cointerventions:** The women were all interviewed, and their babies personally examined within 2 days of delivery. Their progress during the neonatal period was recorded. On the 4th day, or later if the infant was unfit or pre-term, a neurological examination was made using criteria laid down by O'Doherty. The infants were examined 30-60 min before a feed and were in a good 'state of arousal'
Outcomes	Women: Severe hypertension, Superimposed pre-eclampsia, mode of delivery x Babies: perinatal state, clinical signs of fetal distress, apgar score at 5 min, regular respirations not established by 5 min, size at birth
Notes	

Redman 1976

Methods	**Setting:** United Kingdom **Trial design**: Authors state: "randomly allocated" **Funding sources:** Funding by industry Merk, Dorh, Sharp Merk Sharp Dohme?? **Ethical issues:** not mentioned **Withdrawals:** 5 women (2%) withdrawn from exp group. Subgroups: in early or late presentation of hypertension
Participants	**Included Criteria**: BP >/= 140/90 mmHg if < 28 weeks' gestation, or >/= 150/95 mmHg if > 28 weeks' gestation x 2, 24 hrs apart. **Excluded Criteria**: diabetes, multiple pregnancy, Rh immunization. Women > 36 weeks' gestation excluded during first year of the trial, thereafter, excluded if > 32 weeks' gestation **Age:** 28, 2 yr **Number:** 208 participants **Baseline characteristics:** 44,8% of participants was nulliparous, Average Gestational age at admission was 16,2 weeks, The moment of diagnosis of hypertension (prior vs during pregnancy) was not specified. The mean duration of hypertension was not specified,. The mean blood pressure at admission was: 104 mmHg. Average serum creatinine at admission was not specified. Mean serum uric acid at admission was not mentioned. Proteinuria at admission was not specified. Use of antihypertensive prior to study was not specified
Interventions	**Intervention 1**: oral methyldopa 750 mg/day to 4000 mg/day (101 women) **Control:** no antihypertensive (107 women) **Cointerventions:** all patients were tested for Liver function every month until 32 weeks gestation, and then every two weeks until delivery. Measurements were made for bilirubin, alkaline phosphatase, and SGOT. Liver function was assessed every month until 32 weeks gestation, and then every two weeks until delivery. Measurements were made for bilirubin, alkaline phosphatase, and SGOT. Hydralazine if severe HT
Outcomes	Women: severe HT, proteinuria, caesarean section, elective delivery, side-effects, changed drug due to side-effects. Babies: perinatal death, birthweight (mean), gestation at delivery (mean), SGA (< 2 SD below mean), babies nursed in an incubator, neurodevelopment at 4 and 7 years.
Notes	Korotkoff phase IV used for DBP. Random zero sphygmomanometer.

Sibai 1984

Methods	**Setting:** Memphis, Tennessee USA **Trial design:** Randomized **Funding sources:** not mentioned **Ethical issues:** not mentioned **Withdrawals:** not mentioned
Participants	**Included Criteria Long**-term history of hypertension, diastolic BP >90 and <110 mm Hg, receiving diuretics before pregnancy **Excluded Criteria**: not mentioned **Age:** 28 yr **Number:** 20 patients

	Baseline characteristics: Average parity was 2,4, average gestational age at admission was not specified, all patients had diagnosis of hypertension prior to pregnancy, The mean duration of hypertension was 4,15 years, The mean blood pressure at admission was not specified, Average serum creatinine at admission was not specified. Mean serum uric acid at admission was 4,8 mg/mL. Proteinuria at admission was not specified. All patients use diuretics prior to study
Interventions	**Intervention 1:** Diuretics—specific agent(s) and doses not specified **Control:** No treatment (diuretics discontinued) **Cointerventions:** All patients were hospitalized for evaluation of hypertension at the time of their first visit. All patients had nutritional counseling regarding their diet and sodium intake at the time of the first prenatal visit. The mean arterial blood pressure was calculated at each prenatal visit, and these results were averaged at each respective stage of gestation. In addition, serial measurements of each patient were made for maternal weight, hematocrit value, uric acid level, serum creatinine level, endogenous creatinine clearance, and 24-hour urinary excretion of protein. Fetal evaluation included serial ultrasonography and antepartum fetal heart rate monitoring
Outcomes	**Maternal:** Superimposed, pre-eclampsia, mode of delivery, Plasma Volume **Perinatal:** Birth, weight, Preterm birth, Apgar score <7 at 5 min Gestational age (wk), Placental weight (gm), Small-for-gestational age
Notes	

Sibai 1990

Methods	**Setting:** Memphis, Tennessee USA **Trial design:** Allocation concealment: envelope randomization, using computer-generated random numbers. 3-arm study. Duration 4 years, Monocentric **Funding sources:** not mentioned **Ethical issues:** not mentioned **Withdrawals:** 37 patients
Participants	**Included Criteria**: Mild to moderate chronic hypertension ascertained at 6 to 13 weeks' gestation **Excluded Criteria**: Multiple gestation, other comorbidities **Age:** 29,6 ± 0.7 yr **Number:** 300 women **Baseline characteristics:** Average parity was not specified. Average gestational age at admission was 11,3 weeks. The diagnosis of hypertension was prior pregnancy. The mean duration of hypertension was 4,4 years. The mean blood pressure at admission was: 104,7 mmHg. Average serum creatinine at admission: 0,74 mg/mL. Mean serum uric acid at admission was 3,8 mg/mL. Proteinuria at admission was not mentioned, 91% of participants reported use of oral antihypertensive drugs before pregnancy
Interventions	**Intervention 1**: methyldopa 750 mg/day to 4000 mg/day (no other details) (100 women).

	Intervention 2: labetalol 300 mg/ day to 2400 mg/day (no other details) (100 women). If maximum doses of either medication were not adequate to control blood pressure, hydralazine was added to a maximum oral dose of 300 mg/day. **Control:** no antihypertensive (100 women). **Cointerventions:** All patients underwent measurements of systolic and diastolic pressures were then pooled to determine the mean blood pressure for each patient at 6 to 13 weeks' (initial entry), 14 to 26 weeks', 27 to 29 weeks', 30 to 32 weeks', 33 to 36 weeks', and 37 to 41 weeks' gestation. Maternal laboratory studies included serial measurements of hematocrit, serum creatinine, uric acid, endogenous creatinine clearance, and 24-hour urinary excretion of protein. Antepartum fetal surveillance included serial ultrasonograms
Outcomes	Women: PE (defined as HT, proteinuria, and hyperuricaemia), additional antihypertensive, days in hospital, placental abruption, congestive heart failure, serum creatinine, uric acid. Babies: perinatal death, gestation at delivery, birthweight < 2.5 kg, preterm delivery (< 37 weeks), SGA (undefined), admission to special-care neonatal unit, hypoglycemia, 5-min Apgar < 7.
Notes	Korotkoff phase IV used for DBP. 36% of women were taking an antihypertensive at the time of trial entry.

Steyn 1997

Methods	**Setting:** South africa **Trial design:** double-blind, randomized, placebo-controlled trial **Funding sources:** Janssens Pharmaceutical, Belgium. **Ethical issues:** each woman had given written consent
Participants	**Included Criteria**: diastolic blood more than 80 mm Hg, live singleton fetus of less than 20 weeks' gestational age **Excluded Criteria**: obvious major defects on ultrasonography, electrocardiogram showed any signs of pathological bradycardia of less than 50 beats per min, such as grade 1 or 2 atrioventricular block or sick sinus syndrome, ventricular tachycardia, or increased QT time. Patients who required antihypertensive therapy when examined were excluded **Age:** Average 32 yr **Number:** 138 **Baseline characteristics:** Average parity was 3 gestations. Average gestational age at admission was 15.5 w. The moment of diagnosis of hypertension (prior vs during pregnancy) or the mean duration of hypertension was not mentioned, The mean blood pressure, Average serum creatinine, Mean serum uric acid or proteinuria at admission was not reported Use of antihypertensive prior to study was not mentioned
Interventions	**Intervention 1:** ketanserin 40 mg to 80 mg a day **Control:** Placebo **Cointerventions:** Women were first seen for follow-up 1 week after starting treatment, after which they were seen every 2 weeks until 36 weeks' gestation, and thereafter every week. Diastolic blood pressure was taken three times at each visit with the Dinamap Vital Signs monitor with 5 min

	intervals. If each of these readings were more than 90 mm Hg, three more measurements were done after at least 30 min rest. If all six values were more than 90 mm Hg, we increased the medication to two tablets twice daily (80 mg ketanserin daily in the study group)
Outcomes	severe HT, proteinuria, placental abruption, other drugs needed, perinatal deaths, SGA (< 10th centile), birthweight

Vigil de Gracia 2014

Methods	**Setting:** Panamá **Trial design:** A randomized open-label pilot clinical trial Allocation concealment quote: "concealed through the use of sealed envelopes." **Funding sources:** Not mentioned **Ethical issues:** approval by the hospital's Research Committee and teaching staff. Each patient included in the study signed an informed consent form **Withdrawals:** 3 patients
Participants	**Included Criteria**: pregnant women with singleton or twin pregnancy and mild/moderate chronic HT at 20 weeks of gestation. **Excluded Criteria**: chronic HT with BP 160 mmHg systolic or 110 mmHg diastolic; renal failure or pre-existing renal disease; diabetes mellitus; autoimmune disease; major fetal abnormalities; oligohydramnios; fetal death. Three arms **Age:** 34,1 yr. **Number:** 63 patients **Baseline characteristics**: 16% of patients was nulliparous. Average gestational age at admission was 17,3 weeks; 17% of patients had diagnosis of hypertension prior pregnancy. The mean duration of hypertension was not reported. The mean blood pressure at admission was 101,6 mmHg at entry. Average serum creatinine, mean serum uric acid, or proteinuria at admission were not mentioned: Use of antihypertensive prior to study: 17% of participants
Interventions	**Intervention 1:** 20 mg of oral furosemide a day (21 women) **Intervention 2:** 5 mg of oral amlodipine a day (21 women) **Control**: 75 mg of orally administered acetylsalicylic acid a day (21 women) If the blood pressure was >160 mmHg systolic or >110 mmHg diastolic the patients were admitted to the hospital and bolus doses of hydralazine or labetalol were administered to control severe hypertension **Cointerventions:** Maternal evaluation was made every 2–3 weeks, with measurements of blood pressure, fetal heart rate, uterine height. Laboratory evaluation included serial measurement of liver function tests, complete blood cell count, coagulation profile and renal function tests of subjects admitted to the study and each 4–6 weeks if necessary. Fetal status was assessed with ultrasound at admission; serial ultrasound was performed to evaluate fetal growth and amniotic fluid status each 3–4 weeks
Outcomes	Women: gestational age at delivery, indication for delivery, hospitalization during pregnancy and mode of delivery, placental abruption, severe HT,

	aggregate PE, pulmonary oedema, HELLP syndrome, renal insufficiency, eclampsia, disseminated intravascular coagulation. Babies: fetal or neonatal death, birthweight, Apgar scores, intraventricular hemorrhage grade III and IV, necrotizing enterocolitis, neonatal sepsis.
Notes	Methods for measuring BP not stated

Weitz 1987

Methods	**Setting:** Baltimore Medical Center, Florida USA **Trial design:** double-blind, controlled study, Allocation concealment: not stated. Authors state: "randomly allocated", no further information **Funding sources:** funded by industry, Merk Sharp Dohme **Ethical issues:** not mentioned **Withdrawals:** not mentioned
Participants	**Included Criteria**: Pregnant women at < 34 weeks' gestation, singleton pregnancy with BP 140/90 mmHg x 2 at least 6 hours apart and no proteinuria. Presumed chronic HT. **Excluded Criteria**: not mentioned **Age:** Average age 24,05 years (23,7 - 25,4) **Number:** 25 women **Baseline characteristics:** Population 65% black, overweight at entry, 57% of participants are nulliparous. Average gestational age at admission was between 7 – 14 weeks The moment of diagnosis of hypertension (prior vs during pregnancy): was not specified. The mean duration of hypertension was not specified, The mean blood pressure at admission was between 97.6 – 106.8 mmHg. Average serum creatinine at admission: 0.7 mg/mL Mean serum uric acid at admission was: 4.3 mg/mL, Proteinuria at admission was <100 mg/24h. The use of antihypertensive prior to study was not specified
Interventions	**Intervention 1:** oral methyldopa 750 mg x 3/day to 2000 mg x 4/day. (13 women) **Control:** oral placebo, in the same way. (12 women) **Cointerventions:** All patients were tested prior to treatment with: 24-h urine collections for protein, creatinine clearance and VMA; liver function tests (SGOT, SGPT, total and direct bilirubin, alkaline phosphatase), uric acid, hematocrit, platelet count, direct Coomb's test, EKG, and sonogram. A chest X-ray (with abdominal shielding) was performed after 20 weeks gestation. monthly until 32 weeks and then every 2 weeks until delivery: Liver enzymes, hematocrit, platelet count, creatinine clearance and direct Coomb's test Serial sonograms were obtained between 20 and 30 weeks in most patients. Biweekly 24-h urinary estriols (E3/Cr), Weekly non-stress tests (NST) were obtained after 32 weeks. If severe PE, hydralazine or MgSO4 added**.**
Outcomes	Women: MAP, new proteinuria (2+ or greater on urine dipsticks), PE (defined as a sudden rise of 30 mmHg SBP or 15 mmHg DBP and weight gain > 2 lbs./week, or proteinuria > 2+), elective delivery, side effects. Babies: perinatal death, gestation at delivery (mean), birthweight (mean and < 50th centile).
Notes	No information about how BP measured

Welt 1981

Methods	**Setting: USA** **Trial design:** 'randomly and blindly assigned' **Funding sources:** no information about funding source **Ethical issues:** no information
Participants	**Included Criteria**: BP 140/90 mmHg or above in a seated position or at rest, x 2, 6 or more hours apart. **Excluded Criteria**: insulin requiring diabetes; multiple pregnancy, or planning to terminate the pregnancy **Age:** not reported **Number:** 63 **Baseline characteristics:** 84% of women was multiparous**.** Average gestational age at admission was not mentioned. The moment of diagnosis of hypertension or mean duration of hypertension were not reported. The mean blood pressure at admission was 96,4 mmHg. Average serum creatinine at admission, mean serum uric acid at admission, proteinuria at admission, use of antihypertensive prior to study were not reported
Interventions	**Intervention 1: I**ntervention: hydralazine 25 mg x 3/day vs methyldopa 250 mg x 3/day **Control:** placebo x 3/day
Outcomes	MAP, caesarean section, induction of labor, birthweight
Notes	.

Characteristics of excluded studies

Bayliss, 2002	**Excluded for: observational** **Methods: A retrospective cohort study of prospectively collected data in a hypertensive pregnancy database.** **Participants: 491 pregnancies in 380 women with essential or secondary hypertension** **Intervention: -Atenolol < 15 weeks, Calcium antagonists < 15 weeks, Multiple drugs < 15 weeks, Atenolol 15–30 weeks, Labetalol 15–30 weeks, Methyldopa 15–30 weeks. Multiple drugs 15–30 weeks. No medication during pregnancy 189 No Drug Treatment** **Outcomes: The outcome measures used were the infant birth weight, birth weight standardized for gestational age, and the ponderal index at birth Gestational age at delivery (weeks) Systolic BP (mm Hg) Diastolic BP (mm Hg**
Blake 1991	**Excluded for:** Only gestational hypertension **Methods:** randomly allocated two arms **Participants:** Thirty-six women with hypertension, but without proteinuria, were allotted at random to a test group of 17 who received intensive treatment, and a control group of 19 who were managed according to routine methods by hospital staff unconnected with the study. **Intervention:** 50mg to 100 mg daily of atenolol or 250mg to 750mg three times daily of methyldopa, **Outcomes:** severe HT, proteinuria. Babies: perinatal death, birthweight, APGAR score gestational age, perinatal deaths

Chen, 2018	**Excluded for:** Retrospective cohort **Methods:** identified a population-based cohort of women with chronic hypertension who received antihypertensive medications within 120 days before pregnancy and gave birth to a singleton between 2005 and 2014 within three Kaiser Permanente regions. **Participants**: 5,782 pregnant women were included**.** **Intervention:** Treatment vs no treatment **Outcomes:** Prior to pregnancy, the most commonly used medication classes were thiazide diuretics (2,370/5,782, 41%), beta-blockers (1,569/5,782, 27%) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) (1,391/5,782, 24%). In contrast, the predominant medications during pregnancy were labetalol (2,165/5,782, 37%) and methyldopa (1,593/5,782, 28%). During pregnancy, 18% of the cohort (1,037/5,782) had no antihypertensive medication fills. Women taking ACEI/ARBs or thiazides before pregnancy were the most likely to have no medication fills in pregnancy (23% and 20%, respectively). Many women (n=881) had at least one severe high BP (SBP ≥160 or DBP ≥110) before pregnancy, and in this group, 15% (132/881) filled no medications throughout pregnancy
Cruickshank 1991	**Excluded for:** population, pregnant woman with >24 weeks of gestation **Methods:** Randomized Controlled **Participants:** One hundred and fourteen pregnant women with singleton pregnancies and a diastolic blood pressure greater than 90 mmHg in the absence of proteinuria **Intervention:** labetalol was 100 mg twice per day. Twenty of the 51 labetalol treated women were maintained at dose level 3 (300mg x 2 per day). **Outcomes:** preterm delivery, mode of onset of labor or mean birthweight
Flowers 1962	**Excluded for: population included pregnant patients without hypertension** **Methods:** treatment given “at random” to four groups. No further information. Allocation concealment: sealed envelopes with a code known only to the hospital pharmacist.: double blind. **Intervention:** Five hundred and nineteen patients received various doses of chlorothiazide, Exp 1: 134 participants received chlorothiazide 250 mg daily. Exp 2: 141 participants received chlorothiazide 500 mg daily. Exp 3: 110 participants received chlorothiazide 750 mg daily. Control: 134 participants received placebo. **Outcomes:** toxemia (defined as sBP >/= 140 or dBP >/= 90 x 2 in previously normotensive women or appreciable change in BP in women with chronic hypertension); changes in maternal weight (mean) and blood pressure (mean); side effects; intervention stopped due to side effects; biochemical outcomes. Baby: perinatal mortality (fetal deaths and neonatal deaths up to 28 days of life in infants weighing > 1 kg); premature birth (not defined); neonatal jaundice
Freire, 1988	**Excluded for:** No control group all patients exposed to treatment **Methods**: Allocation concealment: consecutive numbered treatment boxes. Two arms

	Participants: 40 pregnant women with chronic HT with DBP =/> 95 mmHg, without proteinuria. **Intervention:** Exp: oral pindolol 10 mg/day to 30 mg/day. (20 women) Control: oral methyldopa 500 mg/day to 2000 mg/day. (20 women **Outcomes:** Women: BP, need for additional antihypertensives, severe HT, superimposed PE. Babies: birthweight, apgar score, fetal and neonatal death, preterm birth, SGA
Lip 1977	**Excluded for: observational study** **Methods:** an analysis of prospectively gathered and computerized database of all women attending our clinic between 1980 and 1995. **Participants:** 398 consecutive pregnancies (137 white, 103 black, 158 Asian women; mean age 30 6 years) attending our antenatal hypertension clinic **Intervention:** Atenolol was taken by 76 women, labetalol by 7, other p blockers by 12, calcium antagonists by 22, diuretics by 26, methyldopa by 17, and angiotensin-converting enzyme inhibitors by 7 women; 18 women were taking multiple drug combinations. **Outcomes:** Gestation (wk.), systolic BP, diastolic BP, birth weight, placental weight, ponderal index
Lunell 1991	**Excluded for:** population, pregnant woman in third trimester of gestation **Methods:** Prospective, randomized **Participants:** 41 pregnant women with a diastolic blood pressure greater than or equal to 95 mm Hg were included in the study **Intervention:** 27 patients received isradipine2.5 to 5 mg twice daily **Outcomes:** mean arterial pressure, Uteroplacental blood flow
Lydakis, 1999	**Excluded for:** retrospective cohort **Methods:** A retrospective cohort study from a computerized database **Participants:** initial cohort of 436 pregnancies in 318 women attending the Antenatal Hypertension Clinic at City Hospital between 1980 and June 1997 was performed Pregnant women were referred to this clinic either due to previous chronic hypertension, increased blood pressure (BP), or preeclampsia during a previous pregnancy, or because of high BP readings in the first weeks of pregnancy measured by the general practitioner or the obstetrician. **Intervention:** prescribe atenolol for mild chronic hypertension but after publication of the paper by Butters et al,13 we reverted to the use of labetalol or methyldopa. **Outcomes:** Duration of treatment, weeks of gestation, baby weight, baby length, ponderal index, emergency cesarean, delivery <37 Weeks , SGA , preeclampsia, stillbirth
Mabie, 1986	**Excluded for:** observational trial **Methods:** The course and outcome pregnancies in women with chronic hypertension were **Participants:** 169 pregnancies in 156 women with chronic hypertension **Intervention:** Methyldopa 64 patients 750 to 2000 mg, Methyldopa + hydrochlorothiazide 18 patients 750 to 2000 mg + 50 mg HTZ día, hydrochlorothiazide 10 patients If patient Use diuretic continued at the same doses, Methyldopa + Hydrochlorothiazide+ propranolol 2000 mg methyldopa+ 40-240 mg propranolol 5 patients and no treatment

	Outcomes: Gestational age, superimposed preeclampsia, stillbirth neonatal dead , Apgar, IUGR
Mito 2019	**Excluded for:** observational study **Methods:** This study compared the pregnancy outcomes of 48 women with amlodipine exposure during the first trimester with those of hypertensive women who received non amlodipine antihypertensives, as well as those who did not receive any antihypertensive drugs **Participants:** 231 women with chronic hypertension, including those who received amlodipine or other antihypertensives during early pregnancy, **Intervention**: women and neonates exposed to amlodipine in the first trimester into the amlodipine group, those exposed to antihypertensives other than amlodipine (including other calcium channel blockers) into the other antihypertensive group, and those not exposed to antihypertensives into the no-antihypertensive group **Outcomes:** Superimposed preeclampsia, Gestational diabetes mellitus, Gestational age, weeks—mean, Delivery weight, g—mean, Preterm birth (<37 weeks) Low birth weight, Apgar score, Birth defects
Niegowska 2004	**Excluded for:** Observational study **Methods**: Prospective Observational study to evaluate the relationship between the blood pressure (BP) and plasma renin activity (PRA) as well as serum and urine aldosterone (ALDO) levels in pregnant women with essential hypertension. Participants: 84 pregnant women with essential hypertension. (97% primigravida) with EH aged 22-40 (mean 29.5 +/- 5.4) years and 60 healthy pregnant women aged 22-40 (mean 28.5 +/- 4.9) years. **Participants:** **Intervention:** PRA and ALDO as well as sodium and potassium excretion were measured three times in different periods of pregnancy: 8-12 weeks, 24-28 weeks, 34-38 weeks. In addition, both PRA and ALDO were analyzed in 4th month after delivery i.e., in the time, in which woman is reached hormonal and hemodynamic stability **Outcomes:** PRA and ALDO concentrations in both: serum and urine
Nzelu 2018	**Excluded for:** observational prospective **Methods:** observational prospective study **Participants:** 586 women with pre-pregnancy chronic hypertension, in the absence of renal or liver disease, booked at a dedicated clinic for the management of hypertension in pregnancy. Intervention: N/A **Outcomes:** severe hypertension (systolic blood pressure >160 mmHg and / or diastolic blood pressure >110 mmHg), preterm and term preeclampsia (in addition to hypertension at least one of renal involvement, liver impairment, neurological complications or thrombocytopenia), and birth of small for gestational age neonates (birth weight <5th percentile for gestational age).
Parazzini 1988	Excluded for: exclusion of women with previous antihypertensive treatment Methods: central telephone randomization, stratified by center and type of HT (chronic, gestational, or unclassified). Multicenter, 33 hospitals. Two

	arms Participants: 283 women Intervention: oral slow-release nifedipine 20 mg to 80 mg x 2/day orally oral slow-release nifedipine 20 mg to 80 mg x 2/day orally vs no treatment Outcomes: Women: severe HT, proteinuria, caesarean section, admission to intensive care. Babies: perinatal death, birthweight, SGA (< 10th centile), preterm delivery (< 34 and < 37 weeks), admission to SCBU, hyperglycaemia, jaundice, RDS, other serious neonatal problems.
Resk/Salama 2019	**Classification pending // ??** **Methods:** randomization was performed using computer-generated simple random tables **Participants:** 486 Pregnant women diagnosed with mild to moderate chronic hypertension without medication and without end-organ affection Intervention: methyl dopa tablets 1–2 gm per day in divided **Outcomes:** Maternal outcome: Severe hypertension, preeclampsia (PE), renal impairment, hepatic impairment, ECG changes, placental abruption hospital admissions, venous thromboembolism, cesarean delivery, maternal mortality Fetal and neonatal outcome: Small for gestational age, intrauterine fetal demise, prematurity, neonatal hypotension, neonatal hypoglycemia, neonatal hyperbilirubinemia, admission to NICU, neonatal mortality
Vasconcellos 2000	**Excluded for:** only fetal hemodynamic outcome **Methods:** randomized, double-blind, placebo-controlled clinical trial **Participants:** 123 pregnant women with mild to chronic hypertension moderate. **Intervention**: study group (n = 61), submitted to 240 mg/day of verapamil, and control group (n = 62), submitted to placebo**.** **Outcomes:** values for the uterine and umbilical artery

Table 1 Quality of Evidence Maternal Outcomes

Summary of findings:

Antihypertensive compared to no antihypertensive for management of chronic hypertension in pregnancy

Patient or population: management of chronic hypertension in pregnancy
Setting: outpatient
Intervention: antihypertensive
Comparison: no antihypertensive

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no antihypertensive	**Risk with antihypertensive**				
Maternal death - not reported	-	-	-	-	-	
Superimposed preeclampsia (Superimposed preeclampsia) assessed with: Sudden rise in systolic BP >30 mm Hg or diastolic BP >20 mm Hg , edema, sudden weight gain >2 lb per week or , proteinuria 2+ or more on dipstick, or >300 mg/L in 24 h, or both follow-up: range 6 weeks to 40 weeks	126 per 1,000	**95 per 1,000** (67 to 133)	**OR 0.73** (0.50 to 1.07)	1103 (10 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	
Admission to intensive care unit - not reported	-	-	-	-	-	

Summary of findings:

Antihypertensive compared to no antihypertensive for management of chronic hypertension in pregnancy

Patient or population: management of chronic hypertension in pregnancy
Setting: outpatient
Intervention: antihypertensive
Comparison: no antihypertensive

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no antihypertensive	**Risk with antihypertensive**				
Adverse reactions (Adverse reactions) assessed with: adverse events caused by the withdrawal or use of antihypertensive medications, including palpitations, headache, joint pain, lower limb edema, orthostatic hypotension or rebound hypertension, in addition to changes in serum biochemistry , heart rate, pulse rate, kidney function, and left ventricular parameters follow-up: range 6 weeks to 40 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 8.52** (1.05 to 69.19)	527 (4 RCTs)	⨁◯◯◯ Very low[a,d,e,f]	
Severe arterial hypertension (Severe arterial hypertension) assessed with: Systolic BP > 160 to 170 mm Hg or diastolic BP > 100 to 110 mm Hg on 2 occasions >4 h apart follow-up: range 6 weeks to 40 weeks	152 per 1,000	**72 per 1,000** (46 to 113)	**OR 0.43** (0.27 to 0.71)	773 (7 RCTs)	⨁◯◯◯ Very low[a,d,g,h]	

Summary of findings:

Antihypertensive compared to no antihypertensive for management of chronic hypertension in pregnancy

Patient or population: management of chronic hypertension in pregnancy
Setting: outpatient
Intervention: antihypertensive
Comparison: no antihypertensive

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no antihypertensive	**Risk with antihypertensive**				
Gestational age at delivery (Gestational age at delivery) assessed with: Weeks from conception to the date of delivery follow-up: range 6 weeks to 40 weeks	The mean gestational age at delivery was **0**	MD **0.07 lower** (0.24 lower to 0.09 higher)	-	843 (9 RCTs)	⨁◯◯◯ Very low[a,d,i,j,k]	
Placental abruption (Placental abruption) assessed with: remature detachment of the placenta characterized by vaginal bleeding, uterine hypertonicity or unsatisfactory fetal status associated with direct visualization of retroplacental hemorrhage or hematoma follow-up: range 6 weeks to 40 weeks	45 per 1,000	**25 per 1,000** (9 to 68)	**OR 0.55** (0.20 to 1.54)	462 (3 RCTs)	⨁◯◯◯ Very low[d,l,m,n]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level for serious limitations from randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.
b. Included studies recruited pregnant women between 24 and 35 years, with pregnancy between 7 and 26 weeks, with systolic blood pressure that ranged from 140 to 170 mmHg and diastolic from 90 to 110 mmHg, before pregnancy up to week 34. Only one of the included studies reports proteinuria on admission and excludes women with this condition prior to admission. Duration of chronic hypertension before pregnancy varied between 3.8 and 4,4 years. One study included only women with history of chronic hypertension who received management with diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, proteinuria, contraindications for the use of b blockers . Four studies included multiple pregnancy.
c. Seven studies evaluated methyldopa in a dose ranging from 250 mg to 4 g/day, two studies used hydralazine 25 mg three times per day, two studies administered hydrochlorothiazide 50 to 5 mg/day, two studies used pindolol 10 to 20 mg/day, one study evaluated atenolol 50 to 20 mg/day, one study labetalol 300 mg to 2400 mg/day, one study furosemide 20 mg each day, another amlodipine 5 mg/ day and other ketanserine 40 a 80 mg/day. One study administered diurectis but did not specified which type. One study divided the intervention groups arbitrarily into methyldopa plus hydrochlorothiazide, hydralazine plus hydrochlorothiazide and methyldopa plus hydralazine plus hydrochlorothiazide. Additionally all the studies offered scheduled clinical evaluation very 2 to 3 weeks with laboratory control and fetal ecography. In two trials patients received aspirin, one of them as comparison. If patients presented severe hypertension, intravenous labetalol or hydralazine were started. Five studies
d. Downgraded by two levels for imprecision as the optimal information size was not achieved.
e. Included studies recruited pregnant women between 24 and 32 years, average gestational age at admission was between 7 and 14 weeks, mean duration of hypertension was 4.2 years, Mean blood pressure was between 97 and 107 mmHg. Two studies included women with BP >140/90 mm Hg before 20 weeks of pregnancy and one before 34 weeks. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, if systolic or diastolic pressures were 160 or 110 mm Hg or more, multiple gestation, major fetal abnormalities or fetal death.
f. Two studies evaluated methyldopa in a dose ranging from 750 mg to 4 g/day. The following drugs were evaluated each in one study: one used pindolol in a dose ranging from 10 mg to 30 mg /day, labetalol 300 mg/ day to 2400 mg/day, ketanserin 40 mg to 80 mg/day . In one of the studies all patients received aspirin. In two studies control group had no treatment, and in two studies placebo was used. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and fetal echocardiography. One trial indicated that if severe hypertension developed, hydralazine or labetalol was used to treat hypertension and magnesium sulfate was administered.
g. Included studies recruited pregnant women between 28 and 34 years, average gestational age at admission was between 11,3 and 24,4 weeks, mean duration of hypertension was 4.4 years, Mean blood pressure was between 98 and 105 mmHg. Three studies included women with BP >140/90 mm Hg before 20 weeks of pregnancy, one before 28 weeks, and another did not specified weeks of pregnancy. One study included women < 35 weeks gestation with DBP 85-99 mmHg. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, if systolic or diastolic pressures were 160 or 110 mm Hg or more, rhesus incompatibility or contraindication to beta blockers, autoimmune disease, major fetal abnormalities or fetal death.
h. Four studies evaluated methyldopa in a dose ranging from 750 mg to 4 g/day. The following drugs were evaluated each in one study: pindolol in a dose ranging from 10 mg to 40 mg /day. hydralazine 75 mg/day , ketanserin 40 mg to 80 mg/day, furosemide 20 mg/ day, amlodipine 5 mg/day . Two studies did use aspirin; in one study as drug of the control group and in the other all patients received aspirin. In three studies control group had no treatment, and in three studies placebo was used. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and fetal echocardiography. Two trials indicated that if severe hypertension developed, hydralazine or labetalol was used to treat hypertension and magnesium sulfate was administered.
i. Evidence quality is downgraded one level due to serious limitations in consistency. Variation of point estimates is substantial due to value of I2> 40%.
j. Included studies recruited pregnant women between 24 and 35 years, with pregnancy between 7 and 26 weeks, with systolic blood pressure that ranged from 140 to 170 mmHg and diastolic from 90 to 110 mmHg, before pregnancy up to week 34. Only one of the included studies reports proteinuria on admission and excludes women with this condition prior to admission. Duration of chronic hypertension before pregnancy varied between 3.8 and 4,4 years. One study included only women with history of chronic hypertension who received management with diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, proteinuria, contraindications for the use of b blockers.
k. Seven studies evaluated methyldopa in a dose ranging from 250 mg to 4 g/day, two studies used hydralazine 25 mg three times per day, one study administered hydrochlorothiazide 50 to 5 mg/day, two studies used pindolol 10 to 20 mg/day, one study evaluated atenolol 50 to 20 mg/day, one study labetalol 300 mg to 2400 mg/day, one study furosemide 20 mg each day, another amlodipine 5 mg/ day and other ketanserine 40 a 80 mg/day. One study administered diuretics but did not specified which type. One study divided the intervention groups arbitrarily into methyldopa plus hydrochlorothiazide, hydralazine plus hydrochlorothiazide and methyldopa plus hydralazine plus hydrochlorothiazide. Additionally all the studies offered scheduled clinical evaluation very 2 to 3 weeks with laboratory control and fetal ecography. In two trials patients received aspirin, one of them as comparison. If patients presented severe hypertension, intravenous labetalol or hydralazine were started.
l. Downgraded by one level for serious limitations from missing outcome data and selection of the reported result.
m. Included studies recruited pregnant women between 30 and 34 years, average gestational age at admission was between 11,3 and 17,3 weeks, mean duration of hypertension was 4,4 years, Mean blood pressure was between 101 and 105 mmHg. Two studies included women with BP >140/90 mm Hg before 20 weeks of pregnancy, and the other include women with mild to moderate chronic hypertension ascertained at 6 to 13 weeks gestation without specifying other details. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, if systolic or diastolic pressures were 160 or 110 mm Hg or more, autoimmune disease or major fetal abnormalities. One study included multiple pregnancies.
n. The following drugs were evaluated each in one study: methyldopa in a dose ranging from 750 mg to 4 g/day, labetalol 300 mg/ day to 2400 mg/day, ketanserin 40 mg to 80 mg/day, furosemide 20 mg/ day, amlodipine 5 mg/day. Two studies did use aspirin; in one study as drug of the control group and in the other all patients received aspirin. In one study control group had no treatment, and in the other the control group received placebo. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and fetal echocardiography. One trial indicated that if severe hypertension developed, labetalol was used to treat hypertension and magnesium sulfate was administered.

Table 2 Quality of Evidence Neonatal outcomes

Summary of findings:

Antihypertensive compared to no antihypertensive for management of chronic hypertension in pregnancy

Patient or population: management of chronic hypertension in pregnancy
Setting: outpatient
Intervention: antihypertensive
Comparison: no antihypertensive

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no antihypertensive	**Risk with antihypertensive**				
Abortion (Abortion) assessed with: death of the product of conception before week 20 or less than 500 g follow-up: range 6 weeks to 20 weeks	40 per 1,000	**17 per 1,000** (6 to 47)	**OR 0.43** (0.15 to 1.19)	551 (4 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	
Stillbirth (Stillbirth) assessed with: eath of a fetus in utero after week 20 and greater than 500 g follow-up: range 6 weeks to 40 weeks	85 per 1,000	**74 per 1,000** (47 to 115)	**OR 0.86** (0.53 to 1.40)	900 (9 RCTs)	⨁◯◯◯ Very low[a,d,e,f]	
Neonatal mortality assessed with: Neonatal mortality follow-up: mean 1 months	9 per 1,000	**5 per 1,000** (1 to 16)	**OR 0.55** (0.17 to 1.84)	1011 (8 RCTs)	⨁◯◯◯ Very low[a,d,g,h]	

Table 2 Quality of Evidence Neonatal outcomes

Summary of findings:

Antihypertensive compared to no antihypertensive for management of chronic hypertension in pregnancy

Patient or population: management of chronic hypertension in pregnancy
Setting: outpatient
Intervention: antihypertensive
Comparison: no antihypertensive

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no antihypertensive	**Risk with antihypertensive**				
Low APGAR assessed with: Apgar lower than 7 at 5 minutes after birth. Apgar scale that assesses the viability of a newborn according to five simple physio-anatomical parameters: muscle tone, respiratory effort, heart rate, reflexes and skin color, each parameter is assigned a score between 0 and 2 follow-up: mean 1 days	28 per 1,000	**42 per 1,000** (17 to 102)	**OR 1.52** (0.59 to 3.90)	504 (4 RCTs)	⨁◯◯◯ Very low[a,d,i,j]	
Neonatal intensive care unit admission (Neonatal intensive care unit admission) assessed with: as admission of a neonate to a neonatal intensive care unit for some neonatal condition that requires surveillance or monitoring follow-up: range 6 weeks to 40 weeks	88 per 1,000	**130 per 1,000** (57 to 268)	**OR 1.54** (0.63 to 3.79)	202 (1 RCT)	⨁◯◯◯ Very low[d,k,l,m]	

Table 2 Quality of Evidence Neonatal outcomes

Summary of findings:

Antihypertensive compared to no antihypertensive for management of chronic hypertension in pregnancy

Patient or population: management of chronic hypertension in pregnancy
Setting: outpatient
Intervention: antihypertensive
Comparison: no antihypertensive

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no antihypertensive	**Risk with antihypertensive**				
Small for gestational age (Small for gestational age) assessed with: estimated fetal weight less than 10 th precentile follow-up: range 6 weeks to 40 weeks	85 per 1,000	**74 per 1,000** (47 to 115)	**OR 0.86** (0.53 to 1.40)	900 (10 RCTs)	⨁◯◯◯ Very low[a,d,n,o]	
Preterm delivery (Preterm delivery) assessed with: Delivery before 37 weeks of gestation follow-up: range 6 weeks to 40 weeks	95 per 1,000	**118 per 1,000** (65 to 206)	**OR 1.28** (0.66 to 2.49)	402 (4 RCTs)	⨁◯◯◯ Very low[a,d,p,q]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level for serious limitations from randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.
b. Included studies recruited pregnant women between 28 and 33 years, average gestational age at admission was between 16,2 and 24,4 weeks, mean duration of hypertension was not reported, Mean blood pressure was 104.5 mmHg. Three studies included women with BP >140/90 mm Hg before 28 weeks of pregnancy, one study included women with BP >150/95 mmHg beyond 28 weeks and another study included women < 35 weeks gestation with DBP 85-99 mmHg . Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, proteinuria, if systolic or diastolic pressures were 170 or 110 mm Hg or more, multiple pregnancy, rhesus incompatibility or contraindication to beta blockers
c. Two studies evaluated methyldopa in a dose ranging from 750 mg to 4 g/day, and two studies used pindolol in a dose ranging from 10 mg to 40 mg /day. In three studies control group had no treatment, and in one study placebo was used. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control
d. Downgraded by two levels for imprecision as the optimal information size was not achieved.
e. Included studies recruited pregnant women between 28 and 35 years, average gestational age at admission was between 11,3 and 24,4 weeks, mean duration of hypertension was 4.2 years, Mean blood pressure was between 98 and 107 mmHg. Four studies included women with BP >140/90 mm Hg before 24 weeks of pregnancy and two before 28 weeks, one study included women < 20 weeks gestation with >DBP 80 mmHg, another study included patients with long-term history of hypertension and diastolic BP >90 and <110 mm Hg who received diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, if systolic or diastolic pressures were 160 or 110 mm Hg or more, rhesus incompatibility or contraindication to beta blockers, autoimmune disease, major fetal abnormalities or fetal death..
f. Two studies evaluated methyldopa in a dose ranging from 750 mg to 4 g/day, and two studies used pindolol in a dose ranging from 10 mg to 40 mg /day. The following drugs were evaluated each in one study: hydrochlorothiazide 50 mg/day, hydralazine 75 mg/day to 250 mg/day, labetalol 300 mg/ day to 2400 mg/day, atenolol 50 mg/day to 200 mg/day, ketanserin 40 mg to 80 mg/day, furosemide 20 mg/ day, amlodipine 5 mg/day . Two studies did use aspirin; in one study as drug of the control group and in the other all patients received aspirin. In six studies control group had no treatment, and in two studies placebo was used. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and fetal echocardiography. Two trials indicated that if severe hypertension developed, hydralazine or labetalol was used to treat hypertension and magnesium sulfate was administered.
g. Included studies recruited pregnant women between 24 and 35 years, average gestational age at admission was between 11,3 and 24,4 weeks, mean duration of hypertension was 4.2 years, Mean blood pressure was between 97 and 107 mmHg. Three studies included women with BP >140/90 mm Hg before 24 weeks of pregnancy and three before 34 weeks, one study included women < 20 weeks gestation with >DBP 80 mmHg, another study included patients with long-term history of hypertension and diastolic BP >90 and <110 mm Hg who received diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, if systolic or diastolic pressures were 160 or 110 mm Hg or more, rhesus incompatibility or contraindication to beta blockers, autoimmune disease, major fetal abnormalities or fetal death.
h. Three studies evaluated methyldopa in a dose ranging from 750 mg to 4 g/day, and two studies used pindolol in a dose ranging from 10 mg to 40 mg /day. The following drugs were evaluated each in one study: hydrochlorothiazide 50 mg/day, hydralazine 75 mg/day to 250 mg/day, labetalol 300 mg/ day to 2400 mg/day, ketanserin 40 mg to 80 mg/day . In one of the studies all patients received aspirin. In six studies control group had no treatment, and in two studies placebo was used. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and fetal echocardiography. Two trials indicated that if severe hypertension developed, hydralazine or labetalol was used to treat hypertension and magnesium sulfate was administered.
i. Included studies recruited pregnant women between 28 and 33 years, average gestational age at admission was between 11,3 and 24,4 weeks, mean duration of hypertension was 4,2 years, Mean blood pressure was 105 mmHg. One study included women with BP >140/90 mm Hg before 28 weeks of pregnancy, one study included women < 35 weeks gestation with DBP 85-99 mmHg and another women with long-term history of hypertension, diastolic BP >90 and <110 mm Hg who received diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, proteinuria, if systolic or diastolic pressures were 170 or 110 mm Hg or more, multiple pregnancy, rhesus incompatibility or contraindication to beta blockers
j. Two studies evaluated methyldopa in a dose ranging from 750 mg to 4 g/day, one study used pindolol in a dose ranging from 10 mg to 40 mg /day, one study evaluated labetalol 300 mg/ day to 2400 mg/day, one study used diuretic without specifying agent and doses. In three studies control group had no treatment, and in one study placebo was used. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and serial ultrasonograms
k. Downgraded by one level for serious limitations from randomization process, deviations from intended interventions, measurement of the outcome and selection of the reported result.
l. Included study recruited pregnant women with mean age 29 years, 43% nulliparous, average gestational age at admission, mean blood pressure and mean duration of hypertension was not reported. Chronic hypertension was defined as BP >140/90 mm Hg before 28 weeks of pregnancy . Participants were excluded if they had blood pressures at the time of assessment were systolic or diastolic pressures of 170 or 110 mm Hg or more, or there were other complications already present such as multiple pregnancy, rhesus incompatibility, or severe associated maternal diseases.
m. This study evaluated methyldopa and dosing regimen not specified. The women were all interviewed and their babies personally examined within 2 days of delivery. Their progress during the neonatal period was recorded. On the 4th day, or later if the infant was unfit or pre-term, a neurological examination was made using criteria laid down by O'Doherty The infants were examined 30-60 min before a feed and were in a good 'state of arousal'.
n. Included studies recruited pregnant women between 24 and 35 years, with pregnancy between 7 and 26 weeks, history of chronic hypertension prior to pregnancy or Systolic BP from 140 to 170 mm Hg OR diastolic BP from 90 to 110 mm Hg on 2 occasions separated by at least 24 h between 12 and 32 weeks. Duration of chronic hypertension before pregnancy varied between 3.8 and 4,4 years. One study included only women with history of chronic hypertension who received management with diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, proteinuria, contraindications for the use of b blockers . Four studies included multiple pregnancy.
o. Seven studies evaluated methyldopa in a dose ranging from 250 mg to 4 g/day, two studies used hydralazine 25 mg three times per day, two studies administered hydrochlorothiazide 50 to 5 mg/day, two studies used pindolol 10 to 20 mg/day, one study evaluated atenolol 50 to 20 mg/day, one study labetalol 300 mg to 2400 mg/day, one study furosemide 20 mg each day, another amlodipine 5 mg/ day and other ketanserine 40 a 80 mg/day. One study administered diurectis but did not specified which type. One study divided the intervention groups arbitrarily into methyldopa plus hydrochlorothiazide, hydralazine plus hydrochlorothiazide and methyldopa plus hydralazine plus hydrochlorothiazide. Additionally all the studies offered scheduled clinical evaluation very 2 to 3 weeks with laboratory control and fetal ecography. In two trials patients received aspirin, one of them as comparison. If patients presented severe hypertension, intravenous labetalol or hydralazine were started.

p. Included studies recruited pregnant women between 28 and 33 years, average gestational age at admission was between 11,3 and 17,3 weeks, mean duration of hypertension was 4,2 years, Mean blood pressure was between 98 and 105 mmHg. Two studies included women with BP >140/90 mm Hg before 20 weeks of pregnancy, and another women with long-term history of hypertension, diastolic BP >90 and <110 mm Hg who received diuretics before pregnancy. Participants were excluded if they had major obstetric or medical problems, as diabetes mellitus or renal disease, if systolic or diastolic pressures were 160 or 100 mm Hg or more, autoimmune disease or major fetal abnormalities. One study included multiple pregnancies.

q. The following drugs were evaluated each in one study: methyldopa in a dose ranging from 750 mg to 4 g/day, hydrochlorothiazide 50 mg/day, hydralazine 75 mg/day to 250 mg/day, furosemide 20 mg/ day, amlodipine 5 mg/day . One study used aspirin as drug of the control group. Additionally all the studies offered scheduled clinical evaluation every 2 to 3 weeks with laboratory control and fetal echocardiography. Two trials indicated that if severe hypertension developed, hydralazine or labetalol was used to treat hypertension and magnesium sulfate was administered.

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