WHO recommendations on drug treatment for non-severe hypertension in pregnancy

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Acronyms and abbreviations

ANC	antenatal care
BMGF	Bill & Melinda Gates Foundation
CI	confidence interval
CS	Caesarean section
DOI	Declaration of Interest
FHR	fetal heart rate
FIGO	International Federation of Gynaecology and Obstetrics
FWC	Family, Women's and Children's Health (a WHO cluster)
GDG	Guideline Development Group
GRC	Guideline Review Committee
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (a WHO project)
GSG	Executive Guideline Steering Group
HELLP	haemolysis, elevated liver enzymes, low platelet
ICM	International Confederation of Midwives
LMIC	low- and middle-income countries
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health and Ageing
MCSP	Maternal and Child Survival Programme
MPH	Maternal and Perinatal Health (a team in WHO's Department of Sexual and Reproductive Health and Research)
NNT	number needed to treat
PICO	Population (P), Intervention (I), Comparison (C), Outcome (O)
RR	relative risk
SDG	Sustainable Development Goals
SRH	[WHO Department of] Sexual and Reproductive Health and Research
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive Summary

Introduction

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both pregnant women and their babies, and account for approximately 14% of all maternal deaths worldwide. Improving care for women around the time of childbirth is a necessary step towards achievement of the health targets of the Sustainable Development Goals (SDGs). Efforts to prevent and reduce morbidity and mortality during pregnancy and childbirth could also help address the profound inequities in maternal and perinatal health globally. To achieve these goals, healthcare providers, health managers, policy-makers and other stakeholders need up-to-date and evidence-based recommendations to inform clinical policies and practices.

In 2019, the Executive Guideline Steering Group (GSG) on WHO maternal and perinatal health recommendations prioritized issuing new WHO recommendations on antihypertensive drugs for non-severe (mild to moderate) hypertension during pregnancy in response to new important evidence on this intervention. For this guideline, non-severe hypertension and mild to moderate hypertension is used interchangeably, defined as diastolic blood pressure of 90–109 mmHg and/or systolic blood pressure of 140–159 mmHg *(1-3)*.

Target audience

The primary audience of these recommendations includes healthcare providers who are responsible for developing national and local health protocols (particularly those related to hypertensive disorders of pregnancy), and those directly providing care to pregnant women and their newborns, including midwives, nurses, general medical practitioners, obstetricians, obstetric physicians, managers of maternal and child health programmes, and relevant staff in ministries of health, in all settings.

Guideline development methods

The updating of these recommendations was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were initially developed using this process, namely:

(i) identification of the priority question and critical outcomes;

(ii) retrieval of evidence;

(iii) assessment and synthesis of evidence;

(iv) formulation of the recommendation; and

(v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The systematic review was used to prepare the evidence profiles for the prioritized question. WHO convened an online meeting on 31 July 2019 where an international group of experts – the Guideline Development Group (GDG) – reviewed and approved the recommendations.

Recommendations

The GDG reviewed the balance between the desirable and undesirable effects and the overall quality of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG issued the new recommendations on antihypertensive drug treatment for non-severe hypertension, with remarks and implementation considerations.

To ensure that the recommendations are correctly understood and applied in practice, guideline users should refer to the remarks, as well as to the evidence summary, if there is any doubt as to the basis of the recommendations and how best to implement them.

Table 1. WHO recommendations on the use of antihypertensive drugs for non-severe hypertension in pregnancy

1. **Women with non-severe hypertension during pregnancy should be offered antihypertensive drug treatment in the context of good quality antenatal care follow-up.**

   (Context specific recommendation)

2. **Oral alpha-agonist (methyldopa) and beta-blockers should be considered as effective treatment options for non-severe hypertension during pregnancy.**

   (Context specific recommendation)

Justification

- When used for non-severe hypertension in pregnancy, use of an antihypertensive drug compared to placebo or no antihypertensive treatment probably reduces the development of severe hypertension, though there may be little or no difference in the risk of developing proteinuria or pre-eclampsia. There may be a slight increase in side-effects with the use of an antihypertensive drug.

- Several antihypertensive drug options have been evaluated for non-severe hypertension in pregnancy, though there is currently insufficient evidence to conclude which drug option is superior over the other. Compared to placebo or no treatment, methyldopa probably reduces severe hypertension. Beta-blockers probably reduce the onset of severe hypertension and pre-eclampsia, though side-effects may increase. Calcium channel blockers probably increase the risk of developing proteinuria/pre-eclampsia. Beta-blockers may reduce the risk of women developing severe hypertension compared to methyldopa.

- The acceptability of drug treatment of non-severe hypertension by women may vary, depending on their knowledge of potential risks of hypertension in pregnancy, the cost of medication and drug side-effects. Feasibility may also be limited by a lack of suitably trained staff and medical equipment (including blood pressure monitoring devices) and local availability of antihypertensive drugs.

- There are insufficient data on how much women value health outcomes associated with use of different classes of antihypertensive drugs, and no direct evidence on cost-effectiveness, acceptability, feasibility and impact on health equity with the use of different classes of antihypertensive drugs.

Remarks

- The Guideline Development Group (GDG) considered that while the use of an antihypertensive drug for the treatment of non-severe hypertension in pregnancy may confer health benefits, pregnant women who are prescribed these drugs require regular outpatient monitoring and review by an antenatal care provider. Access to antenatal care services for monitoring of blood pressure and complications (such as proteinuria), or side-effects due to treatment, is considered integral to initiating antihypertensive treatment.

- The GDG acknowledged that, based on available evidence, alpha-agonist (methyldopa) and beta-blockers are reasonable antihypertensive drug treatment options. The group considered it important that clinicians select an antihypertensive drug regimen appropriate to the woman's individual clinical situation. The choice of antihypertensive should be based on pre-existing antihypertensive treatment, side-effect profiles, risks (including potential fetal effects), cost, local availability and the woman's preferences. Methyldopa has the fewest safety concerns, is listed for use as an antihypertensive agent during pregnancy in the WHO Model List of Essential Medicines, and is widely available in many countries. Available evidence suggests that calcium channel blockers should be avoided.

- Available trials used several different oral beta-blockers (including acebutolol, atenolol, labetalol, mepindolol, metoprolol, oxprenolol, pindolol and propranolol) at different doses. It is therefore not possible to determine the optimal beta-blocker option or dosing regimen for this indication. Atenolol and metoprolol are listed on the WHO Model List of Essential Medicines and are widely available in many countries.

- The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sodium nitroprusside should be avoided due to safety concerns.

1. Background

An estimated 295 000 women and adolescent girls died because of pregnancy and childbirth-related complications in 2015, around 99% of which occurred in low-resource settings *(4)*. Haemorrhage, hypertensive disorders and sepsis are responsible for more than half of all maternal deaths worldwide. Therefore, improving the quality of maternal healthcare is a necessary step towards the achievement of the health targets of the Sustainable Development Goals (SDGs). International human rights law and treaties include fundamental commitments by states to enable women and adolescent girls to enjoy the right to health and preservation of life in the context of pregnancy and childbirth *(5, 6)*; it is regarded as integral to their enjoyment of sexual and reproductive health and rights and living a life of dignity *(7)*. The World Health Organization (WHO) envisions a world where "every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period" *(8)*.

There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications *(9)*. Almost two thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings *(10)*. To provide good quality care, healthcare providers at all levels of maternal healthcare services, particularly in low- and middle-income countries (LMIC), need to have access to appropriate medications and training in relevant procedures. Healthcare providers, health managers, policy-makers and other stakeholders also need up-to-date, evidence-based recommendations to inform clinical policies and practices in order to optimize quality of care and enable improved healthcare outcomes. Efforts to prevent and reduce morbidity and mortality in pregnancy and childbirth could reduce the profound inequities in maternal and perinatal health globally.

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths (11). In 2011, WHO published 22 recommendations for the prevention and treatment of pre-eclampsia and eclampsia *(12)*. These recommendations were developed according to WHO guideline development standards, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and formulation of recommendations by a guideline panel of international experts.

The 2011 recommendations on prevention and treatment of pre-eclampsia and eclampsia included two recommendations on antihypertensive drugs for treatment of severe hypertension during pregnancy. At that time, the guideline development group also reviewed available evidence on the use of antihypertensive drugs for non-severe hypertension in pregnancy, and decided not to issue a recommendation. The recommendations on antihypertensive drugs for treatment of severe hypertension were updated in 2018 *(13)*.

Rationale and objectives

Hypertension during pregnancy is common, complicating approximately one in 10 pregnancies *(14)*. It is a progressive disease with potential to cause severe acute morbidity, long-term disability and death *(15, 16)*. Prevention, early diagnosis and timely, appropriate treatment to lower blood pressure in pregnant women with hypertension are some of the mainstays of management. In 2018, the WHO issued guidance on drug treatment for severe hypertension during pregnancy *(13)*. There is, however, emerging evidence on the possible role of antihypertensives in women with non-severe hypertension during pregnancy to prevent progression to more severe disease.

Therefore, the Executive Guideline Steering Group (GSG), which oversees the prioritization and updating of WHO maternal and perinatal health recommendations, prioritized the development of new WHO recommendations on antihypertensive drug treatment for non-severe hypertension during pregnancy in response to this new, potentially important evidence. The primary goal of these recommendations is to improve the quality of care and outcomes for pregnant women, particularly those related to the treatment of hypertensive disorders of pregnancy. These recommendations provide a foundation for the sustainable implementation of drug treatment for non-severe hypertension in pregnancy globally.

Target audience

The primary audience of these recommendations includes those who are responsible for developing national and local health guidelines and protocols (particularly those related to hypertensive disorders of pregnancy) and those directly providing care to women during labour and childbirth, including midwives, nurses, general medical practitioners, obstetric physicians, obstetricians, managers of maternal and child health programmes, and relevant staff in ministries of health, in all settings.

The recommendations will also be of interest to professional societies involved in the care of pregnant women, nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of maternal and child health programmes. It aims to help in increasing capacity in countries to respond to their needs on interventions to manage non-severe hypertension during pregnancy, and to prioritize essential actions in national health policies, strategies and plans.

Scope of the recommendations

Framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format, the questions directing these recommendations were as follows.

- For women with non-severe (mild to moderate) hypertension in pregnancy (P), does treatment with any antihypertensive drug (I), compared with placebo or no antihypertensive drug (C), improve maternal and perinatal outcomes (O)?
- For women with non-severe (mild to moderate) hypertension in pregnancy (P), does treatment with a specific class of anti-hypertensive drug (I), compared with placebo or no antihypertensive drug (C), improve maternal and perinatal outcomes (O)?
- For women with non-severe (mild to moderate) hypertension in pregnancy (P), does treatment with one antihypertensive drug (I), compared with another (C), improve maternal and perinatal outcomes (O)?

Persons affected by the recommendations

The population affected by the recommendations includes pregnant women in low-, middle- or high-income settings, particularly those who experience non-severe hypertension during pregnancy.

2. Methods

The recommendations were first developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (17)*. In summary, the process included:

(i) identification of the priority question and critical outcomes;

(ii) retrieval of evidence;

(iii) assessment and synthesis of evidence;

(iv) formulation of the recommendation; and

(v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

WHO recommendations on the use of antihypertensive drugs for non-severe (mild to moderate) hypertension in pregnancy were identified by the Executive GSG as a high priority for developing recommendations in response to new, potentially important evidence on this question *(18)*. Six main groups were involved in this process, with their specific roles described in the following sections.

Contributors to the guideline

Executive Guideline Steering Group

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions; African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating *(19)*.

WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research (SRH) and the Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA), managed the guideline development process. The WHO Steering Group drafted the key recommendation questions in PICO format, identified the systematic review team and guideline methodologist, as well as the guideline development and external review groups. In addition, the WHO Steering Group supervised the syntheses and retrieval of evidence, organized the Guideline Development Group meeting, drafted and finalized the guideline document, and managed the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

Guideline Development Group

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool consists of a diverse group of experts who are skilled in critical appraisal of research evidence, implementation of evidence-based recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG were identified in a way that ensured geographic representation, gender balance and no significant conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 17 external experts and relevant stakeholders were invited to constitute the Guideline Development Group (GDG) for updating this recommendation. Those selected were a diverse group of individuals with expertise in research, guideline development methods, and in clinical policy and programmes relating to maternal and perinatal health.

The GDG appraised and interpreted the evidence presented by the guideline methodologists to formulate the recommendations. Following the GDG meeting, the group also reviewed and approved the final guideline document. The members of this Group are listed in Annex 1.

External Review Group

An External Review Group included eight technical experts with interest and expertise in the provision of evidence-informed obstetric care. None of its members declared a conflict of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications

for implementation. They ensured that the decision-making processes had considered and incorporated contextual values, as well as the preferences of potential users of the recommendations, healthcare professionals and policy-makers. They did not change the recommendation that was formulated by the GDG. The names and affiliations of the external reviewers are provided here as an acknowledgement, and by no means indicate their endorsement of the recommendations in this guideline. The acknowledgement of the reviewers does not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. The members of the External Review Group are listed in Annex 1.

Evidence Synthesis Group

A systematic review on this question was commissioned with the support of the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the GRADE methodology. Representatives of the Cochrane Pregnancy and Childbirth Group attended the GDG meeting to provide an overview of the available evidence and GRADE tables, and to respond to technical queries from the GDG.

External partners and observers

Representatives of the United States Agency for International Development (USAID), the Maternal and Child Survival Programme (MCSP)/Jhpiego, the Bill & Melinda Gates Foundation (BMGF), the International Confederation of Midwives (ICM), the International Federation of Gynaecology and Obstetrics (FIGO) and the Population Council participated in the GDG meeting as observers. These organizations, with a long history of collaboration with various WHO departments and programmes in guideline dissemination and implementation, are among the implementers of the recommendations. The list of observers who participated in the GDG meeting is presented in Annex 1.

Identification of critical outcomes

The critical and important outcomes were aligned with the prioritized outcomes from the *WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (12)*. These outcomes were initially identified through a search of key sources of relevant, published, systematic reviews and a prioritization of outcomes by the 2011 GDG panel. All outcomes were included in the scope of this document for evidence searching, retrieval, grading and formulation of the recommendation. The list of outcomes is provided in Annex 2.

Evidence identification and retrieval

Evidence on the effects of antihypertensive drugs for non-severe hypertension in pregnancy

A systematic review was updated in 2019, with the support of the Cochrane Pregnancy and Childbirth Group *(20)*. This systematic review was the primary source of evidence on the effects (harms and benefits) of antihypertensives for non-severe hypertension in pregnancy.

The update of this systematic review was prepared in accordance with Cochrane standard procedures for preparing systematic reviews, based on studies identified from searches of the Cochrane Pregnancy and Childbirth Trials Register[1]. Randomized controlled trials evaluating

[1] The Cochrane Pregnancy and Childbirth (CPC) Trials Register is maintained by the CPC's Trial Search Co-ordinator and contains trials identified from: monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of MEDLINE; weekly searches of Embase; hand-searches of 30 journals and the proceedings of major conferences; weekly "current awareness" alerts for a further 44 journals; and monthly BioMed Central email alerts. For further information, see: http://pregnancy.cochrane.org/pregnancy-and-childbirth-groups-trials-register. In addition, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) were searched for unpublished, planned and ongoing trial reports using key search terms.

any antihypertensive medication for non-severe (mild or moderate) hypertension during pregnancy (whether compared to placebo, no treatment or another antihypertensive medication) were screened by the review authors, and data on relevant outcomes and comparisons were entered into Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). Then the RevMan file was exported to GRADE profiler software (GRADEpro) and GRADE criteria were used to critically appraise the retrieved scientific evidence *(21)*. Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks *(22)*. Further details on the eligibility criteria, search strategies and sources of studies are available in the published systematic review *(20)*.

Evidence on values, resource use and cost-effectiveness, equity, acceptability and feasibility

For questions relating to values, equity, acceptability and feasibility, findings were derived from two recent qualitative systematic reviews (commissioned by WHO) on what matters to women in utilising antenatal care services, and provision and uptake of routine antenatal care services *(23, 24)*. The external experts were asked to prepare a standard protocol before embarking on the review, including:

(i) a clear and focused question;

(ii) criteria for identification of studies, including search strategies for different bibliographic databases;

(iii) methods for assessing risk of bias; and

(iv) a data analysis plan.

The systematic review development process was iterative, with the review teams in regular communication with the WHO Steering Group to discuss challenges and agree on solutions. The search strategies for evidence identification and retrieval can be found in the published systematic reviews *(23, 24)*. Evidence for these domains was also supplemented by update searches of the same databases to identify any additional literature pertinent to the use of antihypertensive medications in pregnant women.

Scoping searches (MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and the National Health Services Economic Evaluation Database) did not identify any direct evidence pertaining to resource use and cost-effectiveness on the use of antihypertensive medications in pregnant women. Trials included in the systematic review of benefits and harms were also reviewed for economic outcomes (no data were identified). The unitary cost of different antihypertensive drug options were obtained from the Management Sciences for Health (MSH) International Medical Products Price Guide *(25)*.

Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence on benefits and harms for each outcome was performed using the GRADE approach *(26)*. Using this approach, the certainty of evidence for each outcome was rated as “high”, “moderate”, “low” or “very low” based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

Study design limitations: The risk of bias was first examined at the level of individual study and then across studies contributing to the outcome. For randomized trials, certainty was first rated as “high” and then downgraded by one (“moderate”) or two (“low”) levels, depending on the minimum criteria met by most of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different

studies. The certainty of evidence was not downgraded when the direction of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence: that is, whenever there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision: This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias: The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

Certainty of evidence assessments are defined according to the GRADE approach.

- **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.

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool *(27)*. The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low, very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding.

Formulation of recommendations

The WHO Steering Group supervised and finalized the preparation of summary of findings tables and narrative evidence summaries in collaboration with the Evidence Synthesis Group using the GRADE evidence-to-decision (EtD) framework. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For the priority questions, judgements were made on the impact of the intervention on each domain in order to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and Evidence Synthesis Group created summary documents for each priority question covering evidence on each domain, as described below.

- **Effects:** The evidence on the priority outcomes was derived from a systematic review *(20)* and summarized in this domain to answer the questions: “What are the desirable and undesirable effects of the

intervention?" and "What is the certainty of the evidence on effects?" Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harms led to a recommendation against the intervention. Where the intervention showed evidence of potential harms, but was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harms, such evidence of potential harms was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.

- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: "Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?" Qualitative evidence from a systematic review on women's and providers' views and experiences with antenatal care *(23)* was used to inform judgement in this domain. When the intervention resulted in benefit for outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the "effects" domain (see above), informed the "balance of effects" judgement.

- **Resources:** For this domain, the questions asked were: "What are the resources associated with the intervention?" and "Is the intervention cost-effective?" The resources required to implement the treatment of non-severe hypertension mainly include the costs of providing supplies, training, equipment and skilled human resources. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively. While no direct evidence was found for this domain, publicly available antihypertensive medication prices, as well as evidence from a multicountry analysis of blood pressure control in pregnant women with non-proteinuric chronic or gestational hypertension, provided additional evidence to inform the judgement in this domain *(28)*.

- **Acceptability:** For this domain, the question was: "Is the intervention acceptable to women and healthcare providers?" Qualitative evidence from a systematic review on provision and uptake of antenatal care services (24) informed the judgements for this domain. Additionally, evidence on the frequency of side-effects for different antihypertensive medication options, from the systematic review of benefits and harms *(20)*, was considered. The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.

- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of healthcare providers responsible for administering it. The question addressed was: "Is it feasible for the relevant stakeholders to implement the intervention?" Qualitative evidence from a systematic review on provision and uptake of ante-

natal care services *(24)* was used to inform judgements for this domain. Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.

- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: "What is the anticipated impact of the intervention on equity?" While no direct evidence was found for this domain, a multicountry analysis of inequities in antenatal care and maternal health outcomes *(29)*, evidence on the frequency of side-effects for different antihypertensive medication options *(20)*, as well as the experiences and opinions of the GDG members, were used to inform judgements for this domain. The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences is described in the "additional considerations" subsections. Such considerations were derived from studies that might not have directly addressed the priority question, but which provided pertinent information in the absence of direct evidence. These were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD frameworks (including evidence summaries, summary of findings tables and other documents related to each recommendation) to GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meetings. During the GDG meeting held on 31 July 2019, which was conducted online under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD frameworks, the draft recommendations and any comments received through preliminary feedback. The purpose of the meetings was to reach consensus on each recommendation, including its direction and, in some instances, the specific context, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members. The GDG were asked to select one of the following categories for the recommendation.

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts ("context-specific recommendation"):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation, and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research ("research-context recommendation"):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties that are related both to effectiveness of the intervention or option, and its acceptability and feasibility.

Management of declaration of interests

WHO has a robust process to protect the integrity of WHO in its normative work as well as to protect the integrity of individual experts the Organization collaborates with. WHO requires that experts serving in an advisory role disclose any

circumstances that could give rise to actual or ostensible conflicts of interest. The disclosure and appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors is a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings, according to the guidelines for declarations of interest (WHO experts) *(30)*.

All GDG and External Review Group members were therefore required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflicts of interest were declared, the Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development process. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflicts of interest, as outlined in the *WHO handbook for guideline development*, to all participating experts.

All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of individuals were published online two weeks prior to the meeting. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting or prior to participation as an external reviewer, and no further actions were taken. Annex 3 shows a summary of the DOI statements, and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

Decision-making during the GDG meeting

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE EtD framework to determine the direction and strength of the recommendations. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experience and opinions of members of the GDG and supported by evidence from a literature search where available. EtD tables were used to describe and synthesize these considerations.

Decisions were made based on consensus defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendations.

Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, evidence summary and other documents relevant to the GDG's deliberations. The draft documents were made available to the participants two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted the recommendation document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members and the External Review Group for final review and approval.

Peer review

Following review and approval by GDG members, the final document was sent to eight external

independent experts (External Review Group), who were not involved in the guideline panel, for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of correcting factual errors and improving language to address any lack of clarity.

3. Recommendations and supporting evidence

The following section outlines the recommendations and the corresponding narrative summary of evidence for the prioritized question. The EtD table, included in the EtD framework (Annex 4), summarizes the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence; values and preferences of stakeholders; and resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendations.

The following recommendations were adopted by the GDG. Evidence on the effectiveness of the intervention was derived from one systematic review and was summarized in GRADE tables (Annex 4). The certainty of the supporting evidence was rated as "very low" for most critical outcomes. To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional "remarks" reflecting the summary of the discussion by the GDG are included under each recommendation.

1. **Women with non-severe hypertension during pregnancy should be offered antihypertensive drug treatment in the context of good quality antenatal care follow-up.**

   (Context specific recommendation)

2. **Oral alpha-agonist (methyldopa) and beta-blockers should be considered as effective treatment options for non-severe hypertension during pregnancy.**

   (Context specific recommendation)

Justification

- When used for non-severe hypertension in pregnancy, use of an antihypertensive drug compared to placebo or no antihypertensive treatment probably reduces the development of severe hypertension, though there may be little or no difference in the risk of developing proteinuria or pre-eclampsia. There may be a slight increase in side-effects with the use of an antihypertensive drug.

- Several antihypertensive drug options have been evaluated for non-severe hypertension in pregnancy, though there is currently insufficient evidence to conclude which drug option is superior over the other. Compared to placebo or no treatment, methyldopa probably reduces severe hypertension. Beta-blockers probably reduce the onset of severe hypertension and pre-eclampsia, though side-effects may increase. Calcium channel blockers probably increase the risk of developing proteinuria/pre-eclampsia. Beta-blockers may reduce the risk of women developing severe hypertension compared to methyldopa.

- The acceptability of drug treatment of non-severe hypertension by women may vary, depending on their knowledge of potential risks of hypertension in pregnancy, the cost of medication and drug side-effects. Feasibility may also be limited by a lack of suitably trained staff and medical equipment (including blood pressure monitoring devices) and local availability of antihypertensive drugs.

- There are insufficient data on how much women value health outcomes associated with use of different classes of antihypertensive drugs, and no direct evidence on cost-effectiveness, acceptability, feasibility and impact on health equity with the use of different classes of antihypertensive drugs.

Remarks

- The GDG considered that while the use of an antihypertensive drug for the treatment of non-severe hypertension in pregnancy may confer health benefits, pregnant women who are prescribed these drugs require regular outpatient monitoring and review by an antenatal care provider. Access to antenatal care services for monitoring of blood pressure and complications (such as proteinuria), or side-effects due to treatment, is considered integral to initiating antihypertensive treatment.

- The GDG acknowledged that, based on available evidence, alpha-agonist (methyldopa) and beta-blockers are reasonable antihypertensive drug treatment options. The group considered it important that clinicians select an antihypertensive drug regimen appropriate to the woman's individual clinical situation. The choice of antihypertensive should be based on pre-existing antihypertensive treatment, side-effect profiles, risks (including potential fetal effects), cost, local availability and the woman's preferences. Methyldopa has the fewest safety concerns, is listed for use as an antihypertensive agent during pregnancy in the WHO Model List of Essential Medicines, and is widely available in many countries. Available evidence suggests that calcium channel blockers should be avoided.

- Available trials used several different oral beta-blockers (including acebutolol, atenolol, labetalol, mepindolol, metoprolol, oxprenolol, pindolol and propranolol) at different doses. It is therefore not possible to determine the optimal beta-blocker option or dosing regimen for this indication. Atenolol and metoprolol are listed on the WHO Model List of Essential Medicines and are widely available in many countries.

- The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sodium nitroprusside should be avoided due to safety concerns.

4. Dissemination and implementation of the recommendations

Dissemination and implementation of the recommendations is to be considered by all stakeholders and organizations involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase access and strengthen the capacity of health centres to provide high quality services to all women giving birth. It is therefore crucial that these recommendations are translated into antenatal and intrapartum care packages and programmes at country and health-facility levels, where appropriate.

Dissemination and evaluation

The recommendations will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. These recommendations will also be available on the WHO website and in the WHO Reproductive Health Library. Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by relevant WHO staff.

The recommendations document will be translated into the six UN languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendations into any of these languages.

Implementation considerations

- The successful introduction of these recommendations into national programmes and healthcare services depends on well planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols.

- The recommendations should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.

- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of antihypertensive drugs and access for continuity of antenatal care), and to ensure that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.

- In order to implement these recommendations, healthcare providers working in antenatal care settings require training and supportive supervision on how to prescribe antihypertensive drugs appropriately and safely, and how to inform and counsel women on the risks and benefits of the available options. In settings where a new antihypertensive drug option is introduced (or where recommended practices are changed), additional training and monitoring may be required.

- Guidance on blood pressure control and antenatal follow-up is available in the WHO handbook *Managing complications of pregnancy and childbirth (31).* An important principle is to maintain blood pressure above the lower limits of normal. Antenatal appointments may be scheduled every two to four weeks if hypertension is well controlled, and more frequently if it is poorly controlled. In this process, the role of local and international professional societies is important, and an all-inclusive and participatory process should be encouraged.

- Healthcare providers should discuss with women the risks, benefits and treatment options, in the management of non-severe hypertension during pregnancy, to facilitate informed decision-making.

- Efforts should be made by procurement agencies at all levels of supply chains to ensure only quality-certified antihypertensive drugs are procured.

5. Research implications

The GDG identified important knowledge gaps that need to be addressed, which may have an impact on these recommendations. The following matters were identified as high priorities for further research.

- What are the main outcomes that women (and their families) value in relation to anti-hypertensive drug options for the treatment of non-severe hypertension in pregnancy?
- What is the most effective antihypertensive drug option for the treatment of non-severe hypertension in pregnancy, including effects on the fetus and newborn?
- How can the management of non-severe hypertension during pregnancy at primary care and community levels be optimised, particularly in low-resource settings?

6. Applicability issues

Anticipated impact on the organization of care and resources

Implementing these evidence-based recommendations will require resources to ensure it is done safely, including staff time for clinical monitoring of women undergoing drug treatment for non-severe hypertension in pregnancy. The GDG noted that updating training curricula and providing training would increase impact and facilitate implementation. Standardization of care, by incorporating the recommendations into existing maternity care packages and protocols, can encourage healthcare provider behaviour change.

Monitoring and evaluating guideline implementation

Implementation should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of maternal and newborn care. This can involve clinical audits or criterion-based clinical reviews to monitor indicators such as the proportion of women with non-severe hypertension who received antihypertensive drug therapy, and the proportion of pregnant women with non-severe hypertension who progressed to a more severe disease, and/or had adverse maternal and perinatal outcomes. In addition, implementation monitoring can be aligned with the standards and indicators described in the WHO document *Standards for improving quality of maternal and newborn care in health facilities (32)*, especially as they relate to the proportion of pregnant women with hypertensive disorders in health facilities who received the recommended antihypertensives, and to the stocking of medicines, supplies and equipment necessary for management of hypertension during pregnancy.

7. Updating the recommendations

The Executive GSG convenes annually to review WHO's current portfolio of maternal and perinatal health recommendations, and to advise WHO on prioritization of new and existing questions for recommendation development and updating. Accordingly, these recommendations will be reviewed by the Executive GSG. In the event that new evidence (that could potentially impact the current evidence base) is identified, the recommendations may be updated. If no new reports or information is identified, the recommendations may be revalidated.

Following publication and dissemination of these recommendations, any concern about their validity will be promptly communicated to the guideline implementers and, in addition, plans will be made to update the recommendations.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendations. Please email your suggestions to mpa-info@who.int.

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Annex 2. Priority outcomes for decision-making

Priority Outcomes
Maternal outcomes • Maternal death • Eclampsia • Recurrent seizures • Severe pre-eclampsia • Pre-eclampsia • Severe maternal morbidity • Intensive care unit (ICU) admission • Adverse effects of interventions • Maternal satisfaction • Maternal well-being
Fetal/neonatal outcomes • Perinatal death • Admission to neonatal intensive care unit (NICU)/special nursery • Fetal/neonatal adverse effects of interventions • Apgar scores

Annex 3. Summary and management of declared interests from GDG and External Review Group members

i. GDG members

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Ebun ADEJUYIGBE	Content expert and end-user	None declared	Not applicable
Shabina ARIFF	Content expert and end-user	None declared	Not applicable
Jemima DENNIS-ANTWI	Content expert and end-user	None declared	Not applicable
Luz Maria DE-REGIL	Content expert and end-user	Grant support – Government of Canada gave funds to Nutrition International, my former employer, for a research study. In the past, as WHO staff, co-ordinated the Guideline *Calcium supplementation in pregnancy* led by the Department of Nutrition.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.
Christine EAST	Content expert and end-user	None declared	Not applicable
Lynn FREEDMAN	Content expert and end-user	None declared	Not applicable
Pisake LUMBIGANON	Content expert and end-user	None declared	Not applicable
Anita MAEPIOH	Content expert and end-user	None declared	Not applicable
Shireen MEHER	Content expert and end-user	Chief investigator of an RCT evaluating calcium supplementation for prevention of pre-eclampsia in high-risk women. National Institute for Health Research (NIHR), United Kingdom.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.
James NEILSON	Content expert and end-user	None declared	Not applicable
Hiromi OBARA	Content expert and implementer	None declared	Not applicable
Cristina PALACIOS	Content expert and end-user	Conducted a landscape review for WHO on the status of calcium fortification worldwide. Investigator on grant entitled *Effect of soluble corn fiber supplementation for 1 year on bone metabolism in adolescents.* National Institutes of Health.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Rachel PLACHCINSKI	Consumer representative	None declared	Not applicable
Zahida QURESHI	Content expert and end-user	None declared	Not applicable
Kathleen RASMUSSEN	Content expert and end-user	None declared	Not applicable
Niveen Abu RMEILEH	Content expert and implementer	None declared	Not applicable
Eleni TSIGAS	Consumer representative	Ms Tsigas represents patient experiences around pre-eclampsia and other hypertensive disorders of pregnancy to organizations, committees and other multidisciplinary bodies. She is also a voting member on the Council for Patient Safety in Women's Healthcare (USA).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.

ii. External Review Group members

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Caroline HOMER	Content expert and end-user	None declared	Not applicable
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Saraswathi VEDAM	Content expert and end-user	None declared	Not applicable
Hayfaa WAHABI	Content expert and end-user	None declared	Not applicable

Annex 4. Evidence-to-decision framework

1. QUESTION

Following are the questions of interest in Population, Intervention, Comparator, Outcome (PICO) format.

(i) For women with non-severe (mild to moderate) hypertension in pregnancy (P), does treatment with any antihypertensive drug (I), compared with placebo or no antihypertensive drug (C), improve maternal and perinatal outcomes (O)?

(ii) For women with non-severe (mild to moderate) hypertension in pregnancy (P), does treatment with a specific class of antihypertensive drug (I), compared with placebo or no antihypertensive drug (C), improve maternal and perinatal outcomes (O)?

(iii) For women with non-severe (mild to moderate) hypertension in pregnancy (P), does treatment with one antihypertensive drug (I), compared with another (C), improve maternal and perinatal outcomes (O)?

Problem: Non-severe (mild to moderate) hypertension during pregnancy
Perspective: Clinical practice recommendation – population perspective
Population (P):

- pregnant women with non-severe (mild to moderate) hypertension during pregnancy

Intervention (I):

- antihypertensive drug

Comparison (C):

- placebo or no antihypertensive drug
- another antihypertensive drug

Setting:

- hospital or community setting

Priority outcomes (O):[2]

Maternal outcomes:

- maternal death
- eclampsia
- recurrent seizures
- severe pre-eclampsia
- pre-eclampsia[3]
- severe maternal morbidity[4]
- intensive care unit (ICU) admission
- adverse effects of interventions[5]
- maternal satisfaction
- maternal well-being.

[2] These outcomes reflect the prioritised outcomes used in the development of the WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (2011). The outcomes "proteinuria/pre-eclampsia" and "severe pre-eclampsia", "maternal ICU admissions", "maternal satisfaction" and "maternal well-being" have been added for this update.
[3] In the systematic review it was defined as "proteinuria/pre-eclampsia", and we have used the Cochrane definition in this framework.
[4] These include severe hypertension, HELLP syndrome, pulmonary oedema, disseminated intravascular coagulation, oliguria, renal failure, placental abruption, or any other severe morbidities reported in the review.
[5] These include: any reported side-effects or severe adverse effects, and changed/stopped drug due to maternal side-effects.

Fetal/neonatal outcomes:

- perinatal death
- admission to neonatal intensive care unit (NICU)/special nursery
- fetal/neonatal adverse effects of interventions
- Apgar scores.

2. ASSESSMENT

EFFECTS OF INTERVENTIONS

What is the effect of antihypertensive drugs on the priority outcomes when used for the treatment of non-severe (mild to moderate) hypertension?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of drug treatments for mild to moderate hypertension in pregnancy was derived from one systematic review, which included 63 randomized trials (6251 women) *(20)*, although it was not possible to extract data on five of these trials because either no data were included in the available reports or the available data were incomplete. Data were extracted from 58 trials (5909 women) that were conducted in Argentina (three trials), Australia (three trials), Brazil (four trials), Caribbean Islands, Denmark and Sweden (one trial), France (three trials), China Hong Kong SAR, India (eight trials), Ireland, Israel (four trials), Italy (four trials), Pakistan, Panama, South Africa (two trials), Sudan, Sweden (two trials), United Kingdom of Great Britain and Northern Ireland (12 trials), United States of America (five trials) and Venezuela.

Five trials recruited women who were admitted in hospital, while five recruited both hospital inpatients and outpatients. Eighteen studies recruited women from hospital outpatient clinics and one recruited women at urban antenatal clinics, while three studies recruited women at antenatal clinics; it was unclear, however, whether these clinics were situated in hospitals. A further seven studies recruited women at hospitals, but provided no further information about the setting. Of the remaining studies, the available information suggests that 16 probably recruited women in hospital settings, whilst for three the setting was unclear.

The trials were published between 1968 and 2017. All the trials were of small sample size, with the majority (43/58 trials) including fewer than 130 women; the largest study included 314 women. Four studies included three arms, whilst all the rest included two arms; only six studies had arms containing more than 100 women. The gestational age of the women at trial entry varied: 21 trials recruited only women in their third trimester of pregnancy; 20 trials recruited women in their second and third trimesters; eight trials recruited women in their first and second trimesters; and the remaining nine trials did not report gestational age at entry to the trial. In trials that compared any antihypertensive drug versus placebo or no antihypertensive drug, 11 trials recruited women before 32 weeks' gestation; two trials recruited women at 32 weeks' gestation or later; and for

the remaining 16 trials, either gestation at trial entry was not specified, or the data were not disaggregated by gestation.

Women also differed in the degree or severity of hypertension at trial entry, due to varying inclusion criteria between trials. Mild to moderate hypertension was defined with different thresholds across studies, with the lowest thresholds used being 140 mmHg for systolic blood pressure, and 85 mmHg for diastolic blood pressure. Five trials did not define the blood pressure thresholds for mild to moderate hypertension. Women with severe hypertension (where available, defined as systolic blood pressure ≥170 mmHg or diastolic blood pressure ≥110 mmHg) were excluded. In eight trials, all women had proteinuria at recruitment; 19 trials excluded women with proteinuria; 14 trials included women regardless of whether they had proteinuria or not; and in the remaining 17 trials proteinuria at trial entry was not reported. Ten trials only recruited women with chronic hypertension; 22 trials excluded women with chronic hypertension; 10 trials included women regardless of whether or not they had chronic hypertension; and, in the remaining 16 trials, chronic hypertension at trial entry was not mentioned.

A range of antihypertensive drugs and doses were used in the studies. All drugs were given orally, except glyceryl trinitrate, which was given transdermally.

Beta-blockers

- acebutolol – 400 to 1200 mg/day
- atenolol – 50 to 100 mg/day
- labetalol – 200 to 2500 mg/day (divided between two or three doses per day)
- mepindolol – 5 to 10 mg/day
- metoprolol – 50 to 400 mg/day (divided between one or two doses per day)
- oxprenolol – 80 to 640 mg/day (divided between one or two doses per day)
- pindolol – 5 to 30 mg/day
- propranolol – 30 to 160 mg/day

Alpha-agonists

- methyldopa – 250 to 8000 mg/day (divided between one to four doses per day)
  One trial gave methyldopa as the control, giving 750 mg/day and adjusting where necessary until blood pressure controlled, with no upper limit specified.

Calcium channel blockers

- amlodipine – 5 mg/day
- isradipine – 10 mg/day (divided between two doses)
- nicardipine – 60 mg/day (divided between three doses)
- nifedipine – 20 to 160 mg/day. One trial gave 30 mg/day, adjusting where necessary until blood pressure controlled, with no upper limit specified
- nimodipine – 120 mg/day (divided into six-hourly doses)
- verapamil – 720 mg/day (divided into three doses)

Alpha-blockers

- prazosin – 3 to 15 mg/day (divided between three doses)

Nitric oxide donors

- glyceryl trinitrate (GTN) – 10 mg/day

Phosphodiesterase 5 inhibitors

- sildenafil – 60 to 150 mg/day (divided between three doses)

Direct vasodilators

- hydralazine – 50 to 100 mg/day. Three trials gave hydralazine to both trial arms (i.e. the intervention and control group). In these trials, the doses of hydralazine given ranged from 50 to 300 mg, but in addition beta-blockers were given to the intervention group. In this review, they were meta-analysed within the "beta-blockers versus placebo" comparison.

Serotonin-2 receptor blockers

- ketanserin – 20 to 80 mg/day

Loop diuretics

- furosemide – 20 mg/day

The outcomes "pre-eclampsia" and "severe pre-eclampsia" were defined in different ways between trials. Wherever possible, the review defined proteinuria/pre-eclampsia as new proteinuria (1+ or more, or 300 mg or more/24 h), however some included studies in the review used higher thresholds (2+ or more, or up to 5 g or more/24 h), especially where all women had proteinuria at trial entry. Other trials did not define their criteria for pre-eclampsia.

Changes since last update

Since the publication of the 2011 *WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (12)*, this review has been updated twice, in 2014 and 2018 *(20, 33)*.

Since 2011, data has been added from 12 trials (1627 women), and four antihypertensive drugs have also been added (oxprenolol, amlodipine, furosemide and sildenafil). The 2011 recommendation included only the following comparisons:

- any antihypertensive drug versus placebo or no antihypertensive drug
- any hypertensive drug versus methyldopa
- any antihypertensive drug versus calcium channel blockers.

The updated review published in 2018 included one further comparison: any other antihypertensive drugs versus beta-blockers (19 trials).

For this recommendation update, trials were organized by drug class in order to assess the effects of each class of antihypertensive drug on the outcomes of interest.

Comparison 1: Effects of any antihypertensive drug versus placebo or no antihypertensive drug

Maternal outcomes

Maternal death: It is unclear whether antihypertensive drugs reduce maternal death when compared with placebo/no antihypertensive drugs, because the evidence was very low-certainty. Maternal death was rare in the included studies.

Eclampsia: It is unclear whether antihypertensive drugs reduce eclampsia, because the evidence was very low-certainty.

Severe pre-eclampsia: It is unclear whether antihypertensive drugs reduce severe pre-eclampsia, because the evidence was very low-certainty.

Proteinuria/pre-eclampsia: Low-certainty evidence suggests that there may be little or no difference between antihypertensive drugs and placebo or no treatment in the risk of proteinuria/pre-eclampsia (23 studies, 2851 women; 251/1476 vs 255/1375; RR 0.92, 95% CI 0.75 to 1.14).

Severe maternal morbidity: Moderate-certainty evidence suggests that antihypertensive drugs probably reduce the development of **severe hypertension** among women with mild to moderate high blood pressure in pregnancy (20 studies, 2558 women; 125/1336 vs 242/1222; RR 0.49 95% CI 0.40 to 0.60). It is unclear whether antihypertensive drugs reduce **haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome** or **pulmonary oedema**, because the evidence was very low-certainty. No other severe maternal morbidity outcomes were reported in this review.

Adverse effects of interventions: Low-certainty evidence suggests there may be a slight increase in **side-effects**[6] with the use of antihypertensive drugs compared with placebo/no antihypertensive (11 studies, 934 women; 69/468 vs 39/466; RR 1.99, 95% CI 0.89 to 4.43). Moderate certainty of evidence suggests there may be no difference in the need to **change/stop drugs due to maternal side-effects** (16 studies, 1503 women; 25/754 vs 9/749; RR 1.93, 95% CI 0.92 to 4.06).

Recurrent seizures, maternal ICU admissions, maternal satisfaction and **maternal well-being:** No included trials reported on these outcomes.

Fetal/neonatal outcomes

Perinatal death: Low-certainty evidence suggests that antihypertensive drugs may make little or no difference to perinatal death when compared with placebo or no treatment (22 studies, 2517 infants; 33/1310 vs 37/1207; RR 0.89, 95% CI 0.56 to 1.41).

Admission to NICU/special nursery: Moderate-evidence suggests that antihypertensive drugs probably make little or no difference to infant admissions to NICUs (10 studies, 1570 infants; 226/796 vs 220/774; RR 1.01, 95% CI 0.83 to 1.22).

Fetal/neonatal adverse effects of interventions: Low-certainty evidence suggests that antihypertensive drugs may make little or no difference to the incidence of **neonatal hypoglycaemia** (6 studies, 962 infants; 38/520 vs 48/442; RR 0.77, 95% CI 0.51 to 1.15) and **neonatal jaundice** (3 studies, 529 infants; 47/260 vs 62/269; RR 0.78, 95% CI 0.53 to 1.15). It is unclear what impact antihypertensive drugs have on **neonatal bradycardia**, because the evidence was of very low-certainty.

Apgar scores: The review did not report this outcome.[7]

[6] Side-effects included any reported side-effects or severe adverse events.

[7] The pre-specified review outcome was very low Apgar score (less than four) at five minutes.

Comparison 2: Effects of a specific class of antihypertensive drug versus placebo or no antihypertensive drug

2.1 Effects of beta-blockers versus placebo or no antihypertensive drug

Maternal outcomes

Maternal death: It is unclear whether beta-blockers reduce maternal death, because the evidence was very low-certainty. There were no events in either group and the sample sizes were very small.

Eclampsia: It is unclear whether beta-blockers reduce eclampsia, because the evidence was very low-certainty. There were no events in either group and the sample sizes were very small.

Severe pre-eclampsia: It was not reported in any included studies.

Proteinuria/pre-eclampsia: Moderate-certainty evidence suggests that, among women with mild to moderate hypertension, beta-blockers probably reduce pre-eclampsia when compared with placebo or no antihypertensive (8 studies, 883 women; 73/433 vs 106/450; RR 0.74, 95% CI 0.56 to 0.99).

Severe maternal morbidity: Moderate-certainty evidence suggests that beta-blockers probably reduce **severe hypertension** compared with placebo or no antihypertensive drug (8 studies, 762 women; 28/378 vs 76/384; RR 0.38, 95% 0.26 to 0.57). The effects of beta-blockers on **pulmonary oedema** and **placental abruption** are unclear because the evidence was very low-certainty. No other severe maternal morbidity outcomes were reported in this review.

Adverse effects of interventions: Low-certainty evidence suggests there may be an increase in **side-effects** with beta-blockers compared with placebo (7 studies, 554 women; 33/279 vs 9/275; RR 3.14, 95% CI 0.66 to 15.02). It was unclear whether beta-blockers increase the need to **change/stop drugs due to maternal side-effects** because the evidence was of very low-certainty.

Recurrent seizures, maternal ICU admissions, maternal satisfaction and **maternal well-being:** No included trials reported on these outcomes.

Fetal/neonatal outcomes

Perinatal death: It is unclear whether beta-blockers reduce perinatal death, because the evidence was very low-certainty.

Admission to NICU/special nursery: Low-certainty evidence suggests that beta-blockers may make little or no difference to this outcome (3 studies, 449 babies; 66/215 vs 66/234; RR 1.07, 95% CI 0.82 to 1.41).

Fetal/neonatal adverse effects of interventions: Low-certainty evidence did not identify any clear effect of beta-blockers on **neonatal hypoglycaemia** (2 studies, 261 babies; 5/129 vs 7/132; RR 0.71, 95% CI 0.13 to 3.83) or **neonatal jaundice** (1 study, 144 babies; 5/70 vs 10/74; RR 0.53, 95% CI 0.19 to 1.47). The effects of beta-blockers on **neonatal bradycardia** are unclear because the evidence was very low-certainty for this outcome.

Apgar scores: The review did not report this outcome.[8]

2.2 Effects of methyldopa versus placebo or no antihypertensive drug

Maternal outcomes

It is unclear whether methyldopa affects the risk of **maternal death, eclampsia, severe pre-eclampsia** or **proteinuria/pre-eclampsia,** because the evidence was very low-certainty for all of these outcomes.

Severe maternal morbidities: Moderate-certainty evidence suggests that methyldopa probably reduces **severe hypertension** when compared with placebo (2 studies, 310 women; 12/151 vs 40/159; RR 0.32, 95% CI 0.17 to 0.58). It is unclear whether methyldopa reduces **placental abruption** because the evidence was very low-certainty. No other severe maternal morbidity outcomes were reported in this review.

Adverse effects of interventions: It is unclear whether women who receive methyldopa experience more **side-effects** or have an increase in the need to **change/stop drugs due to side-effects** because the evidence was very low-certainty.

Recurrent seizures, maternal ICU admissions, maternal satisfaction and **maternal well-being:** No included trials were reported on these outcomes.

Fetal/neonatal outcomes

It is unclear whether methyldopa reduces **perinatal death** or **admission to NICU/special nursery** because the evidence was very low-certainty.

Fetal/neonatal adverse effects of interventions: Although this review reported on **neonatal jaundice,** the effects of methyldopa are unclear because the evidence was very low-certainty.

Apgar scores: The review did not report this outcome.[9]

2.3 Effects of calcium channel blockers versus placebo or no antihypertensive drug

Maternal outcomes

Maternal death: The included studies did not report on maternal death.

Eclampsia: It is unclear whether calcium channel blockers reduce eclampsia, because the evidence was very low-certainty.

Severe pre-eclampsia: The effects of calcium channel blockers on severe pre-eclampsia are unclear because the evidence was very low-certainty.

[8] The pre-specified review outcome was very low Apgar score (less than four) at five minutes.
[9] The pre-specified review outcome was very low Apgar score (less than four) at five minutes.

Proteinuria/pre-eclampsia: Moderate-certainty evidence suggests that calcium channel blockers probably increase proteinuria/pre-eclampsia compared with placebo or no antihypertensive drug (4 studies, 725 women; 89/360 vs 65/365; RR 1.40, 95% CI 1.02 to 1.92).

Severe maternal morbidity: Low-certainty evidence suggests that calcium channel blockers may make little or no difference to pregnant women with mild to moderate hypertension developing **severe hypertension** when compared with placebo or no antihypertensive drugs (4 studies, 662 women; 58/330 to 71/332; RR 0.81, 95% CI 0.60 to 1.11). The effects of calcium channel blockers on **HELLP syndrome** and **placental abruption** are unclear because the evidence was very low-certainty. No other severe maternal morbidity outcomes were reported in this review.

Maternal adverse effects of interventions: It is unclear whether women who receive calcium channel blockers experienced more **side-effects** or had an increase in the need to **change/stop drugs due to side-effects,** because the evidence was very low-certainty.

Recurrent seizures, maternal ICU admissions, maternal satisfaction and **maternal well-being:** No included trials reported on these outcomes.

Fetal/neonatal outcomes

It is unclear whether calcium channel blockers reduce **perinatal death** or have **fetal/neonatal adverse effects** (including **neonatal hypoglycaemia** and **neonatal jaundice**), because the evidence was very low-certainty.

Admission to NICU/special nursery: Low-certainty evidence suggests that calcium channel blockers may make little or no difference to NICU admissions when compared with placebo/no antihypertensive drug (2 studies, 449 babies; 72/222 vs 62/227; RR 1.18, 95% CI 0.87 to 1.62).

Apgar scores: The review did not report this outcome.[10]

2.4 Effects of alpha-blockers versus placebo or no antihypertensive drug

One small study compared prazosin versus no antihypertensive drug; however, the findings were unclear for all reported outcomes (**proteinuria/pre-eclampsia, severe hypertension, placental abruption** and **perinatal death**), because the evidence was very low-certainty.

2.5 Effects of glyceryl trinitrate (GTN) versus placebo or no antihypertensive drug

One study included comparison of GTN versus no antihypertensive drug (the control was a dummy patch that did not match the intervention patch), and it only reported on three of the priority outcomes included in this review: **proteinuria/pre-eclampsia, side-effects** and **changed/stopped drugs due to side-effects.** The evidence for all three outcomes was assessed to be very low-certainty. This trial had planned to recruit 220 women; however, it was stopped early due to side-effects (headaches) in the treatment group.

[10] The pre-specified review outcome was very low Apgar score (less than four) at five minutes.

2.6 Effects of sildenafil versus placebo or no antihypertensive drug

Two small studies provided evidence on this comparison; however, the effects of sildenafil compared with placebo were unclear for all priority outcomes (**eclampsia, HELLP syndrome, placental abruption, changed/stopped drugs due to side-effects, perinatal death, admission to NICU/special nursery** and **neonatal hypoglycaemia**) reported by the studies, because the evidence was very low-certainty.

The included studies did not report on any other comparisons of specific antihypertensive drugs versus placebo or no antihypertensive drug.

Comparison 3: Effects of one antihypertensive drug versus another antihypertensive drug

3.1 Effects of beta-blockers versus methyldopa[11]

Low-certainty evidence suggests that among pregnant women with mild to moderate hypertension, there may be little or no difference between beta-blockers and methyldopa in the risk of developing **proteinuria/pre-eclampsia** (10 studies, 903 women; 52/470 vs 64/433; RR 0.82, 95% CI 0.58 to 1.16), although beta-blockers may reduce the risk of women developing **severe hypertension** (9 studies, 592 women; 63/308 vs 83/284; RR 0.59, 95% CI 0.33 to 1.05). In terms of fetal/neonatal outcomes, the included studies did not report on **perinatal death**, but they did provide low-certainty evidence on **total reported fetal or neonatal death (including miscarriage)**, which suggests that there may be little or no difference between beta-blockers and methyldopa for this outcome (16 studies, 1280 women; 19/660 vs 24/660; RR 0.80, 95% CI 0.43 to 1.50). Similarly, there may be little or no difference between the two drugs for **admission to NICU/special nursery** (4 studies, 571 babies; 57/295 vs 58/276; RR 0.92, 95% CI 0.67 vs 1.25).

The effects of beta-blockers compared with methyldopa were unclear for the remaining priority outcomes that were reported in the review (**severe pre-eclampsia, placental abruption, maternal side-effects, changed/stopped drugs due to maternal side-effects, neonatal hypoglycaemia, neonatal bradycardia, neonatal jaundice**), because the evidence was very low-certainty.

3.2 Effects of calcium channel blockers versus methyldopa

Four studies (251 women) provided evidence on this comparison; however, the findings were unclear for all reported outcomes (**eclampsia, proteinuria/pre-eclampsia, severe hypertension, maternal side-effects,** and **total reported fetal or neonatal death (including miscarriage)** and **admission to NICU/special nursery**), because the evidence was very low-certainty.

3.3 Effects of ketanserin versus methyldopa

The single small study (20 women) that reported this comparison only provided data on one priority outcome, **total reported fetal or neonatal death (including miscarriage)**, but the findings were unclear because the evidence was very low-certainty.

[11] The trials compared different beta-blockers to methyldopa.

3.4 Effects of glyceryl trinitrate (GTN) versus calcium channel blockers

The findings from the one small study (36 women) that reported on this comparison were unclear, because the evidence was very low-certainty for all reported outcomes; the study reported on **proteinuria/pre-eclampsia, severe hypertension, changed/stopped drugs due to maternal side-effects** and **total reported fetal or neonatal death (including miscarriage).**

3.5 Effects of furosemide versus calcium channel blockers

One small study (41 women) provided data on this comparison; however, the findings on the priority outcomes reported in the review (**proteinuria/pre-eclampsia, severe hypertension, placental abruption,** and **total reported fetal or neonatal death, including miscarriage**) were unclear, because the evidence was very low-certainty.

3.6 Effects of beta-blockers versus calcium channel blockers

Low-certainty evidence suggests that there may be little or no difference between beta-blockers and calcium channel blockers in terms of risk of **total reported fetal or neonatal death, including miscarriage** (3 studies, 372 women; 18/185 vs 22/187; RR 0.82, 95% CI 0.46 to 1.46).

The findings were unclear for all other reported outcomes (**maternal death, eclampsia, proteinuria/pre-eclampsia, severe hypertension, HELLP syndrome, pulmonary oedema, maternal side-effects, changed/stopped drugs due to maternal side-effects, admission to NICU/special nursery** and **neonatal hypoglycaemia**), because the evidence was very low-certainty.

Although this outcome was not included in the review, one small trial also reported on **maternal ICU admissions.** The mean number of nights women stayed in a maternal ICU and/or high dependency unit with beta-blockers was 0.4 nights (55 women; standard deviation (SD) 1.1), while the mean number of nights with calcium channel blockers was 0.9 nights (57 women; SD 1.9).

The included trials did not compare any other single antihypertensive drugs with another.

Additional considerations

The British National Formulary *(34)*[12] indicates the following drugs are not known to be harmful in pregnancy:

- methyldopa
- glyceryl trinitrate.

[12] BNF accessed 25 June 2019. Antihypertensive drug options not listed in the British National Formulary are not reported (isradipine and ketanserin).

The following drugs have safety considerations when used in pregnancy *(34)*:

- beta-blockers – carry risk of intra-uterine growth restriction, neonatal hypoglycaemia and bradycardia *(36)*;
- nicardipine – may inhibit labour; carries risk of maternal hypotension and fetal hypoxia;
- verapamil – may reduce uterine blood flow leading to fetal hypoxia; may also inhibit labour; advised by manufacturer against use in first trimester unless necessary; and
- furosemide – should not be used to treat gestational hypertension due to maternal hypovolaemia.

BNF indicates that the balance of risks and benefits should be considered for the following drug options:

- nifedipine
- amlodipine
- nimodipine
- prazosin
- sildenafil
- hydralazine.

Desirable effects

How substantial are the desirable anticipated effects of antihypertensive drug treatment for non-severe (mild to moderate) hypertension in pregnancy?

Judgement

☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☑ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of antihypertensive drug treatment for non-severe (mild to moderate) hypertension in pregnancy?

Judgement

☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☑ Small	☐ Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects?

☐ No included studies	☑ Very low	☐ Low	☐ Moderate	☐ High

Additional considerations

3. VALUES

Is there important uncertainty about, or variability in, how much women value the main outcomes associated with use of an antihypertensive drug treatment for non-severe (mild to moderate) hypertension in pregnancy?

Research evidence

In a qualitative systematic review *(23)*, evidence showed that women from high-, middle- and low-resource settings generally valued having a "positive pregnancy experience", achieved through three equally important antenatal care components – effective clinical practices (interventions and tests), relevant and timely information, and psychosocial and emotional support – each provided by practitioners with good clinical and interpersonal skills within a well functioning health system.

Additional considerations

Evidence from a qualitative systematic review of what women want from antenatal care showed that healthy pregnant women from high-, medium- and low-resource settings valued maintenance of optimal health for mother and baby *(23)*. A qualitative study of 30 women who had experienced pre-eclampsia in the UK (conducted in the context of developing a core outcome set for pre-eclampsia) reported that women value a range of outcomes relating to their childbirth experience, their physical and emotional health, as well as their child's physical health and future well-being *(35)*.

Hypertensive disorders in pregnancy can increase the risk of adverse outcomes to mother and baby, as well as increase the need for additional interventions. Considering these risks, the GDG considers it unlikely that there would be important variability in how women value this outcome.

Judgement

☐	☐	☑	☐
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement

☐ Don't know	☐ Varies	☐ Favours placebo/no treatment	☐ Probably favours placebo/no treatment	☐ Does not favour either	☑ Probably favours intervention	☐ Favours intervention

4. RESOURCES

How large are the resource requirements (costs) of antihypertensive drug treatment for non-severe (mild to moderate) hypertension in pregnancy?

Research evidence

The review did not pre-specify any economic outcomes. No direct evidence comparing the cost-effectiveness of different antihypertensive drug treatments for mild to moderate hypertension in pregnancy was identified.

Indirect evidence is available from a cost-effectiveness analysis of a multicountry randomized controlled trial of **"tight"** (target diastolic 85 mmHg) compared to **"less tight"** (target diastolic 100 mmHg) blood pressure control in pregnant women with **non-proteinuric** chronic or gestational hypertension *(28)*. Data on resource use were collected from 94 centres in 15 countries and costed as if the trial took place in Canada. The mean total cost per woman–infant dyad was higher in **"less tight"** versus **"tight"** control, although the difference in mean total cost was not statistically significant.

Presumably, there may be no significant increase in overall services and hospital costs when a mild to moderate hypertension is tightly controlled.

Antihypertensive drug prices

The MSH International Medical Products Price Guide reports the following unitary costs for antihypertensive drug options:[13]

Class	Drug	Median unitary price, 2015 ($US) *(25)*
Beta-blockers	Atenolol	0.0107 per 50 mg tablet
	Metoprolol	0.0444 per 100 mg tablet
	Propranolol	0.0365 per 10 mg tablet
Alpha-agonists	Methyldopa	0.0324 per 250 mg tablet
Calcium channel blockers	Amlodipine	0.0158 per 5 mg tablet
	Nifedipine	0.0332 per 10 mg tablet
	Nimodipine	0.0266 per 30 mg tablet
	Verapamil	0.0366 per 40 mg tablet
Alpha-blockers	Prazosin	0.0663 per 1 mg tablet
Direct vasodilators	Hydralazine	0.0407 per 25 mg tablet
Loop diuretic	Furosemide	0.0061 per 40 mg tablet

Main resource requirements

Resource	Description
Staff training	• Correct performance of blood pressure measurement • Recognition and treatment of mild to moderate hypertension • How to advise women on taking antihypertensive medications
Supplies	• Adequate supplies of antihypertensive drugs • Regular testing for proteinuria (dipstick)
Equipment	• Sphygmomanometer • Treatment algorithm
Infrastructure	–

Additional considerations

On the WHO Essential Medicines List (EML), the following drug options are listed under antihypertensive medications:

- methyldopa (250 mg tablet) only for the management of hypertension in pregnancy
- amlodipine (5 mg tablets as maleate, mesylate or besylate).

Other antihypertensive drug options are listed in the EML but for other indications:

- metoprolol (as an alternative to bisoprolol) and glyceryl trinitrate (500 mcg) under "12.1 Antianginal medicines"
- nifedipine (10 mg) under "22.2 tocolytics"
- verapamil (40 mg or 80 mg) under "12.2 Antiarrhythmic medicines".

[13] Antihypertensive drug options where a unitary price is not available in the MSH International Medical Products Price Guide are not reported.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☑ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☑ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Cost-effectiveness

Judgement

☑ Don't know	☐ Varies	☐ Favours placebo/no treatment	☐ Probably favours placebo/no treatment	☐ Does not favour either	☐ Probably favours treatment	☐ Favours treatment

5. EQUITY

What would be the impact of antihypertensive drug therapy on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

Amongst women with **non-severe (mild to moderate)** hypertension who participated in trials of any antihypertensive drug versus placebo or no treatment (Comparison 1), of those in the untreated (placebo or no treatment) arm:

- 19.8% of women experienced severe hypertension
- 18.5% of women experienced proteinuria/pre-eclampsia
- 7.6% of women experienced severe pre-eclampsia
- 1.4% of women experienced eclampsia.

It is likely that adverse consequences of mild or moderate hypertension in pregnancy are worse in women living in disadvantaged circumstances: the poorest, least educated and those residing in rural areas, with poor access to quality antenatal care *(37)*. Therefore, effective and equitable implementation of this intervention could reduce health inequities.

It is also possible that treating women with non-severe (mild to moderate) hypertension may lead to inequity, as disadvantaged women may be unable to procure the drug, which may not necessarily improve critical outcomes of their pregnancy.

Judgement

☑ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

6. ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

Research evidence

No direct evidence was identified on whether drug treatments for **non-severe (mild to moderate)** hypertension were acceptable to women or healthcare providers.

A qualitative evidence synthesis, exploring provision and uptake of routine antenatal services *(24)*, suggests that women tend to view antenatal care as a source of knowledge and information, and generally appreciate advice or interventions that may lead to a healthy baby and a positive pregnancy experience *(high confidence in the evidence)*. However, in some low-income settings, the indirect costs associated with procuring drugs and/or travelling to clinics for additional check-ups may restrict access *(high confidence in the evidence)*, and a reliance on traditional beliefs or practices to treat common pregnancy-related conditions may limit engagement in these contexts *(moderate confidence in the evidence).*

Additional considerations

This intervention involves taking an antihypertensive drug every day (multiple doses per day may be required). Women may not be aware of the potential risks of hypertension in pregnancy, which may also affect acceptability.

Several side-effects have been associated with antihypertensive drug options (see *Effects of interventions* section above) *(20)*. In the included trials, comparing any antihypertensive drug with placebo or no treatment (comparison 1), 14.7% of women taking any antihypertensive drug experienced some form of side-effect. Of the women taking beta-blockers (compared to placebo or no treatment), 11.8% of women experienced side-effects (there were insufficient data on the risk of side-effects for other drugs). Considering that elevated blood pressure alone is generally asymptomatic, these side-effects may limit the acceptability of taking antihypertensive drugs.

Women taking antihypertensive drugs for non-severe (mild to moderate) hypertension in pregnancy would also need to attend additional antenatal care visits for monitoring of blood pressure and proteinuria, and refilling of prescribed drugs. These additional visits, as well as any associated additional direct or indirect financial costs to the woman, may affect acceptability of the intervention.

Judgement

☐	☑	☐	☐	☐	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

7. FEASIBILITY

Is the intervention feasible to implement?

Research evidence

No direct evidence was identified on whether the use of drug treatments for non-severe (mild to moderate) hypertension was feasible for women or healthcare providers.

A qualitative evidence synthesis exploring provision and uptake of routine antenatal services *(24)* suggests that a lack of basic medical equipment (including blood pressure monitoring devices) and inconsistent supplies of pharmaceuticals may be an issue in some LMICs *(high confidence in the evidence)*. A lack of suitably trained staff may also be a problem, particularly in rural areas of LMICs *(moderate confidence in the evidence)*.

Additional considerations

This intervention involves taking an antihypertensive drug every day (multiple doses per day may be required) and would require additional antenatal care visits for blood pressure monitoring and additional prescriptions. Some women will experience side-effects; however, the type and frequency of side-effects will vary between antihypertensive drug options.

In settings where antihypertensive drug prescriptions and attending antenatal care visits carry additional direct or indirect costs to the woman, the feasibility of this intervention may be more limited. Feasibility may also be limited in settings where women have limited access to good-quality antenatal care services *(29)*.

In settings where antihypertensive drugs are not routinely prescribed for non-severe (mild to moderate) hypertension in pregnancy, routine implementation would require updates to relevant national guidelines and clinical protocols, ensuring staff are trained and supported, and ensuring sufficient supplies of antihypertensive drugs are available. Addressing these factors will likely increase the feasibility of this intervention.

Several antihypertensive drug options (amlodipine, methyldopa, metoprolol, nifedipine and verapamil) are listed on the WHO Essential Medicines List, and are also commonly found in essential medicine lists of many countries *(38)*, indicating that these drugs may be available to healthcare providers.

Judgement

☐ Don't know	☑ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

8. SUMMARY OF JUDGEMENTS TABLE

Desirable effects	– Don't know	– Varies		– Trivial	– Small	✓ **Moderate**	– Large
Undesirable effects	– Don't know	– Varies		– Large	– Moderate	✓ **Small**	– Trivial
Certainty of the evidence	– No included studies			✓ **Very low**	– Low	– Moderate	– High
Values				– Important uncertainty or variability	– Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	– No important uncertainty or variability
Balance of effects	– Don't know	– Varies	– Favours placebo/no treatment	– Probably favours placebo/no treatment	– Does not favour either	✓ **Probably favours intervention**	– Favours oxytocin
Resources required	– Don't know	– Varies	– Large costs	✓ **Moderate costs**	– Negligible costs or savings	– Moderate savings	– Large savings
Certainty of the evidence on required resources	✓ **No included studies**			– Very low	– Low	– Moderate	– High
Cost–effectiveness	✓ **Don't know**	– Varies	– Favours placebo/no treatment	– Probably favours placebo/no treatment	– Does not favour either	– Probably favours intervention	– Favours oxytocin
Equity	✓ **Don't know**	– Varies	– Reduced	– Probably reduced	– Probably no impact	– Probably increased	– Increased
Acceptability	– Don't know	✓ **Varies**		– No	– Probably No	– Probably Yes	– Yes
Feasibility	– Don't know	✓ **Varies**		– No	– Probably No	–	– Yes

References

1. Magee LA, Abalos E, von Dadelszen P, Sibai B, Easterling T, Walkinshaw S, et al. How to manage hypertension in pregnancy effectively. Br J Clin Pharmacol. 2011;72(3):394-401.
2. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015;372(5):407-17.
3. Malha L, Podymow T, Augus P. Hypertension in Pregnancy. In: Bakris GL, Sorrentino MJ, editors. Hypertension: A Companion to Braunwald's heart disease, third edition. 2018:361-73.
4. Trends in maternal mortality: 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2019.
5. Yamin AE, Maine DP. Maternal morality as a human rights issue: measuring compliance with international treaty obligations. Human Rights Quarterly. 1999;21:563.
6. Women's Rights are Human Rights. New York and Geneva: United Nations Office of the High Commissioner for Human Rights; 2014 (https://www.ohchr.org/Documents/Events/WHRD/WomenRightsAreHR.pdf)
7. United Nations High Commissioner for Human Rights. Technical guidance on the application of a human rights-based approach to the implementation of policies and programmes to reduce preventable maternal morbidity and mortality. Human Rights Council, twentieth session, New York: United Nations General Assembly; 2012.
8. Tunçalp Ö, Were W, MacLennan C, Oladapo O, Gülmezoglu A, Bahl R, et al. Quality of care for pregnant women and newborns – the WHO vision. BJOG. 2015;122(8):1045-9.
9. Campbell OM, Graham WJ, group LMSSs. Strategies for reducing maternal mortality: getting on with what works. Lancet. 2006;368(9543):1284-99.
10. Fisk NM, McKee M, Atun R. Relative and absolute addressability of global disease burden in maternal and perinatal health by investment. In: R&D. Trop Med & Int Health. 2011;16(6):662-8.
11. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-e33.
12. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: World Health Organization; 2011.
13. WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018.
14. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1-7.
15. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel J, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization multicountry survey on maternal and newborn health. BJOG. 2014;121:14-24.
16. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066-74.
17. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014.
18. Vogel JP, Dowswell T, Lewin S, Bonet M, Hampson L, Kellie F, et al. Developing and applying a "living guidelines" approach to WHO recommendations on maternal and perinatal health. BMJ Glob Health. 2019;4(4):e001683.
19. Executive Guideline Steering Group for updating WHO maternal and perinatal health recommendations (2017–2019). Geneva: World Health Organization; 2017 (http://www.who.int/reproductivehealth/publications/updating-mnh-recommendations/en/2017).

20. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018;10:Cd002252.

21. McMaster University, Evidence Prime Inc. GRADEpro GDT: GRADE your evidence and improve your guideline development in health care (https://gradepro.org/2015, available from: https://gradepro.org/).

22. Schünemann H, Brožek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013.

23. Downe S, Finlayson K, Tunçalp Ö, Metin Gülmezoglu A. What matters to women: a systematic scoping review to identify the processes and outcomes of antenatal care provision that are important to healthy pregnant women. BJOG. 2016;123(4):529-39.

24. Downe S, Finlayson K, Tunçalp Ö, Gülmezoglu AM. Provision and uptake of routine antenatal services: a qualitative evidence synthesis. Cochrane Database Syst Rev. 2019(6).

25. Management Sciences for Health. International medical products price guide. Management Sciences for Health; 2015 (http://mshpriceguide.org/en/home/).

26. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

27. Lewin S, Booth A, Glenton C, Munthe-Kaas H, Rashidian A, Wainwright M, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings: introduction to the series. Implement Sci. 2018;13(Suppl 1):2.

28. Ahmed RJ, Gafni A, Hutton EK, Hu ZJ, Pullenayegum E, von Dadelszen P, et al. The cost implications of less tight versus tight control of hypertension in pregnancy (CHIPS Trial). Hypertension. 2016;68(4):1049-55.

29. Arsenault C, Jordan K, Lee D, Dinsa G, Manzi F, Marchant T, et al. Equity in antenatal care quality: an analysis of 91 national household surveys. Lancet Glob Health. 2018;6(11):e1186-e95.

30. Guidelines for declarations of interest (WHO experts). Geneva: World Health Organization.

31. Managing complications in pregnancy and childbirth: a guide for midwives and doctors, second edition. Geneva: World Health Organization; 2017.

32. Standards for improving quality of maternal and newborn care in health facilities. Geneva: World Health Organization; 2016.

33. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2014(2):CD002252.

34. Joint Formulary Committee. British National Formulary 77 (March 2019). 2019.

35. Duffy J, Thompson T, Hinton L, Salinas M, McManus RJ, Ziebland S, et al. What outcomes should researchers select, collect and report in pre-eclampsia research? A qualitative study exploring the views of women with lived experience of pre-eclampsia. BJOG. 2019;126(5):637-46.

36. Kayser A, Beck E, Hoeltzenbein M, Zinke S, Meister R, Weber-Schoendorfer C, et al. Neonatal effects of intrauterine metoprolol/bisoprolol exposure during the second and third trimester: a cohort study with two comparison groups. Journal of Hypertension. 2020;38(2):354-61.

37. Arsenault C, Jordan K, Lee D, Dinsa G, Manzi F, Marchant T, et al. Equity in antenatal care quality: an analysis of 91 national household surveys. Lancet Glob Health. 2018;6(11):e1186-e95.

38. Persaud N, Jiang M, Shaikh R, Bali A, Oronsaye E, Woods H, et al. Comparison of essential medicines lists in 137 countries. Bull World Health Organ. 2019;97(6):394-404C.

GRADE tables

Question: Any antihypertensive drug compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital, urban antenatal clinics[14] (Australia, Brazil, Caribbean Islands, Hong Kong, India, Ireland, Israel, Italy, South Africa, Sudan, Sweden, UK, USA)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any antihypertensive drug	No antihypertensive drugs/placebo	Relative (95% CI)	Absolute (95% CI)		
Maternal death												
5	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	2/289 (0.7%)	1/236 (0.4%)	**RR 1.11** (0.18 to 7.02)	**0 fewer per 1000** (from 3 fewer to 26 more)	⨁◯◯◯ VERY LOW	PRIORITY
Eclampsia												
7	randomized trials	very serious[d]	not serious	not serious	very serious[b,c]	none	2/365 (0.5%)	5/348 (1.4%)	**RR 0.52** (0.13 to 2.06)	**7 fewer per 1000** (from 12 fewer to 15 more)	⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia												
3	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	8/231 (3.5%)	14/185 (7.6%)	**RR 0.56** (0.15 to 2.02)	**33 fewer per 1000** (from 64 fewer to 77 more)	⨁◯◯◯ VERY LOW	PRIORITY
Proteinuria/pre-eclampsia												
23	randomized trials	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[e]	251/1476 (17.0%)	255/1375 (18.5%)	**RR 0.92** (0.75 to 1.14)	**15 fewer per 1000** (from 46 fewer to 26 more)	⨁⨁◯◯ LOW	PRIORITY

[14] In some trials, the setting was not clearly described.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Any antihypertensive drug**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: severe hypertension												
20	randomized trials	serious[a]	not serious	not serious	not serious	none	125/1336 (9.4%)	242/1222 (19.8%)	**RR 0.49** (0.40 to 0.60)	**101 fewer per 1000** (from 119 fewer to 79 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Severe maternal morbidity: HELLP syndrome												
3	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	6/165 (3.6%)	6/167 (3.6%)	**RR 1.06** (0.32 to 3.50)	**2 more per 1000** (from 24 fewer to 90 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: pulmonary oedema												
2	randomized trials	very serious[d]	not serious	not serious	very serious[b,c]	none	4/185 (2.2%)	2/140 (1.4%)	**RR 1.22** (0.13 to 11.75)	**3 more per 1000** (from 12 fewer to 154 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: side-effects												
11	randomized trials	serious[a]	not serious	not serious	serious[f]	none	69/468 (14.7%)	39/466 (8.4%)	**RR 1.99** (0.89 to 4.43)	**83 more per 1000** (from 9 fewer to 287 more)	⨁⨁◯◯ LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects												
16	randomized trials	not serious	not serious	not serious	serious[f]	none	25/754 (3.3%)	9/749 (1.2%)	**RR 1.93** (0.92 to 4.06)	**11 more per 1000** (from 1 fewer to 37 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Any antihypertensive drug**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death												
22	randomized trials	serious[a]	not serious	not serious	serious[b]	none	33/1310 (2.5%)	37/1207 (3.1%)	**RR 0.89** (0.56 to 1.41)	**3 fewer per 1000** (from 13 fewer to 13 more)	⨁⨁◯◯ LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery												
10	randomized trials	serious[a]	not serious	not serious	not serious	none	226/796 (28.4%)	220/774 (28.4%)	**RR 1.01** (0.83 to 1.22)	**3 more per 1000** (from 48 fewer to 63 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal hypoglycaemia												
6	randomized trials	serious[a]	not serious	not serious	serious[g]	none	38/520 (7.3%)	48/442 (10.9%)	**RR 0.77** (0.51 to 1.15)	**25 fewer per 1000** (from 53 fewer to 16 more)	⨁⨁◯◯ LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal bradycardia												
3	randomized trials	serious[a]	serious[h]	not serious	serious[b]	none	27/208 (13.0%)	14/210 (6.7%)	**RR 1.28** (0.31 to 5.24)	**19 more per 1000** (from 46 fewer to 283 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal jaundice												
3	randomized trials	serious[a]	not serious	not serious	serious[g]	none	47/260 (18.1%)	62/269 (23.0%)	**RR 0.78** (0.53 to 1.15)	**51 fewer per 1000** (from 108 fewer to 35 more)	⨁⨁◯◯ LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Any antihypertensive drug**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Apgar score: very low (less than four) at five minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
b. Wide confidence interval including appreciable benefit for both antihypertensive drugs and placebo/no treatment.
c. Few events (< 30)
d. Most of pooled effect provided by studies with moderate or high risk of bias, but with a substantial proportion (> 50%) from studies with high risk of bias.
e. There is asymmetry in funnel plot, and substantial statistical heterogeneity (i^2 = 35%) which indicates possible publication bias favouring antihypertensive drugs.
f. Wide confidence interval crossing line of no difference between interventions, and including appreciable benefit for placebo/no treatment.
g. Wide confidence interval crossing line of no difference between interventions, and including appreciable benefit for antihypertensive drugs.
h. Severe, unexplained statistical heterogeneity ($i^2 \geq 60\%$), which could possibly be explained by differing interventions, however studies too few to conduct subgroup analysis.

Question: Beta-blockers compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital and urban antenatal clinics[15] (Brazil, Hong Kong, India, Israel, Sweden, UK, USA)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/26 (0.0%)	0/26 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Eclampsia												
2	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/128 (0.0%)	0/109 (0.0%)	not pooled	see comment	⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
8	randomized trials	serious[a]	not serious	not serious	not serious	none	73/433 (16.9%)	106/450 (23.6%)	**RR 0.74** (0.56 to 0.99)	**61 fewer per 1000** (from 104 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY

[15] In some trials, the setting was not clearly described.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: severe hypertension												
8	randomized trials	serious[a]	not serious	not serious	not serious	none	28/378 (7.4%)	76/384 (19.8%)	**RR 0.38** (0.26 to 0.57)	**123 fewer per 1000** (from 146 fewer to 85 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Severe maternal morbidity: pulmonary oedema												
1	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	2/86 (2.3%)	0/90 (0.0%)	**RR 5.23** (0.25 to 107.39)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: placental abruption												
3	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	2/182 (1.1%)	0/182 (0.0%)	**RR 5.11** (0.25 to 104.96)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal adverse effects of intervention: side-effects												
7	randomized trials	serious[a]	not serious	not serious	serious[c]	none	33/279 (11.8%)	9/275 (3.3%)	**RR 3.14** (0.66 to 15.02)	**70 more per 1000** (from 11 fewer to 459 more)	⨁⨁◯◯ LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects												
9	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	10/375 (2.7%)	4/370 (1.1%)	**RR 1.85** (0.61 to 5.57)	**9 more per 1000** (from 4 fewer to 49 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blockers	No antihypertensive drugs/placebo	Relative (95% CI)	Absolute (95% CI)		
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death												
9	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	4/477 (0.8%)	6/473 (1.3%)	**RR 0.79** (0.23 to 2.70)	**3 fewer per 1000** (from 10 fewer to 22 more)	⨁◯◯◯ VERY LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery												
3	randomized trials	serious[a]	not serious	not serious	serious[c]	none	66/215 (30.7%)	66/234 (28.2%)	**RR 1.07** (0.82 to 1.41)	**20 more per 1000** (from 51 fewer to 116 more)	⨁⨁◯◯ LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal hypoglycaemia												
2	randomized trials	not serious	not serious	not serious	very serious[c,d]	none	5/129 (3.9%)	7/132 (5.3%)	**RR 0.71** (0.13 to 3.83)	**15 fewer per 1000** (from 46 fewer to 150 more)	⨁⨁◯◯ LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal bradycardia												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,f]	none	26/129 (20.2%)	10/132 (7.6%)	**RR 2.20** (0.68 to 7.16)	**91 more per 1000** (from 24 fewer to 467 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal jaundice												
1	randomized trials	not serious	not serious	not serious	very serious[c,d]	none	5/70 (7.1%)	10/74 (13.5%)	**RR 0.53** (0.19 to 1.47)	**64 fewer per 1000** (from 109 fewer to 64 more)	⨁⨁◯◯ LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Apgar scores: very low (less than four) at five minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
b. No events, not estimable.
c. Wide confidence interval including both appreciable benefit and appreciable harm.
d. Few events, small sample size.
e. Few events.
f. Small sample size.

Question: Methyldopa compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital[16] (Sudan, UK, USA)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methyldopa**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/34 (0.0%)	0/36 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/34 (0.0%)	0/36 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[d,f]	none	3/34 (8.8%)	10/36 (27.8%)	**RR 0.32** (0.10 to 1.06)	**189 fewer per 1000** (from 250 fewer to 17 more)	⨁◯◯◯ VERY LOW	PRIORITY
Proteinuria/pre-eclampsia												
2	randomized trials	serious[a]	not serious	not serious	very serious[d,e]	none	11/130 (8.5%)	9/137 (6.6%)	**RR 1.21** (0.55 to 2.64)	**14 more per 1000** (from 30 fewer to 108 more)	⨁◯◯◯ VERY LOW	

[16] In some trials, the setting was not clearly described.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methyldopa**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: severe hypertension												
2	randomized trials	serious[a]	not serious	not serious	not serious	none	12/151 (7.9%)	40/159 (25.2%)	**RR 0.32** (0.17 to 0.58)	**171 fewer per 1000** (from 209 fewer to 106 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Severe maternal morbidity: placental abruption												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/34 (0.0%)	0/36 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	**-**	**-**	-	
Maternal adverse effects of intervention: side-effects												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/13 (0.0%)	0/12 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/13 (0.0%)	0/12 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death												
2	randomized trials	serious[a]	not serious	not serious	very serious[d,e]	none	4/47 (8.5%)	6/48 (12.5%)	**RR 0.71** (0.22 to 2.29)	**36 fewer per 1000** (from 98 fewer to 161 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methyldopa**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Admission to neonatal intensive care unit (NICU)/special nursery												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,g]	none	24/134 (17.9%)	16/138 (11.6%)	**RR 1.56** (0.88 to 2.78)	**65 more per 1000** (from 14 fewer to 206 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal jaundice												
1	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	27/100 (27.0%)	27/102 (26.5%)	**RR 1.02** (0.65 to 1.61)	**5 more per 1000** (from 93 fewer to 161 more)	⨁◯◯◯ VERY LOW	PRIORITY
Apgar scores: very low (less than four) at five minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
b. No events, not estimable.
c. Small sample size.
d. Small sample size, few events.
e. Wide confidence interval including both appreciable harm and appreciable benefit.
f. Wide confidence interval crossing line of no effect and line of appreciable benefit.
g. Wide confidence interval crossing line of no effect and line of appreciable harm.

Question: Calcium channel blockers compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital[17] (Brazil, Italy, Sweden, USA)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	0/58 (0.0%)	1/59 (1.7%)	**RR 0.34** (0.01 to 8.15)	**11 fewer per 1000** (from 17 fewer to 121 more)	⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia												
1	randomized trials	serious[d]	not serious	not serious	very serious[b,c]	none	4/98 (4.1%)	2/99 (2.0%)	**RR 2.02** (0.38 to 10.78)	**21 more per 1000** (from 13 fewer to 198 more)	⨁◯◯◯ VERY LOW	PRIORITY
Proteinuria/pre-eclampsia												
4	randomized trials	serious[d]	not serious	not serious	not serious	none	89/360 (24.7%)	65/365 (17.8%)	**RR 1.40** (1.02 to 1.92)	**71 more per 1000** (from 4 more to 164 more)	⨁⨁⨁◯ MODERATE	PRIORITY

[17] In some trials, the setting was not clearly described.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium channel blockers	No antihypertensive drugs/placebo	Relative (95% CI)	Absolute (95% CI)		
Severe maternal morbidity: severe hypertension												
4	randomized trials	serious[d]	not serious	not serious	serious[b]	none	58/330 (17.6%)	71/332 (21.4%)	**RR 0.81** (0.60 to 1.11)	**41 fewer per 1000** (from 86 fewer to 24 more)	⨁⨁◯◯ LOW	PRIORITY
Severe maternal morbidity: HELLP syndrome												
1	randomized trials	serious[d]	not serious	not serious	very serious[b,c]	none	4/98 (4.1%)	2/99 (2.0%)	**RR 2.02** (0.38 to 10.78)	**21 more per 1000** (from 13 fewer to 198 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: placental abruption												
1	randomized trials	serious[d]	not serious	not serious	very serious[b,c]	none	3/98 (3.1%)	2/99 (2.0%)	**RR 1.52** (0.26 to 8.87)	**11 more per 1000** (from 15 fewer to 159 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: side-effects												
1	randomized trials	serious[d]	not serious	not serious	very serious[b,e]	none	25/91 (27.5%)	27/94 (28.7%)	**RR 0.96** (0.60 to 1.52)	**11 fewer per 1000** (from 115 fewer to 149 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects												
2	randomized trials	very serious[a]	not serious	not serious	very serious[b,f]	none	3/149 (2.0%)	0/153 (0.0%)	**RR 4.02** (0.45 to 35.97)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Perinatal death												
3	randomized trials	serious[d]	not serious	not serious	very serious[b,f]	none	5/281 (1.8%)	4/281 (1.4%)	**RR 1.22** (0.34 to 4.45)	**3 more per 1000** (from 9 fewer to 49 more)	⨁◯◯◯ VERY LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery												
2	randomized trials	serious[d]	not serious	not serious	serious[b]	none	72/222 (32.4%)	62/227 (27.3%)	**RR 1.18** (0.87 to 1.62)	**49 more per 1000** (from 36 fewer to 169 more)	⨁⨁◯◯ LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal hypoglycaemia												
1	randomized trials	serious[d]	not serious	not serious	very serious[e,g]	none	16/90 (17.8%)	24/93 (25.8%)	**RR 0.69** (0.39 to 1.21)	**80 fewer per 1000** (from 157 fewer to 54 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal jaundice												
1	randomized trials	serious[d]	not serious	not serious	very serious[e,g]	none	15/90 (16.7%)	25/93 (26.9%)	**RR 0.62** (0.35 to 1.10)	**102 fewer per 1000** (from 175 fewer to 27 more)	⨁◯◯◯ VERY LOW	PRIORITY
Apgar scores: very low (less than four) at five minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but with a substantial proportion (> 50%) from studies with high risk of bias.
b. Wide confidence interval including both appreciable harm and appreciable benefit.
c. Small sample size, few events.
d. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
e. Small sample size.
f. Few events.
g. Wide confidence interval crossing line of no effect and including appreciable benefit.

Question: Alpha-blockers compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital (South Africa)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Alpha-blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	1/12 (8.3%)	5/20 (25.0%)	**RR 0.33** (0.04 to 2.52)	**167 fewer per 1000** (from 240 fewer to 380 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: severe hypertension												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/12 (0.0%)	11/20 (55.0%)	**RR 0.07** (0.00 to 1.09)	**511 fewer per 1000** (from -- to 50 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Alpha-blockers**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: placental abruption												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	2/12 (16.7%)	1/20 (5.0%)	**RR 3.33** (0.34 to 32.96)	**117 more per 1000** (from 33 fewer to 1000 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	**-**	**-**	-	PRIORITY
Maternal adverse effects of intervention: side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	2/11 (18.2%)	3/17 (17.6%)	**RR 1.03** (0.20 to 5.21)	**5 more per 1000** (from 141 fewer to 743 more)	⨁◯◯◯ VERY LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alpha-blockers	No antihypertensive drugs/placebo	Relative (95% CI)	Absolute (95% CI)		
Fetal/neonatal adverse effects of intervention – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Apgar scores: very low (less than four) at five-minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Effect provided by study with moderate risk of bias.
b. Small sample size, few events.
c. Wide confidence interval including both appreciable harm and appreciable benefit.

Question: Glyceryl trinitrate compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital[18] (Australia)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glyceryl trinitrate**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	1/7 (14.3%)	3/9 (33.3%)	**RR 0.43** (0.06 to 3.28)	**190 fewer per 1000** (from 313 fewer to 760 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidities – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

[18] The setting was not explicitly described, but the trial was probably conducted in a hospital.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glyceryl trinitrate**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	**-**	**-**	-	PRIORITY
Maternal adverse effects of intervention: side-effects												
1	randomized trials	serious[a]	not serious	not serious	serious[b,d]	none	7/7 (100.0%)	0/9 (0.0%)	**RR 18.75** (1.25 to 281.11)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects												
1	randomized trials	serious[a]	not serious	not serious	serious[b,d]	none	7/7 (100.0%)	0/9 (0.0%)	**RR 18.75** (1.25 to 281.11)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glyceryl trinitrate**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fetal/neonatal adverse effects of intervention: neonatal jaundice – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Apgar scores: very low (less than four) at five minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Effect provided by study with moderate risk of bias. Study stopped early due to side-effects (headaches) in intervention group.
b. Small sample size, few events.
c. Wide confidence interval including both appreciable harm and appreciable benefit.
d. Very wide confidence interval.

Question: Sildenafil compared to no antihypertensive drugs/placebo for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital (Brazil, UK)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sildenafil**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia												
2	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	2/67 (3.0%)	4/68 (5.9%)	**RR 0.57** (0.12 to 2.63)	**25 fewer per 1000** (from 52 fewer to 96 more)	⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe maternal morbidity: HELLP syndrome												
2	randomized trials	very serious[a]	not serious	not serious	very serious[b,d]	none	2/67 (3.0%)	4/68 (5.9%)	**RR 0.53** (0.10 to 2.97)	**28 fewer per 1000** (from 53 fewer to 116 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sildenafil**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: placental abruption												
2	randomized trials	serious[e]	not serious	not serious	very serious[b,d]	none	4/67 (6.0%)	2/68 (2.9%)	**RR 2.06** (0.39 to 10.75)	**31 more per 1000** (from 18 fewer to 287 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,d]	none	1/50 (2.0%)	2/50 (4.0%)	**RR 0.50** (0.05 to 5.34)	**20 fewer per 1000** (from 38 fewer to 174 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death												
2	randomized trials	very serious[a]	not serious	not serious	very serious[b,d]	none	3/67 (4.5%)	6/68 (8.8%)	**RR 0.51** (0.13 to 1.95)	**43 fewer per 1000** (from 77 fewer to 84 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sildenafil**	**No antihypertensive drugs/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Admission to neonatal intensive care unit (NICU)/special nursery												
2	randomized trials	very serious[a]	not serious	not serious	very serious[f,g]	none	33/50 (66.0%)	37/50 (74.0%)	**RR 0.89** (0.69 to 1.15)	**81 fewer per 1000** (from 229 fewer to 111 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal hypoglycaemia												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,d]	none	4/50 (8.0%)	5/50 (10.0%)	**RR 0.80** (0.23 to 2.81)	**20 fewer per 1000** (from 77 fewer to 181 more)	⨁◯◯◯ VERY LOW	PRIORITY
Apgar scores: very low (less than four) at five minutes – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but with a substantial proportion (> 50%) from studies with high risk of bias.
b. Wide confidence interval including both appreciable harm and appreciable benefit.
c. Few events.
d. Small sample size, few events.
e. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
f. Small sample size.
g. Wide confidence interval crossing line of no effect and also including appreciable harm.

Question: Beta-blockers compared to methyldopa for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital[19] (Argentina, Australia, Brazil, France, India, Israel, Pakistan, UK, USA, Venezuela)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia												
1	randomized trials	very serious[d]	not serious	not serious	very serious[e,f]	none	15/156 (9.6%)	13/155 (8.4%)	**RR 1.15** (0.56 to 2.33)	**13 more per 1000** (from 37 fewer to 112 more)	⨁◯◯◯ VERY LOW	PRIORITY
Proteinuria/pre-eclampsia												
10	randomized trials	serious[a]	not serious	not serious	serious[b]	none[c]	52/470 (11.1%)	64/433 (14.8%)	**RR 0.82** (0.58 to 1.16)	**27 fewer per 1000** (from 62 fewer to 24 more)	⨁⨁◯◯ LOW	PRIORITY

[19] In some trials, the setting was not clearly described.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blockers	Methyldopa	Relative (95% CI)	Absolute (95% CI)		
Severe maternal morbidity: severe hypertension												
9	randomized trials	serious[a]	not serious[g]	not serious	serious[b]	none	63/308 (20.5%)	83/284 (29.2%)	**RR 0.59** (0.33 to 1.05)	**120 fewer per 1000** (from 196 fewer to 15 more)	⨁⨁◯◯ LOW	PRIORITY
Severe maternal morbidity: placental abruption												
1	randomized trials	serious[a]	not serious	not serious	very serious[e,h]	none	2/86 (2.3%)	1/87 (1.1%)	**RR 2.02** (0.19 to 21.90)	**12 more per 1000** (from 9 fewer to 240 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: side-effects												
5	randomized trials	serious[a]	serious[i]	not serious	serious[e]	none	45/152 (29.6%)	65/150 (43.3%)	**RR 0.22** (0.02 to 2.09)	**338 fewer per 1000** (from 425 fewer to 472 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to side-effects												
4	randomized trials	serious[a]	not serious	not serious	very serious[e,h]	none	1/139 (0.7%)	0/133 (0.0%)	**RR 2.80** (0.12 to 67.91)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Total reported fetal or neonatal death (including miscarriage)												
16	randomized trials	serious[a]	not serious	not serious	serious[e]	none	19/660 (2.9%)	24/620 (3.9%)	**RR 0.80** (0.43 to 1.50)	**8 fewer per 1000** (from 22 fewer to 19 more)	⨁⨁◯◯ LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery												
4	randomized trials	serious[a]	not serious	not serious	serious[e]	none	57/295 (19.3%)	58/276 (21.0%)	**RR 0.92** (0.67 to 1.25)	**17 fewer per 1000** (from 69 fewer to 53 more)	⨁⨁◯◯ LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal hypoglycaemia												
5	randomized trials	serious[a]	not serious	not serious	very serious[e,f]	none	16/229 (7.0%)	11/210 (5.2%)	**RR 0.99** (0.47 to 2.05)	**1 fewer per 1000** (from 28 fewer to 55 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal bradycardia												
2	randomized trials	serious[a]	not serious	not serious	very serious[e,h]	none	1/73 (1.4%)	0/73 (0.0%)	**RR 3.00** (0.12 to 72.18)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blockers	Methyldopa	Relative (95% CI)	Absolute (95% CI)		
Fetal/neonatal adverse effects of intervention: neonatal jaundice												
2	randomized trials	serious[a]	not serious	not serious	very serious[e,h]	none	9/73 (12.3%)	9/73 (12.3%)	**RR 1.05** (0.48 to 2.29)	**6 more per 1000** (from 64 fewer to 159 more)	⨁◯◯◯ VERY LOW	PRIORITY
Apgar scores – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
b. Wide confidence interval crossing line of no difference and including appreciable benefit.
c. Possible asymmetry in funnel plot favouring beta-blockers. Because publication bias is hard to assess with only ten studies, and the pooled effect suggests no clear evidence of difference between interventions, the evidence was not downgraded for publication bias.
d. Most of pooled effect provided by studies with moderate or high risk of bias, but with a substantial proportion (> 50%) from studies with high risk of bias.
e. Wide confidence interval including both appreciable benefit and appreciable harm.
f. Few events.
g. Statistical heterogeneity (i^2 = 62%); however, the evidence has not been downgraded because this heterogeneity may be due to the pooled effect being drawn from many small studies (the evidence has been downgraded for imprecision).
h. Few events, small sample size.
i. Severe unexplained statistical heterogeneity (i^2 > 60%).

Question: Calcium channel blockers compared to methyldopa for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital[20] (India, Italy, South Africa)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium channel blockers	Methyldopa	Relative (95% CI)	Absolute (95% CI)		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/45 (0.0%)	0/47 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	10/43 (23.3%)	18/51 (35.3%)	**RR 0.66** (0.34 to 1.27)	**120 fewer per 1000** (from 233 fewer to 95 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: severe hypertension												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	1/23 (4.3%)	6/23 (26.1%)	**RR 0.23** (0.04 to 1.22)	**201 fewer per 1000** (from 250 fewer to 57 more)	⨁◯◯◯ VERY LOW	PRIORITY

[20] In some trials, the setting was not clearly described.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal adverse effects of intervention: side-effects												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/54 (0.0%)	0/56 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Total reported fetal or neonatal death (including miscarriage)												
4	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	1/124 (0.8%)	3/127 (2.4%)	**RR 0.31** (0.04 to 2.65)	**16 fewer per 1000** (from 23 fewer to 39 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Admission to neonatal intensive care unit (NICU)/special nursery												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	11/56 (19.6%)	10/61 (16.4%)	**RR 1.22** (0.56 to 2.64)	**36 more per 1000** (from 72 fewer to 269 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of interventions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Apgar scores – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
b. No events, small sample size. Not estimable.
c. Few events, small sample size.
d. Wide confidence interval including both appreciable harm and appreciable benefit.

Question: Ketanserin compared to methyldopa for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital[21] (Argentina)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketanserin	Methyldopa	Relative (95% CI)	Absolute (95% CI)		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe maternal morbidities – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

[21] The setting was not explicitly described but was likely conducted in a hospital.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: changed/stopped drugs due to maternal side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Total reported fetal or neonatal death (including miscarriage)												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	1/10 (10.0%)	0/10 (0.0%)	**RR 3.00** (0.14 to 65.90)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketanserin	Methyldopa	Relative (95% CI)	Absolute (95% CI)		
Fetal/neonatal adverse effects of interventions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Apgar scores – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Effect provided by study with moderate risk of bias.
b. Few events, small sample size.
c. Wide confidence interval including appreciable harm and appreciable benefit.

Question: Glyceryl trinitrate (GTN) compared to calcium channel blockers for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital (Italy)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glyceryl trinitrate (GTN)	Calcium channel blockers	Relative (95% CI)	Absolute (95% CI)		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	2/24 (8.3%)	1/12 (8.3%)	**RR 1.00** (0.10 to 9.96)	**0 fewer per 1000** (from 75 fewer to 747 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: severe hypertension												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	1/24 (4.2%)	0/12 (0.0%)	**RR 1.56** (0.07 to 35.67)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glyceryl trinitrate (GTN)**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal adverse effects of intervention: side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of intervention: changed/stopped drug due to side-effects												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	2/24 (8.3%)	0/12 (0.0%)	**RR 2.60** (0.13 to 50.25)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Total reported fetal or neonatal death (including miscarriage)												
1	randomized trials	very serious[a]	not serious	not serious	very serious[d]	none	0/24 (0.0%)	0/12 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glyceryl trinitrate (GTN)**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Admission to neonatal intensive care unit (NICU)/special nursery – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Fetal/neonatal adverse effects of interventions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Apgar scores – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Effect provided by study with high risk of bias.
b. Few events, small sample size.
c. Wide confidence interval including both appreciable harm and appreciable benefit.
d. Small sample size. No events, not estimable.

Question: Furosemide compared to calcium channel blockers for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital (Panama)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Furosemide**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	7/21 (33.3%)	4/20 (20.0%)	**RR 1.67** (0.57 to 4.83)	**134 more per 1000** (from 86 fewer to 766 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: severe hypertension												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,d]	none	8/21 (38.1%)	7/20 (35.0%)	**RR 1.09** (0.48 to 2.44)	**32 more per 1000** (from 182 fewer to 504 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Furosemide**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: placental abruption												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b,c]	none	2/21 (9.5%)	1/20 (5.0%)	**RR 1.90** (0.19 to 19.40)	**45 more per 1000** (from 41 fewer to 920 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal adverse effects of interventions: side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal adverse effects of interventions: changed/stopped drug due to side-effects – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Total reported fetal or neonatal death (including miscarriage)												
1	randomized trials	very serious[a]	not serious	not serious	very serious[e]	none	0/21 (0.0%)	0/20 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Furosemide	Calcium channel blockers	Relative (95% CI)	Absolute (95% CI)		
Fetal/neonatal adverse effects of intervention – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Apgar scores – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Effect provided by study with high risk of bias.
b. Few events, small sample size.
c. Wide confidence interval including both appreciable harm and appreciable benefit.
d. Wide confidence interval including appreciable harm and crossing line of no difference.
e. Small sample size, no events. Not estimable.

Question: Beta-blockers compared to calcium channel blockers for non-severe (mild to moderate) hypertension during pregnancy

Setting: Hospital (France, India, UK)

Bibliography: Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2018, Issue 10.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/55 (0.0%)	0/57 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/55 (0.0%)	0/57 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Severe pre-eclampsia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Proteinuria/pre-eclampsia												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	16/101 (15.8%)	18/103 (17.5%)	**RR 1.12** (0.24 to 5.23)	**21 more per 1000** (from 133 fewer to 739 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: severe hypertension												
1	randomized trials	serious[a]	not serious	not serious	very serious[e,f]	none	15/50 (30.0%)	7/50 (14.0%)	**RR 2.14** (0.96 to 4.80)	**160 more per 1000** (from 6 fewer to 532 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe maternal morbidity: HELLP syndrome												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	4/105 (3.8%)	2/107 (1.9%)	**RR 1.78** (0.38 to 8.20)	**15 more per 1000** (from 12 fewer to 135 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: pulmonary oedema												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/55 (0.0%)	0/57 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: placental abruption												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	0/105 (0.0%)	1/107 (0.9%)	**RR 0.35** (0.01 to 8.30)	**6 fewer per 1000** (from 9 fewer to 68 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal Intensive Care Unit (ICU) admissions – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal adverse effects of interventions: side-effects												
2	randomized trials	serious[a]	not serious	not serious	very serious[d,f]	none	27/105 (25.7%)	20/107 (18.7%)	**RR 1.40** (0.85 to 2.29)	**75 more per 1000** (from 28 fewer to 241 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention: changed/stopped drug due to side-effects												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	7/105 (6.7%)	5/107 (4.7%)	**RR 1.45** (0.49 to 4.30)	**21 more per 1000** (from 24 fewer to 154 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Maternal well-being – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Perinatal death – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Total reported fetal or neonatal death (including miscarriage)												
3	randomized trials	serious[a]	not serious	not serious	serious[c]	none	18/185 (9.7%)	22/187 (11.8%)	**RR 0.82** (0.46 to 1.46)	**21 fewer per 1000** (from 64 fewer to 54 more)	⨁⨁◯◯ LOW	PRIORITY
Admission to neonatal intensive care unit (NICU)/special nursery												
2	randomized trials	serious[a]	not serious	not serious	very serious[c,d]	none	17/101 (16.8%)	19/101 (18.8%)	**RR 0.88** (0.49 to 1.58)	**23 fewer per 1000** (from 96 fewer to 109 more)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal/neonatal adverse effects of intervention: neonatal hypoglycaemia												
1	randomized trials	serious[a]	not serious	not serious	very serious[c,e]	none	6/51 (11.8%)	8/52 (15.4%)	**RR 0.76** (0.29 to 2.05)	**37 fewer per 1000** (from 109 fewer to 162 more)	⨁◯◯◯ VERY LOW	PRIORITY
Apgar scores – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most of pooled effect provided by studies with moderate or high risk of bias, but without a substantial proportion (< 50%) from studies with high risk of bias.
b. Small sample size. No events, not estimable.
c. Wide confidence interval including both appreciable harm and appreciable benefit.
d. Small sample size.
e. Few events, small sample size.
f. Wide confidence interval crossing line of no effect and including appreciable harm.

For more information, please contact the following departments:

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