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Anna Cuthbert, Leanne Jones, Frances Kellie and Myfanwy Williams reviewed the scientific evidence, prepared the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tables and drafted the narrative summary of evidence. Joshua Vogel and Olufemi Oladapo revised the narrative summaries and double-checked the corresponding GRADE tables and prepared the Evidence-to-Decision frameworks. Joshua Vogel, Olufemi Oladapo, A. Metin Gülmezoglu, Ana Pilar Betrán, Özge Tuncalp and Mercedes Bonet commented on the draft document before it was reviewed by participants at the WHO Guideline Development Group meeting. The External Review Group peer reviewed the final document.

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Abbreviations

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 country
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health
MCSP	Maternal and Child Survival Programme
MPA	Maternal and Perinatal Health and Preventing Unsafe Abortion (a team in WHO's Department of Reproductive Health and Research)
MPH	Maternal and perinatal health
NNT	Number needed to treat
PICO	Population (P), intervention (I), comparison (C), outcome (O)
RHR	[WHO Department of] Reproductive Health and Research
RR	Relative risk
SDG	Sustainable Development Goals
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization

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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 2017, the Executive Guideline Steering Group (GSG) on WHO maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendations on antihypertensive drugs for severe hypertension in pregnancy in response to important new evidence on these interventions. These recommendations are a revalidation of the previous recommendations issued in 2011 in the *WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia.*

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, 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 recommendations; 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 evidence profiles for the prioritized question. WHO convened an online meeting on 2 May 2018 where an international group of experts – the Guideline Development Group (GDG) – reviewed and approved the recommendations.

The 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 revalidated the WHO recommendations published in 2011 with minor revisions to the 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: drug treatment for severe hypertension in pregnancy.

1. Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs (*strong recommendation, very low certainty evidence*)
Remarks • The guideline development group considered that there is no clinical uncertainty over whether treatment of severe hypertension during pregnancy is beneficial. This recommendation was made based on expert opinion; the group considered that most maternal deaths related to hypertensive disorders are associated with complications of uncontrolled severe high blood pressure. Based on that, the group agreed that antihypertensive treatment should be recommended in all cases of severe hypertension.
2. The choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost and local availability *(conditional recommendation, very low certainty evidence)*
Remarks • In terms of the choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, the guideline development group noted that not only is the evidence base for this recommendation limited, but also some antihypertensive drugs may not be feasible options in many settings. • The group acknowledged that hydralazine, alpha methyldopa, beta blockers (including labetalol) and nifedipine have been extensively used, and therefore, these agents would seem to be reasonable choices until further evidence becomes available. • The group noted that there was no evidence to suggest that nifedipine interacts adversely with magnesium sulfate. In addition, the group considered that the use of angiotensin- converting enzyme inhibitors, angiotensin receptor blockers and sodium nitroprusside should be avoided due to safety concerns.

1. Background

An estimated 303 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2015, around 99% of which occurred in low-resource settings *(1)*. Haemorrhage, hypertensive disorders and sepsis are responsible for more than half of all maternal deaths worldwide. Thus, improving the quality of maternal healthcare for women is a necessary step towards the achievement of the health targets of the Sustainable Development Goals (SDGs). International human rights law includes fundamental commitments by states to enable women and adolescent girls to survive pregnancy and childbirth as part of their enjoyment of sexual and reproductive health and rights and living a life of dignity *(2)*. The World Health Organization (WHO) envisions a world where "every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and the postnatal period" *(3)*.

There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications *(4)*. Almost two-thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings *(5)*. To provide good quality care, healthcare providers at all levels of maternal healthcare services (particularly in low and middle-income countries) need to have access to appropriate medications and training in relevant procedures. Healthcare providers, health managers, policymakers 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 *(6)*. In 2011, WHO published 22 recommendations for the prevention and treatment of pre-eclampsia and eclampsia, including two recommendations on the use and choice of antihypertensive drugs for the treatment of severe hypertension during pregnancy *(7)*. These recommendations were developed according to the 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.

Rationale and objectives

In 2017, WHO established a new process for prioritizing and updating maternal and perinatal health recommendations whereby an Executive Guideline Steering Group (GSG) oversaw a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating (8). Recommendations were prioritized on the basis of changes or important, new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized the updating of the existing WHO recommendations on antihypertensive drugs for severe hypertension during pregnancy in response to 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 severe hypertension in pregnancy globally.

Target audience

The primary audience of these recommendations includes healthcare providers 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, 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.

Scope of the recommendations

Framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format, the question directing these recommendations was:

- For women with severe 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 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 (9)*. 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 recommendations; and

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

WHO recommendations on the use of antihypertensive drugs for severe hypertension in pregnancy were identified by the Executive GSG as a high priority for updating in response to new, potentially important evidence on this question. 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 (Executive GSG)

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 *(10)*.

WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Reproductive Health and Research (RHR) and the Department of Maternal, Newborn, Child and Adolescent Health (MCA) managed the updating process. The 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 are identified in a way that ensures geographic representation and gender balance and there are no significant conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 16 external experts and relevant stakeholders were invited to constitute the Guideline Development Group (GDG) for updating these recommendations. Those selected were a diverse group of individuals with expertise in research, guideline development methods, and clinical policy and programmes relating to maternal and perinatal health.

In accordance with WHO guidelines, the GDG members were selected in a way that ensured geographic representation and gender balance and there were no important conflicts of interest The Group appraised the evidence that was used to inform the recommendations, advised on the interpretation of this evidence, formulated the final recommendations based on the draft prepared by the Steering Group, and reviewed and approved the final document. The members of this Group are listed in Annex 1.

External Review Group

This Group included eight technical experts with interest and expertise in the provision of evidence- based obstetric care. None of its members declared a conflict of interest. The Group reviewed the final document to identify any errors of fact and commented on the clarity of the language, contextual issues and implications for implementation. The Group ensured that the decision-making processes have considered and incorporated contextual values and preferences of potential users of the recommendations, healthcare providers and policy makers. They did not change the recommendations that were formulated by the GDG. The members of the External Review Group are presented in Annex 1.

Systematic review team and guideline methodologists

A Cochrane systematic review on this question was updated, supported by 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 Grading of

Recommendations Assessment, Development and Evaluation (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 Population Council participated in the GDG meeting as observers. These organizations, with a long history of collaboration with the RHR Department in guideline dissemination and implementation, are 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 (7)*. 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 recommendations. The list of outcomes is provided in Annex 2.

Evidence identification and retrieval

A Cochrane systematic review was updated by the Cochrane Pregnancy and Childbirth Group. This systematic review was the primary source of evidence for these recommendations.

Randomized controlled trials (RCT) relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were fed into Review Manager (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 recommendations 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. Finally, evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach *(11)*. 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 the majority 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, whether there were important differences between the research reported and the context for which the recommendations were 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

Formulation of recommendations

The WHO Steering Group used the evidence profiles to summarise evidence on effects on the pre- specified outcomes. The evidence summary and corresponding GRADE tables, other related documents for assessment of values and preferences, resource requirements and cost-effectiveness, acceptability, feasibility and equity were provided in advance to meeting participants, who were invited to submit their comments electronically in advance of the meeting.

The GDG members and other participants were then invited to attend an online GDG meeting (see Annex 1 for the list of participants) organized by the Steering Group on 2 May 2018. During the meeting, the GDG members reviewed and discussed the balance between the desirable and undesirable effects of the intervention and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity, before finalizing the recommendations and remarks.

Declaration of interests by external contributors

According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings. All GDG 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 meeting. The WHO Steering Group reviewed each declaration before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the Steering Group determined whether

such conflicts were serious enough to affect the expert's objective judgement on the guideline development process. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO Handbook for Guideline Development* to all participating experts. All findings from the received DOI statements were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare such conflict of interest at the beginning of the GDG meeting, and no further actions were taken.

Annex 3 shows a summary of the DOI statements, and how the conflicts of interest declared by the experts were managed by the Steering Group.

Decision-making during the Guideline Development Group 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 evidence-to-decision 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. Evidence-to-decision 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 deliberation of the GDG. The draft documents were made available to the participants of the meeting 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 a 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 and the External Review Group, the final document was sent to eight external independent experts 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 evidence-to-decision table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendations, is included in the evidence-to-decision framework (Annex 4).

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 5). 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.

Table 1: WHO recommendations: drug treatment for severe hypertension in pregnancy.

1. Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs *(strong recommendation, very low certainty evidence)*
Remarks • The guideline development group considered that there is no clinical uncertainty over whether treatment of severe hypertension during pregnancy is beneficial. This recommendation was made based on expert opinion; the group considered that most maternal deaths related to hypertensive disorders are associated with complications of uncontrolled severe high blood pressure. Based on that, the group agreed that antihypertensive treatment should be recommended in all cases of severe hypertension.
2. The choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost and local availability *(conditional recommendation, very low certainty evidence)*
Remarks • In terms of the choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, the guideline development group noted that not only is the evidence base for this recommendation limited, but also some antihypertensive drugs may not be feasible options in many settings. • The group acknowledged that hydralazine, alpha methyldopa, beta blockers (including labetalol) and nifedipine have been extensively used, and therefore, these agents would seem to be reasonable choices until further evidence becomes available. • The group noted that there was no evidence to suggest that nifedipine interacts adversely with magnesium sulfate. In addition, the group considered that 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).

Recommendation dissemination and evaluation

A shorter document containing the recommendations, remarks, implementation considerations and research priorities will be formulated for public dissemination. This document will have annexes (also made publicly available) containing all the information in this document, including methods, evidence-to-decision frameworks and GRADE tables.

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 be also 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 that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.

- In this process, the role of local 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 severe hypertension during pregnancy, to facilitate informed decision-making.

- Guidance on the management of severe hypertension in pregnancy, including doses and routes of administration, is available in the WHO handbook *Managing complications of pregnancy and childbirth* (Second edition) *(17)*.

5. Research implications

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

- The relative effectiveness of available drugs for severe acute hypertension, including effects on the fetus and newborn;
- Conducting further research to understand the relative importance that women with hypertension during pregnancy place on health outcomes, and their preferences regarding treatment options;
- The evaluation of interventions on how women can manage their own blood pressure during pregnancy (including diet, exercise and other interventions);
- The management of severe hypertension in pregnancy at primary and secondary level care (prior to referral to higher-level facility) in low-resource settings; and
- The evaluation of health education interventions for communicating with women who experience hypertension during pregnancy.

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 monitoring of women undergoing drug treatment for severe hypertension in pregnancy. The GDG noted that updating training curricula and providing training would increase impact and facilitate implementation. Standardization of care by including 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. For example, interrupted time series, clinical audits or criterion-based clinical audits can be used to obtain relevant data related to induction of labour. Clearly defined review criteria and indicators are needed; these could be associated with locally agreed targets. These 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 (18)*.

7. Updating the recommendations

The Executive GSG convenes regularly 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 and prioritized 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 are identified, the recommendations may be revalidated.

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

References

1. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2015.
2. Office of the 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.
3. Tunçalp Ö, Were WM, MacLennan C, Oladapo OT, Gülmezoglu AM, Bahl R, et al. Quality of care for pregnant women and newborns-the WHO vision. BJOG. 2015; 122(8): 1045-9.
4. Campbell OM, Graham WJ, Lancet Maternal Survival Series steering group. Strategies for reducing maternal mortality: getting on with what works. Lancet. 2006; 368(9543): 1284-99.
5. 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.
6. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2*(6)*: e323-33.
7. WHO recommendations for prevention and treatment pre-eclampsia and eclampsia. Geneva: World Health Organization; 2011.
8. 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).
9. WHO Handbook for Guideline Development (second edition). Geneva: World Health Organization; 2014.
10. 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/, accessed 7 December 2018).
11. 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.
12. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013 (7): CD001449.
13. 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.
14. State of inequality: Reproductive, maternal, newborn and child health. Geneva: World Health Organization; 2015.
15. Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ. 2012; 345: e3953.
16. Vogel JP, Moore JE, Timmings C, Khan S, Khan DN, Defar A, et al. Barriers, Facilitators and Priorities for Implementation of WHO Maternal and Perinatal Health Guidelines in Four Lower-Income Countries: A GREAT Network Research Activity. PLoS One. 2016; 11*(11)*: e0160020.
17. Managing complications in pregnancy and childbirth: a guide for midwives and doctors. Geneva: World Health Organization; 2017.
18. Standards for improving quality of maternal and newborn care in health facilities. Geneva: World Health Organization;2016.

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Annex 2. Priority outcomes for decision-making

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

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

Name		Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Edgardo	**ABALOS**	Content expert and end-user	None declared	Not applicable
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	Global Affairs Canada awarded a grant to Dr De-Regil's institution to implement nutrition interventions in low and middle-income countries. Some of the funded work included support for implementation research on calcium supplementation in pregnancy in Kenya and Ethiopia. The work was sub-granted to Cornell University, and Dr De-Regil was not part of the research team. As a former WHO staff member, she supported the development of a guideline on calcium supplementation in pregnancy (led by NHD).	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
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Anita	**MAEPIOH**	Content expert and end-user	None declared	Not applicable
James	**NEILSON**	Content expert and end-user	None declared	Not applicable
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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 preeclampsia 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

Annex 4. Evidence-to-decision framework

A) QUESTION

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

Problem: severe hypertension in pregnancy
Perspective: clinical practice recommendation – population perspective
Population: pregnant women with hypertension in pregnancy
Intervention: antihypertensive drug treatment
Comparison: other antihypertensive drugs
Outcomes: [1]

Maternal

- Persistent high blood pressure
- Eclampsia
- Recurrent seizures
- Severe maternal morbidity[2]
- Maternal death
- Adverse effects of interventions[3]

Fetal/Neonatal

- Apgar scores
- Admission to neonatal intensive care unit or special nursery
- Perinatal deaths

[1] These outcomes reflect the prioritized outcomes used in the WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (2011)
[2] including conditions such as maternal pulmonary oedema, haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, acute renal insufficiency, oliguria, disseminated intravascular coagulation, placental abruption, stroke, heart failure or other severe conditions
[3] These adverse effects vary depending on the drugs being investigated, but can include: hypotension, tachycardia, headache, nausea, vomiting, palpitations, chest pain, shortness of breath, flushing, visual symptoms, epigastralgia, dyspnoea, fetal heart decelerations, somnolence

B) ASSESSMENT

1. EFFECTS OF INTERVENTIONS

Research evidence

Summary of the evidence

Evidence related to the differential effects of various antihypertensive drugs when used for the treatment of very high blood pressure in pregnancy came from an updated Cochrane systematic review of 49 RCTs involving 4739 women, 42 of which, involving 4371 women, contributed data. This was an update of a previously published Cochrane review *(12)*. Most of the trials were relatively small and only eight of them recruited more than 100 women. Most of the women recruited had diastolic blood pressure of 100 mmHg or higher at trial entry. Trials contributing data were conducted in hospital settings in Argentina (1), Australia (2), Brazil (4), China (2), France (1), Germany (2), India (4), Iran (2), Malaysia (1), Mexico (3), the Netherlands (3), New Zealand (1), Panama (2), South Africa (8), Tunisia (1), Turkey (1), United Kingdom (1), United States (2), and one multi-centre trial took place in eight countries (Argentina, Brazil, Chile, Dominican Republic, Manila, South Africa, Turkey, United States).

The antihypertensive drugs investigated in these trials were hydralazine, calcium channel blockers (nifedipine, nimodipine, nicardipine and isradopine), labetalol, methyldopa, diazoxide, prostacyclin, ketanserin, urapidil, magnesium sulfate, prazosin, atenolol, and isosorbide. All drugs were administered intravenously, except for chlopromazine (intravenous [IV] and intramuscular [IM]), nifedipine (oral and sublingual) and prazosin (oral). In two older trials in which women were given atenolol, ketanserin, labetalol and methyldopa, routes of administration were not reported although the dosing regimens are suggestive of oral route. Hydralazine was compared with another drug in 6 out of the 17 comparisons in the review. There were considerable variations between the studies regarding antihypertensive drug dosages.

In summary, the analysis of the evidence related to the multiple comparisons of antihypertensive drugs for very high hypertension during pregnancy is complicated by the evidence's low quality which is due primarily to the small samples used in the trials, rare events as outcomes and variations in the administered drug regimens. Hydralazine is the most studied drug, though in the comparison with calcium channel blockers (nifedipine and isradipine) the latter have been associated with a greater reduction in the risk of persistent high blood pressure.

IV labetalol versus IV hydralazine

Maternal outcomes

There were no events in either labetalol or hydralazine groups for several outcomes, that were all very low certainty evidence: **maternal death**, **eclampsia**, **serious morbidities in women (**including **acute renal insufficiency** and **disseminated intravascular coagulation)**.

Persistent high blood pressure: It is uncertain whether labetalol reduces persistent high blood pressure when compared with hydralazine because the certainty of the evidence is very low.

HELLP syndrome: It is uncertain whether labetalol reduces the incidence of haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome when compared with hydralazine because the certainty of this evidence is very low.

Serious morbidity in women: oliguria: It is uncertain whether labetalol reduces the incidence of oliguria when compared with hydralazine because the certainty of the evidence is very low.

Serious morbidity in women: pulmonary oedema: It is uncertain whether labetalol reduces the incidence of pulmonary oedema when compared with hydralazine because the certainty of the evidence is very low.

Placental abruption: It is uncertain whether labetalol reduces the incidence of placental abruption when compared with hydralazine because the certainty of the evidence is very low.

Hypotension: It is uncertain whether labetalol reduces hypotension when compared with hydralazine because the certainty of the evidence is very low.

Side effects in women: It is uncertain whether labetalol reduces the incidence of any **side effects** when compared with hydralazine because the certainty of the evidence is very low, including **headaches, visual symptoms, epigastralgia, palpitations, nausea, flushing** and **emesis**.

Infant outcomes

Fetal or neonatal deaths: It is uncertain whether labetalol reduces the incidence of fetal or neonatal death when compared with hydralazine because the certainty of the evidence is very low.

Apgar score less than 7 at one minute: It is uncertain whether labetalol improves Apgar scores at one minute when compared with hydralazine because the certainty of the evidence is very low.

Apgar score less than 7 at five minutes: It is uncertain whether labetalol improves Apgar scores at five minutes when compared with hydralazine because the certainty of the evidence is very low.

Fetal heart rate decelerations: It is uncertain whether labetalol reduces fetal heart rate decelerations when compared with hydralazine because the certainty of the evidence is very low.

Admission to special care baby unit: It is uncertain whether labetalol reduces admissions to special care baby units when compared with hydralazine because the certainty of the evidence is very low.

Calcium channel blockers (oral or sublingual nifedipine, or IV isradipine) versus IV hydralazine

Maternal outcomes

Maternal death: There were no maternal deaths in either group (one trial, 60 women; 0/30 vs 0/30; effect not estimable; low-certainty evidence).

Persistent high blood pressure: Moderate certainty evidence suggests that calcium channel blockers probably reduce persistent high blood pressure at a greater rate than hydralazine (six trials, 313 women; 13/160 vs 34/153; RR 0.37, 95% CI 0.21 to 0.66).

Further episodes of very high blood pressure: It is uncertain whether calcium channel blockers reduce further episodes when compared with hydralazine because the certainty of the evidence is very low.

Hypotension: It is uncertain whether calcium channel blockers reduce hypotension when compared with hydralazine because the certainty of the evidence is very low.

Side-effects in women: It is uncertain whether calcium channel blockers reduce any **side effects** when compared with hydralazine because the certainty of the evidence is very low, as for **headaches, nausea, vomiting or both, palpitations** and **flushing**. Low-certainty evidence suggests little or no difference in the incidence of **dyspnoea** between the calcium channel blocker and hydralazine groups (one trial, 37 women; 1/20 vs 1/17; RR 0.85, 95% CI 0.06 to 12.59; low-certainty evidence), and little or no difference in the incidence of **tachycardia** between the calcium channel blocker and hydralazine groups (one trial, 60 women; 2/30 vs 0/30; RR 5.00, 95% CI 0.25 to 99.95; low-certainty evidence).

Infant outcomes

Fetal or neonatal death: It is uncertain whether calcium channel blockers reduce the incidence of fetal or neonatal death when compared with hydralazine because the certainty of the evidence is very low.

Apgar scores less than 7 at 5 minutes: Low-certainty evidence suggests little or no difference between the calcium channel blocker and hydralazine groups (two trials, 110 infants; 2/55 vs 1/55; RR 2.00, 95% CI 0.19 to 20.90).

Fetal heart rate decelerations: It is uncertain whether labetalol reduces fetal heart rate decelerations when compared with hydralazine because the certainty of the evidence is very low (four trials, 274 infants; 9/141 vs 10/133; RR 0.80, 95% CI 0.13 to 4.95).

Admission to neonatal intensive care unit: Low-certainty evidence suggests little or no difference between the calcium channel blocker and hydralazine groups (one trial, 60 infants; 2/30 vs 1/30; RR 2.00, 95% CI 0.19 to 20.90).

IV prostacyclin versus IV hydralazine

Maternal outcomes

Persistent high blood pressure: It is uncertain whether prostacyclin reduces persistent high blood pressure when compared with hydralazine because the certainty of the evidence is very low.

Side-effects in women: It is uncertain whether prostacyclin reduces side effects when compared with hydralazine because the certainty of the evidence is very low.

Infant outcomes

Neonatal death: It is uncertain whether prostacyclin reduces neonatal death when compared with hydralazine because the certainty of the evidence is very low.

IV ketanserin versus IV hydralazine

Maternal outcomes

Maternal death: It is uncertain whether ketanserin reduces maternal death when compared with hydralazine because the certainty of the evidence is very low.

Eclampsia: It is uncertain whether ketanserin reduces eclampsia when compared with hydralazine because the certainty of the evidence is very low.

Persistent high blood pressure: Low-certainty evidence suggests that ketanserin may increase the incidence of persistent high blood pressure (four trials, 210 women; 37/111 vs 7/99; RR 4.99, 95% CI 2.37 to 10.48).

Severe maternal morbidity: It is uncertain whether ketanserin reduces severe maternal morbidity when compared with hydralazine because the certainty of the evidence is very low.

HELLP syndrome: It is uncertain whether ketanserin reduces the incidence of HELLP syndrome when compared with hydralazine because the certainty of the evidence is very low.

Serious morbidity in women: disseminated intravascular coagulation: It is uncertain whether ketanserin reduces disseminated intravascular coagulation when compared with hydralazine because the certainty of the evidence is very low.

Serious morbidity in women: pulmonary oedema: It is uncertain whether ketanserin reduces pulmonary oedema when compared with hydralazine because the certainty of the evidence is very low.

Hypotension: Low-certainty evidence suggests ketanserin may slightly reduce hypotension when compared with hydralazine (three trials, 106 women; 4/57 vs 11/49; RR 0.34, 95% CI 0.12 to 0.93).

Placental abruption: It is uncertain whether ketanserin reduces placental abruption when compared with hydralazine because the certainty of the evidence is very low.

Side-effects for woman: Low-certainty evidence suggests ketanserin may reduce side-effects when compared with hydralazine (three trials, 120 women; 13/64 vs 36/56; RR 0.32, 95% CI 0.19 to 0.53).

Low-certainty evidence suggests little or no difference between the ketanserin and hydralazine groups for specific side-effects: **headaches** (one trial, 30 women; 4/15 vs 6/15; RR 0.67, 95% CI 0.23 to 1.89), **nausea, vomiting or both** (one trial, 30 women; 0/15 vs 6/15; RR 0.08, 95% CI 0.00 to 1.25), **palpitations** (one trial, 30 women; 4/15 vs 5/15; RR 0.80, 95% CI 0.27 to 2.41), **tachycardia** (one trial, 30 women; 1/15 vs 6/15; RR 0.17, 95% CI 0.02 to 1.22), **diarrhoea** (one trial, 30 women; 1/15 vs 2/15; RR 0.50, 95% CI 0.05 to 4.94), **tiredness** (one trial, 30 women; 6/15 vs 8/15; RR 0.75, 95% CI 0.34 to 1.64), **sleepiness** (one trial, 30 women; 7/15 vs 9/15; RR 0.78, 95% CI 0.39 to 1.54), **dry mouth** (one trial, 30 women; 9/15 vs 5/15; RR 1.80, 95% CI 0.79 to 4.11), or **stuffy nose** (one trial, 30 women; 9/15 vs 7/15; RR 1.29, 95% CI 0.65 to 2.54).

Infant outcomes

Perinatal death: It is uncertain whether ketanserin reduces perinatal death when compared with hydralazine because the certainty of the evidence is very low.

Side-effects – neonatal hypotension: Low certainty evidence suggests little or no difference between the ketanserin and hydralazine groups (one trial, 27 infants; 4/12 vs 1/15; RR 5.00, 95% CI 0.64 to 39.06).

IV urapidil versus IV hydralazine

Maternal outcomes

Eclampsia: There were no eclampsia cases in either group (one study, 26 women; 0/13 vs 0/13; effect not estimable; *very low certainty evidence*).

Persistent high blood pressure: It is uncertain whether urapidil reduces persistent high blood pressure when compared with hydralazine because the certainty of the evidence is very low.

Hypotension: It is uncertain whether urapidil reduces hypotension when compared with hydralazine because the certainty of the evidence is very low.

Side-effects in women: It is uncertain whether urapidil is associated with fewer side-effects when compared with hydralazine because the certainty of the evidence is very low.

Placental abruption: It is uncertain whether urapidil reduces placental abruption when compared with hydralazine because the certainty of the evidence is very low.

Infant outcomes

Stillbirth: There were no stillbirths in either group (one study, 26 infants; 0/13 vs 0/13; effect not estimable; *very low certainty evidence*).

Neonatal death: It is uncertain whether urapidil reduces neonatal death when compared with hydralazine because the certainty of the evidence is very low.

IV labetalol versus calcium channel blockers (oral nifedipine or IV nicardopine)

Maternal outcomes

Maternal death: There were no maternal deaths in either group (one trial, 100 women; 0/50 vs 0/50; effect not estimable; *low-certainty evidence*).

Eclampsia: It is uncertain whether labetalol reduces eclampsia when compared with calcium channel blockers because the certainty of the evidence is very low.

Stroke: Low certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (one trial, 100 women; 2/50 vs 1/50; RR 2.00, 95% CI 0.19 to 21.36).

Persistent high blood pressure: It is uncertain whether labetalol reduces persistent high blood pressure when compared with calcium channel blockers because the certainty of the evidence is very low.

Any serious morbidity: heart failure: Low-certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (one trial, 100 women; 1/50 vs 1/50; RR 1.00, 95% CI 0.06 to 15.55).

Hypotension: There were no cases of hypotension in either group (five studies, 337 women; 0/168 vs 0/169; effect not estimable; *very low certainty evidence*).

Side-effects for woman: It is uncertain whether labetalol is associated with fewer **side-effects** when compared with calcium channel blockers because the certainty of the evidence is very low, including for **mild headache, nausea, vomiting or both, moderate tachycardia, tachycardia,** and **dizziness**.

There were no incidences of **palpitations** (one study, 60 women; 0/30 vs 0/30; effect not estimable; *very low certainty evidence*), **chest pain** (one study, 147 women; 0/73 vs 0/74; effect not estimable; *very low certainty evidence*), or **shortness of breath** (one study, 147 women; 0/73 vs 0/74; effect not estimable; *very low certainty evidence*).

Postpartum haemorrhage (500ml or more): Low-certainty evidence suggests that labetalol may reduce postpartum haemorrhage when compared with calcium channel blockers (one trial, 120 women; 2/60 vs 15/60; RR 0.13, 95% CI 0.03 to 0.56).

Admission to intensive care: Low-certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (one trial, 50 women; 2/25 vs 0/25; RR 5.00, 95% CI 0.25 to 99.16).

Infant outcomes

Perinatal death: Low-certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (one trial, 60 infants; 2/30 vs 0/30; RR 5.00, 95% CI 0.25 to 99.95).

Apgar score less than 7 at 5 minutes: Low certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (four trials, 427 infants; 24/213 vs 25/214; RR 1.02, 95% CI 0.40 to 2.62).

Side-effects associated with the drug – fetal heart rate (FHR) abnormality: Low certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (one trial, 100 infants; 3/50 vs 6/50; RR 0.50, 95% CI 0.13 to 1.89).

Admission to special care baby unit: Low-certainty evidence suggests little or no difference between the labetalol and calcium channel blocker groups (three trials, 210 infants; 11/105 vs 6/105; RR 1.83, 95% CI 0.71 to 4.75).

Labetalol versus methyldopa (route unclear but dosing regimens suggestive of oral route)

Maternal outcomes

Persistent high blood pressure: It is uncertain whether labetalol reduces persistent high blood pressure when compared with methyldopa because the certainty of the evidence is very low.

Changed drugs due to side-effects: It is uncertain whether labetalol is associated with changes in drugs due to side effects when compared with methyldopa because the certainty of the evidence is very low.

Infant outcomes

Stillbirth: There were no stillbirths in either group (one study, 72 infants; 0/38 vs 0/34; effect not estimable; *very low certainty evidence*).

Neonatal death: It is uncertain whether labetalol reduces neonatal death when compared with methyldopa because the certainty of the evidence is very low.

Admission to special care baby unit: It is uncertain whether labetalol reduces admissions to special care baby units when compared with methyldopa because the certainty of the evidence is very low.

IV labetalol versus IV diazoxide

Maternal outcomes

Persistent high blood pressure: It is uncertain whether labetalol reduces persistent high blood pressure when compared with diazoxide because the certainty of the evidence is very low.

Hypotension: It is uncertain whether labetalol reduces hypotension when compared with diazoxide because the certainty of the evidence is very low.

Infant outcomes

Perinatal deaths: It is uncertain whether labetalol reduces perinatal death when compared with diazoxide because the certainty of the evidence is very low.

Nitrates versus magnesium sulfate

Maternal outcomes

Eclampsia: There were no cases of eclampsia in either group (one trial, 36 women; 0/18 vs 0/18; effect not estimable; *very low certainty evidence*).

Persistent high blood pressure: It is uncertain whether nitrates reduces persistent high blood pressure when compared with magnesium sulfate because the certainty of the evidence is very low.

Oral or IV nimodipine versus IV magnesium sulfate

Maternal outcomes

Eclampsia: Low-certainty evidence suggests little or no difference between the nimodipine and magnesium sulfate groups (two trials, 1683 women; 21/837 vs 9/846; RR 1.03, 95% CI 0.07 to 16.03).

Stroke: There were no cases of stroke in either group (one trial, 1650 women; 0/819 vs 0/831; effect not estimable; *low-certainty evidence*).

Persistent high blood pressure: Moderate certainty evidence suggests that nimodipine probably slightly reduces persistent high blood pressure compared with magnesium sulfate (one trial, 1650 women; 374/819 vs 451/831; RR 0.84, 95% CI 0.76 to 0.93).

Coagulopathy in women: It is uncertain whether nimodipine reduces coagulopathy when compared with magnesium sulfate because the certainty of the evidence is very low.

Serious morbidity in women: oliguria: Low certainty evidence suggests little or no difference between the nimodipine and magnesium sulfate groups (one trial, 1650 women; 47/819 vs 55/831; RR 0.87, 95% CI 0.59 to 1.26).

Hypotension: It is uncertain whether nimodipine reduces hypotension when compared with magnesium sulfate because the certainty of the evidence is very low.

Postpartum haemorrhage: Low-certainty evidence suggests nimodipine may slightly reduce the incidence of postpartum haemorrhage when compared with magnesium sulfate (one trial, 1650 women; 8/819 vs 20/831; RR 0.41, 95% CI 0.18 to 0.92).

Placental abruption: It is uncertain whether nimodipine reduces placental abruption when compared with magnesium sulfate because the certainty of the evidence is very low.

Respiratory difficulty in women: Low certainty evidence suggests nimodipine may slightly reduce the incidence of respiratory difficulty when compared with magnesium sulfate (one trial, 1650 women; 3/819 vs 11/831; RR 0.28, 95% CI 0.08 to 0.99).

Side-effects in women: Moderate certainty evidence suggests nimodipine probably slightly reduces all (unspecified) **side-effects** when compared with magnesium sulfate (one trial, 1650 women; 109/819 vs 162/831; RR 0.68, 95% CI 0.55 to 0.85) and **flushing** is probably also reduced by nimodipine (one trial, 1650 women; 13/819 vs 59/831; RR 0.22, 95% CI 0.12 to 0.40).

There was little or no difference between the nimodipine and magnesium sulfate groups in **nausea, vomiting or both** (one trial, 1650 women; 49/819 vs 58/831; RR 0.86, 95% CI 0.59 to 1.24; low certainty evidence), and it is uncertain whether nimodipine reduces **headaches** when compared with magnesium sulfate because the certainty of the evidence is very low (one trial, 1650 women; 47/819 vs 45/831; RR 1.06, 95% CI 0.71 to 1.58).

Infant outcomes

Side-effects in babies - low blood pressure: It is uncertain whether nimodipine reduces low blood pressure when compared with magnesium sulfate because the certainty of the evidence is very low.

Oral nifedipine versus oral prazosin

Maternal outcomes

Maternal death: It is uncertain whether nifedipine reduces maternal death when compared with prazosin because the certainty of the evidence is very low.

Eclampsia: There were no cases of eclampsia in either group (one trial, 145 women; 0/74 vs 0/71; effect not estimable; *very low certainty evidence*).

HELLP syndrome: It is uncertain whether nifedipine reduces the incidence of HELLP syndrome when compared with prazosin because the certainty of the evidence is very low.

Renal failure: It is uncertain whether nifedipine reduces the incidence of renal failure when compared with prazosin because the certainty of the evidence is very low.

Pulmonary oedema: It is uncertain whether nifedipine reduces pulmonary oedema when compared with prazosin because the certainty of the evidence is very low.

Placental abruption: It is uncertain whether nifedipine reduces the incidence of placental abruption when compared with prazosin because the certainty of the evidence is very low.

Admission to intensive care: It is uncertain whether nifedipine reduces admissions to intensive care when compared with prazosin because the certainty of the evidence is very low.

Infant outcomes

Stillbirth: It is uncertain whether nifedipine reduces the incidence of stillbirth when compared with prazosin because the certainty of the evidence is very low.

Admission to special care baby unit: It is uncertain whether nifedipine reduces admissions to special care baby units when compared with prazosin because the certainty of the evidence is very low.

Sublingual nifedipine versus IV and IM chlorpromazine

Maternal outcomes

Eclampsia: It is uncertain whether nifedipine reduces the incidence of eclampsia when compared with chlorpromazine because the certainty of the evidence is very low.

Persistent high blood pressure: It is uncertain whether nifedipine reduces the incidence of persistent high blood pressure when compared with chlorpromazine because the certainty of the evidence is very low.

IV hydralazine versus IV diazoxide

Infant outcomes

Perinatal death: It is uncertain whether hydralazine reduces the incidence of perinatal death when compared with diazoxide because the certainty of the evidence is very low.

Stillbirth: It is uncertain whether hydralazine reduces the incidence of stillbirth when compared with diazoxide because the certainty of the evidence is very low.

Neonatal death: It is uncertain whether hydralazine reduces the incidence of neonatal death when compared with diazoxide because the certainty of the evidence is very low.

Apgar score less than 7 at 5 minutes: It is uncertain whether hydralazine is associated with fewer babies with Apgar scores of less than 7 at 5 minutes when compared with diazoxide because the certainty of the evidence is very low.

Methyldopa versus atenolol (routes unclear but dosing regimens suggestive of oral route)

Maternal outcomes

Side-effects in women: somnolence: Low-certainty evidence suggests methyldopa might slightly increase the incidence of somnolence (one trial, 60 women; 10/30 vs 0/30; RR 21.00, 95% CI 1.29 to 342.93).

Infant outcomes

Stillbirth: It is uncertain whether methyldopa reduces the incidence of stillbirth when compared with atenolol because the certainty of the evidence is very low.

Neonatal death: It is uncertain whether methyldopa reduces the incidence of neonatal death when compared with atenolol because the certainty of the evidence is very low.

Side-effects in babies: There were no cases of neonatal side-effects in either group (one trial, 60 infants; 0/30 vs 0/30; effect not estimable; *very low certainty evidence*).

Methyldopa versus ketanserin (routes unclear but dosing regimens suggestive of oral route)

Maternal outcomes

Side-effects in women: somnolence: Low-certainty evidence suggests methyldopa might slightly increase the incidence of somnolence (one trial, 60 women; 10/30 vs 0/30; RR 21.00, 95% CI 1.29 to 342.93).

Infant outcomes

Stillbirth: It is uncertain whether methyldopa reduces the incidence of stillbirth when compared with ketanserin because the certainty of the evidence is very low.

Neonatal death: It is uncertain whether methyldopa reduces the incidence of stillbirth when compared with ketanserin because the certainty of the evidence is very low.

Side-effects in babies: There were no cases of neonatal side-effects in either group (one trial, 60 infants; 0/30 vs 0/30; effect not estimable; *very low certainty evidence*).

Ketanserin versus atenolol (routes unclear but dosing regimens suggestive of oral route)

Maternal outcomes

Side-effects in women: somnolence: There were no cases of somnolence in either group (one trial, 60 women; 0/30 vs 0/30; effect not estimable; very low certainty evidence).

Infant outcomes

Stillbirth: It is uncertain whether ketanserin reduces the incidence of stillbirth when compared with atenolol because the certainty of the evidence is very low.

Neonatal death: It is uncertain whether ketanserin reduces the incidence of neonatal death when compared with atenolol because the certainty of the evidence is very low.

Side-effects in babies: There were no cases of neonatal side-effects in either group (one trial, 60 infants; 0/30 vs 0/30; effect not estimable; *very low certainty evidence*).

IV urapidil versus calcium channel blockers (IV nicardipine)

Maternal outcomes

Side-effects in women: It is uncertain whether urapidil is associated with fewer side-effects when compared with calcium channel blockers because the certainty of the evidence is very low.

Infant outcomes

Side-effects in babies: There were no cases of neonatal side-effects in either group (one trial, 18 infants; 0/9 vs 0/9; effect not estimable; *very low certainty evidence*).

Desirable effects

How substantial are the desirable anticipated effects of antihypertensive drug treatment for severe 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 severe hypertension in pregnancy?

Judgement

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

Certainty of the evidence

What is the overall certainty of the evidence of effects?

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

Additional considerations

None.

Values

Is there important uncertainty about, or variability in, how much women value the main outcomes associated with the choice of an antihypertensive drug treatment for severe hypertension in pregnancy?

Research evidence

No direct evidence.

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 *(13)*. No studies were identified on the values and preferences of pregnant women with severe hypertension, with regards to the choice of antihypertensive drugs.

A diagnosis of severe hypertension in pregnancy can increase the risk of adverse outcomes to mother and baby, as well as increase the need for of additional interventions and hospital admission. 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 the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention

2. RESOURCES

How large are the resource requirements (costs) of antihypertensive drug treatment for severe hypertension in pregnancy?

Research evidence

The Cochrane review had pre-specified economic outcomes, however none of the studies included reported data on these outcomes. No direct evidence on the cost-effectiveness of antihypertensive drug treatments for severe hypertension in pregnancy was identified.

Main resource requirements

Resource	Description
Staff training	• Correct performance of blood pressure measurement • Recognition and treatment of severe hypertension • Administration and monitoring of IV drugs and infusions, and IV-line maintenance
Supplies	• Adequate supplies of antihypertensive drugs • Regular testing for proteinuria (dipstick) • Intravenous lines, syringes, needles, normal saline for injection
Equipment	• Sphygmomanometer • Treatment algorithm • Pumps for IV infusion
Infrastructure	-
Staff time	• Regular (weekly) visits for blood pressure monitoring • and urine tests (10 minutes of a nurse's time per visit). • Time for management of IV drug infusions

Additional considerations

Hydralazine and methyldopa are listed on the WHO Essential Medicines List for the management of severe hypertension in pregnancy.

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 the comparison	☐ Probably favours the comparison	☐ Does not favour either the intervention or the comparison	☐ Probably favours the intervention	☐ Favours the intervention

3. EQUITY

What would be the impact of antihypertensive drug treatment for severe hypertension in pregnancy on health equity?

Research evidence

No direct evidence identified.

Additional considerations

In LMICs, women who are poor, least educated, and residing in rural areas have lower health intervention coverage and worse health outcomes than more advantaged women. In the 2015 WHO State of Inequalities Report, antenatal care coverage of at least four visits differed by at least 25% between the most and least educated, and the richest and poorest in half the LMICs studied *(14)*. It is therefore likely that adverse consequences of severe hypertension in pregnancy are worse in women living in disadvantaged circumstances. Effective, equitable implementation of this intervention could therefore reduce health inequities.

Judgement

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

4. ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

Research evidence

No direct evidence was identified in relation to this question, for women or healthcare providers.

Additional considerations

A 2012 qualitative evidence synthesis provided indirect evidence with regards to patient understanding and experiences of hypertension and drug taking *(15)*. The review findings related to management of chronic hypertension; pregnancy-related hypertension was specifically excluded. In total, 53 qualitative studies from 16 high, middle and low-income countries were identified. Participants reported intentionally reducing or stopping treatment without consulting their doctor, and commonly perceived that their blood pressure improved when symptoms abated or when they were not stressed, and that treatment was therefore not needed. Participants disliked treatments and side effects and feared addiction. These findings were consistent across countries and ethnic groups.

Judgement

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

5. FEASIBILITY

Is the intervention feasible to implement?

Research evidence

No direct evidence was identified.

Additional considerations

A mixed-methods study of multi-stakeholder groups in Uganda and Tanzania on implementation of the WHO pre-eclampsia and eclampsia guidelines *(16)* identified key factors affecting implementation: at the health system level (access to resources, drugs, equipment and supplies, and adequate drug procurement, distribution and management mechanisms); health provider level (the need for buy-in, improving knowledge and skills through training and mentorship) and woman and community level (including traditional beliefs and perceptions of healthcare services, knowledge and awareness of illnesses and interventions, and engaging community healthcare workers).

Judgement

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

C) SUMMARY OF JUDGEMENTS

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 the comparison	– Probably favours the comparison	– Does not favour either the intervention or the comparison	– Probably favours the intervention	– Favours the intervention
Resources required	– Don't know	– Varies	– Large costs	✔ **Moderate costs**	– Negligible costs or savings	– Moderate savings	– Large savings
Certainty of evidence of required resources	✔ **No included studies**			– Very low	– Low	– Moderate	– High
Cost-effectiveness	✔ **Don't know**	– Varies	– Favours the comparison	– Probably favours the comparison	Does not favour either the intervention or the comparison	– Probably favours the intervention	– Favours the intervention
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	✔ **Probably Yes**	– Yes

Annex 5. GRADE Tables

Question: Labetalol compared to hydralazine for treatment of very high blood pressure during pregnancy

Setting: hospitals in Northern Ireland, Panama (2), South Africa, United States (2)

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal deaths												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/100 (0.0%)	0/100 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Eclampsia												
2	randomized trials	serious [c]	not serious	not serious	very serious [b]	none	0/110 (0.0%)	0/110 (0.0%)	not pooled	see comment	⨁◯◯◯ VERY LOW	
Persistent high blood pressure												
4	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	13/256 (5.1%)	13/254 (5.1%)	**RR 1.05** (0.32 to 3.43)	**3 more per 1,000** (from 35 fewer to 124 more)	⨁◯◯◯ VERY LOW	
Serious morbidity in women: acute renal insufficiency												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/100 (0.0%)	0/100 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
HELLP syndrome												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	2/100 (2.0%)	2/100 (2.0%)	**RR 1.00** (0.14 to 6.96)	**0 fewer per 1,000** (from 17 fewer to 119 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Serious morbidity in women: oliguria												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	2/100 (2.0%)	4/100 (4.0%)	**RR 0.50** (0.09 to 2.67)	**20 fewer per 1,000** (from 36 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Serious morbidity in women: disseminated intravascular coagulation												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/100 (0.0%)	0/100 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Serious morbidity in women: pulmonary oedema												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	1/100 (1.0%)	0/100 (0.0%)	**RR 3.00** (0.12 to 72.77)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Placental abruption												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	1/100 (1.0%)	2/100 (2.0%)	**RR 0.50** (0.05 to 5.43)	**10 fewer per 1,000** (from 19 fewer to 89 more)	⨁◯◯◯ VERY LOW	
Hypotension												
4	randomized trials	serious [c]	not serious	not serious	very serious [e]	none	0/140 (0.0%)	2/139 (1.4%)	**RR 0.20** (0.01 to 4.11)	**12 fewer per 1,000** (from 14 fewer to 45 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women												
3	randomized trials	serious [c]	not serious	not serious	very serious [f]	none	24/125 (19.2%)	31/125 (24.8%)	**RR 0.78** (0.49 to 1.23)	**55 fewer per 1,000** (from 57 more to 126 fewer)	⨁◯◯◯ VERY LOW	
Side-effects in women (headaches)												
1	randomized trials	serious [a]	not serious	not serious	very serious [f]	none	23/131 (17.6%)	30/130 (23.1%)	**RR 0.76** (0.47 to 1.24)	**55 fewer per 1,000** (from 55 more to 122 fewer)	⨁◯◯◯ VERY LOW	
Side-effects in women (visual symptoms)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	11/131 (8.4%)	11/130 (8.5%)	**RR 0.99** (0.45 to 2.21)	**1 fewer per 1,000** (from 47 fewer to 102 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (epigastralgia)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	9/131 (6.9%)	10/130 (7.7%)	**RR 0.89** (0.38 to 2.13)	**8 fewer per 1,000** (from 48 fewer to 87 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (palpitations)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	8/131 (6.1%)	10/130 (7.7%)	**RR 0.79** (0.32 to 1.95)	**16 fewer per 1,000** (from 52 fewer to 73 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (nausea)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	6/131 (4.6%)	8/130 (6.2%)	**RR 0.74** (0.27 to 2.09)	**16 fewer per 1,000** (from 45 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (flushing)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	6/131 (4.6%)	4/130 (3.1%)	**RR 1.49** (0.43 to 5.15)	**15 more per 1,000** (from 18 fewer to 128 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (emesis)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	2/131 (1.5%)	3/130 (2.3%)	**RR 0.66** (0.11 to 3.89)	**8 fewer per 1,000** (from 21 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Fetal or neonatal deaths												
5	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	3/155 (1.9%)	5/147 (3.4%)	**RR 0.63** (0.17 to 2.34)	**13 fewer per 1,000** (from 28 fewer to 46 more)	⨁◯◯◯ VERY LOW	
Apgar < 7 at 1 minute												
1	randomized trials	serious [a]	not serious	not serious	very serious [f]	none	20/103 (19.4%)	14/102 (13.7%)	**RR 1.41** (0.76 to 2.64)	**56 more per 1,000** (from 33 fewer to 225 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Apgar < 7 at 5 minutes												
2	randomized trials	serious [c]	serious [g]	not serious	very serious [e]	none	4/116 (3.4%)	4/108 (3.7%)	**RR 0.57** (0.03 to 10.36)	**16 fewer per 1,000** (from 36 fewer to 347 more)	⨁◯◯◯ VERY LOW	
Fetal heart rate decelerations												
4	randomized trials	serious [c]	not serious	not serious	very serious [e]	none	9/141 (6.4%)	10/133 (7.5%)	**RR 0.80** (0.13 to 4.95)	**15 fewer per 1,000** (from 65 fewer to 297 more)	⨁◯◯◯ VERY LOW	
Admission to special care baby unit												
1	randomized trials	serious [a]	not serious	not serious	very serious [f]	none	32/103 (31.1%)	32/102 (31.4%)	**RR 0.99** (0.66 to 1.49)	**3 fewer per 1,000** (from 107 fewer to 154 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (no blinding) contributing data (-1)
b. No events and small sample size (-2)
c. All studies have design limitations (-1)
d. Wide 95% CI crossing the line of no effect, low event rate (-2)
e. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)
f. Wide 95% CI crossing the line of no effect and small sample size (-2)
g. Heterogeneity I2 = 68% (-1)

Question: Calcium channel blockers compared to hydralazine for treatment of very high blood pressure during pregnancy

Setting: hospitals in Brazil (2), India, Iran (2), Mexico, South Africa (2)

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁⨁◯◯ LOW	
Persistent high blood pressure												
6	randomized trials	serious [b]	not serious	not serious	not serious	none	13/160 (8.1%)	34/153 (22.2%)	**RR 0.37** (0.21 to 0.66)	**140 fewer per 1,000** (from 76 fewer to 176 fewer)	⨁⨁⨁◯ MODERATE	
Further episode/s of very high blood pressure												
2	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	39/85 (45.9%)	43/78 (55.1%)	**RR 0.85** (0.65 to 1.11)	**83 fewer per 1,000** (from 61 more to 193 fewer)	⨁◯◯◯ VERY LOW	
Hypotension												
6	randomized trials	serious [b]	not serious	not serious	very serious [e]	none	3/167 (1.8%)	2/158 (1.3%)	**RR 1.12** (0.29 to 4.28)	**2 more per 1,000** (from 9 fewer to 42 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women												
5	randomized trials	serious [b]	not serious	not serious	very serious [d]	none	25/147 (17.0%)	28/139 (20.1%)	**RR 0.81** (0.52 to 1.25)	**38 fewer per 1,000** (from 50 more to 97 fewer)	⨁◯◯◯ VERY LOW	
Side-effects in women (headache)												
5	randomized trials	serious [b]	not serious	not serious	very serious [f]	none	14/152 (9.2%)	11/144 (7.6%)	**RR 1.16** (0.56 to 2.42)	**12 more per 1,000** (from 34 fewer to 108 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (nausea and/or vomiting)												
5	randomized trials	serious [b]	not serious [g]	not serious	very serious [f]	none	12/117 (10.3%)	12/113 (10.6%)	**RR 0.97** (0.18 to 5.11)	**3 fewer per 1,000** (from 87 fewer to 436 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (palpitations)												
2	randomized trials	serious [c]	not serious	not serious	very serious [f]	none	8/45 (17.8%)	12/42 (28.6%)	**RR 0.63** (0.29 to 1.39)	**106 fewer per 1,000** (from 111 more to 203 fewer)	⨁◯◯◯ VERY LOW	
Side-effects in women (flushing)												
4	randomized trials	serious [b]	not serious	not serious	very serious [f]	none	11/87 (12.6%)	5/83 (6.0%)	**RR 1.04** (0.15 to 7.51)	**2 more per 1,000** (from 51 fewer to 392 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (nausea)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	6/131 (4.6%)	8/130 (6.2%)	**RR 0.74** (0.27 to 2.09)	**16 fewer per 1,000** (from 45 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (flushing)												
1	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	6/131 (4.6%)	4/130 (3.1%)	**RR 1.49** (0.43 to 5.15)	**15 more per 1,000** (from 18 fewer to 128 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (dyspnoea)												
1	randomized trials	not serious	not serious	not serious	very serious [f]	none	1/20 (5.0%)	1/17 (5.9%)	**RR 0.85** (0.06 to 12.59)	**9 fewer per 1,000** (from 55 fewer to 682 more)	⨁⨁◯◯ LOW	
Side-effects in women (tachycardia)												
1	randomized trials	not serious	not serious	not serious	very serious [f]	none	2/30 (6.7%)	0/30 (0.0%)	**RR 5.00** (0.25 to 99.95)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Fetal or neonatal death												
5	randomized trials	serious [b]	not serious	not serious	very serious [f]	none	6/113 (5.3%)	4/108 (3.7%)	**RR 1.36** (0.42 to 4.41)	**13 more per 1,000** (from 21 fewer to 126 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium channel blockers**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Apgar < 7 at 5 minutes												
2	randomized trials	not serious	not serious	not serious	very serious [f]	none	2/55 (3.6%)	1/55 (1.8%)	**RR 2.00** (0.19 to 20.90)	**18 more per 1,000** (from 15 fewer to 362 more)	⨁⨁◯◯ LOW	
Fetal heart rate decelerations												
4	randomized trials	serious [b]	not serious	not serious	very serious [f]	none	3/130 (2.3%)	8/123 (6.5%)	**RR 0.38** (0.11 to 1.31)	**40 fewer per 1,000** (from 20 more to 58 fewer)	⨁◯◯◯ VERY LOW	
Admission to NICU												
1	randomized trials	not serious	not serious	not serious	very serious [f]	none	2/30 (6.7%)	1/30 (3.3%)	**RR 2.00** (0.19 to 20.90)	**33 more per 1,000** (from 27 fewer to 663 more)	⨁⨁◯◯ LOW	

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

Explanations

a. No events and small sample size (-2)
b. Most studies contributing data had design limitations (-1)
c. Most of the pooled effect provided by a study with design limitations (-1)
d. Wide 95% CI crossing the line of no effect, and small sample size (-2)
e. Wide 95% CI crossing the line of no effect and few events (-2)
f. Wide 95% CI crossing the line of no effect, small sample size and few events (-2)
g. Heterogeneity I2=58% (not downgraded)

Question: Prostacyclin compared to hydralazine for treatment of very high blood pressure during pregnancy

Setting: hospital in South Africa

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prostacyclin**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Persistent high blood pressure												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/22 (0.0%)	2/25 (8.0%)	**RR 0.23** (0.01 to 4.47)	**62 fewer per 1,000** (from 79 fewer to 278 more)	⨁◯◯◯ VERY LOW	
Side-effects in women												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/22 (4.5%)	1/25 (4.0%)	**RR 1.14** (0.08 to 17.11)	**6 more per 1,000** (from 37 fewer to 644 more)	⨁◯◯◯ VERY LOW	
Neonatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/22 (4.5%)	1/25 (4.0%)	**RR 1.14** (0.08 to 17.11)	**6 more per 1,000** (from 37 fewer to 644 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)

b. Wide 95% CI crossing the line of no effect, few events, and small sample size (-2)

Question: Ketanserin compared to hydralazine for treatment of very high blood pressure during pregnancy

Setting: hospitals in Netherlands (3), and South Africa (2)

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal deaths												
2	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/64 (0.0%)	2/60 (3.3%)	**RR 0.32** (0.03 to 2.96)	**23 fewer per 1,000** (from 32 fewer to 65 more)	⨁◯◯◯ VERY LOW	
Eclampsia												
2	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/32 (3.1%)	2/32 (6.3%)	**RR 0.60** (0.08 to 4.24)	**25 fewer per 1,000** (from 58 fewer to 203 more)	⨁◯◯◯ VERY LOW	
Persistent high blood pressure												
4	randomized trials	serious [a]	not serious	not serious	serious [c]	none	37/111 (33.3%)	7/99 (7.1%)	**RR 4.99** (2.37 to 10.48)	**282 more per 1,000** (from 97 more to 670 more)	⨁⨁◯◯ LOW	
Severe maternal morbidity												
1	randomized trials	serious [d]	not serious	not serious	very serious [b]	none	3/32 (9.4%)	7/24 (29.2%)	**RR 0.32** (0.09 to 1.12)	**198 fewer per 1,000** (from 35 more to 265 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
HELLP syndrome												
2	randomized trials	serious [a]	not serious [e]	not serious	very serious [b]	none	3/37 (8.1%)	10/37 (27.0%)	**RR 0.53** (0.04 to 6.86)	**127 fewer per 1,000** (from 259 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	
Serious morbidity in women: disseminated intravascular coagulation												
1	randomized trials	serious [d]	not serious	not serious	very serious [b]	none	1/22 (4.5%)	0/22 (0.0%)	**RR 3.00** (0.13 to 69.87)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Pulmonary oedema												
1	randomized trials	serious [d]	not serious	not serious	very serious [b]	none	0/22 (0.0%)	4/22 (18.2%)	**RR 0.11** (0.01 to 1.95)	**162 fewer per 1,000** (from 173 more to 180 fewer)	⨁◯◯◯ VERY LOW	
Hypotension												
3	randomized trials	serious [d]	not serious	not serious	serious [f]	none	4/57 (7.0%)	11/49 (22.4%)	**RR 0.34** (0.12 to 0.93)	**148 fewer per 1,000** (from 16 fewer to 198 fewer)	⨁⨁◯◯ LOW	
Placental abruption												
2	randomized trials	serious [d]	not serious	not serious	very serious [b]	none	0/32 (0.0%)	6/32 (18.8%)	**RR 0.14** (0.02 to 1.10)	**161 fewer per 1,000** (from 19 more to 184 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women												
3	randomized trials	serious [a]	not serious	not serious	serious [c]	none	13/64 (20.3%)	36/56 (64.3%)	**RR 0.32** (0.19 to 0.53)	**437 fewer per 1,000** (from 302 fewer to 521 fewer)	⨁⨁◯◯ LOW	
Side-effects in women (headache)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	4/15 (26.7%)	6/15 (40.0%)	**RR 0.67** (0.23 to 1.89)	**132 fewer per 1,000** (from 308 fewer to 356 more)	⨁⨁◯◯ LOW	
Side-effects in women (nausea and/or vomiting)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	0/15 (0.0%)	6/15 (40.0%)	**RR 0.08** (0.00 to 1.25)	**368 fewer per 1,000** (from -- to 100 more)	⨁⨁◯◯ LOW	
Side-effects in women (palpitations)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	4/15 (26.7%)	5/15 (33.3%)	**RR 0.80** (0.27 to 2.41)	**67 fewer per 1,000** (from 243 fewer to 470 more)	⨁⨁◯◯ LOW	
Side-effects in women (tachycardia)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	1/15 (6.7%)	6/15 (40.0%)	**RR 0.17** (0.02 to 1.22)	**332 fewer per 1,000** (from 88 more to 392 fewer)	⨁⨁◯◯ LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (diarrhoea)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	1/15 (6.7%)	2/15 (13.3%)	**RR 0.50** (0.05 to 4.94)	**67 fewer per 1,000** (from 127 fewer to 525 more)	⨁⨁◯◯ LOW	
Side-effects in women (tiredness)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	6/15 (40.0%)	8/15 (53.3%)	**RR 0.75** (0.34 to 1.64)	**133 fewer per 1,000** (from 341 more to 352 fewer)	⨁⨁◯◯ LOW	
Side-effects in women (sleepiness)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	7/15 (46.7%)	9/15 (60.0%)	**RR 0.78** (0.39 to 1.54)	**132 fewer per 1,000** (from 324 more to 366 fewer)	⨁⨁◯◯ LOW	
Side-effects in women (dry mouth)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	9/15 (60.0%)	5/15 (33.3%)	**RR 1.80** (0.79 to 4.11)	**267 more per 1,000** (from 70 fewer to 1,000 more)	⨁⨁◯◯ LOW	
Side-effects in women (stuffy nose)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	9/15 (60.0%)	7/15 (46.7%)	**RR 1.29** (0.65 to 2.54)	**135 more per 1,000** (from 163 fewer to 719 more)	⨁⨁◯◯ LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Perinatal death												
3	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	5/74 (6.8%)	5/72 (6.9%)	**RR 0.84** (0.09 to 8.19)	**11 fewer per 1,000** (from 63 fewer to 499 more)	⨁◯◯◯ VERY LOW	
Side effects - neonatal hypotension												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	4/12 (33.3%)	1/15 (6.7%)	**RR 5.00** (0.64 to 39.06)	**267 more per 1,000** (from 24 fewer to 1,000 more)	⨁⨁◯◯ LOW	

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

Explanations

a. Studies contributing data have design limitations (-1)
b. Wide 95% CI crossing the line of no effect, few events, and small sample size (-2)
c. Small sample size (-1)
d. Single study with design limitations (-1)
e. Heterogeneity I2 = 59% (not downgraded)
f. Few events and small sample size (-1)

Question: Urapidil compared to hydralazine for treatment of very high blood pressure during pregnancy

Setting: hospitals in Germany (2), and South Africa

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Urapidil**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Eclampsia												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/13 (0.0%)	0/13 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Persistent high blood pressure												
3	randomized trials	serious c	not serious	not serious	very serious d	none	1/56 (1.8%)	1/45 (2.2%)	**RR 0.69** (0.08 to 5.66)	**7 fewer per 1,000** (from 20 fewer to 104 more)	⨁◯◯◯ VERY LOW	
Hypotension												
3	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	3/56 (5.4%)	8/45 (17.8%)	**RR 0.32** (0.09 to 1.19)	**121 fewer per 1,000** (from 34 more to 162 fewer)	⨁◯◯◯ VERY LOW	
Side-effects in women												
3	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	3/56 (5.4%)	8/45 (17.8%)	**RR 0.32** (0.09 to 1.19)	**121 fewer per 1,000** (from 34 more to 162 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Urapidil**	**Hydralazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Placental abruption												
1	randomized trials	serious [a]	not serious	not serious	very serious [d]	none	0/23 (0.0%)	1/10 (10.0%)	**RR 0.15** (0.01 to 3.46)	**85 fewer per 1,000** (from 99 fewer to 246 more)	⨁◯◯◯ VERY LOW	
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/13 (0.0%)	0/13 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Neonatal death												
3	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	1/56 (1.8%)	2/45 (4.4%)	**RR 0.54** (0.10 to 3.03)	**20 fewer per 1,000** (from 40 fewer to 90 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. No events, and small sample size (-2)
c. Most of the pooled effect provided by studies with design limitations (-1)
d. Wide confidence intervals crossing the line of no effect, few events, and small sample size (-2)

Question: Labetalol compared to calcium channel blockers for treatment of very high blood pressure during pregnancy

Setting: hospitals in China (2), India (2), Malaysia, and Tunisia

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	0/50 (0.0%)	0/50 (0.0%)	not estimable		⨁⨁◯◯ LOW	
Eclampsia												
3	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	4/85 (4.7%)	3/85 (3.5%)	**RR 1.25** (0.35 to 4.52)	**9 more per 1,000** (from 23 fewer to 124 more)	⨁◯◯◯ VERY LOW	
Stroke												
1	randomized trials	not serious	not serious	not serious	very serious [c]	none	2/50 (4.0%)	1/50 (2.0%)	**RR 2.00** (0.19 to 21.36)	**20 more per 1,000** (from 16 fewer to 407 more)	⨁⨁◯◯ LOW	
Persistent high blood pressure												
3	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	21/85 (24.7%)	15/85 (17.6%)	**RR 1.29** (0.72 to 2.31)	**51 more per 1,000** (from 49 fewer to 231 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any serious morbidity: heart failure												
1	randomized trials	not serious	not serious	not serious	very serious [c]	none	1/50 (2.0%)	1/50 (2.0%)	**RR 1.00** (0.06 to 15.55)	**0 fewer per 1,000** (from 19 fewer to 291 more)	⨁⨁◯◯ LOW	
Hypotension												
5	randomized trials	serious [d]	not serious	not serious	very serious [e]	none	0/168 (0.0%)	0/169 (0.0%)	not pooled	see comment	⨁◯◯◯ VERY LOW	
Side-effects in women												
2	randomized trials	serious [b]	not serious	not serious	very serious [f]	none	27/98 (27.6%)	17/99 (17.2%)	**RR 1.60** (0.94 to 2.72)	**103 more per 1,000** (from 10 fewer to 295 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (headache - mild)												
1	randomized trials	serious [g]	not serious	not serious	very serious [c]	none	2/73 (2.7%)	4/74 (5.4%)	**RR 0.51** (0.10 to 2.68)	**26 fewer per 1,000** (from 49 fewer to 91 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (nausea and/or vomiting)												
2	randomized trials	serious [d]	not serious	not serious	very serious [c]	none	4/103 (3.9%)	2/104 (1.9%)	**RR 2.02** (0.38 to 10.77)	**20 more per 1,000** (from 12 fewer to 188 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (palpitations)												
1	randomized trials	serious [g]	not serious	not serious	very serious [a]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Side-effects in women (moderate tachycardia)												
1	randomized trials	serious [g]	not serious	not serious	very serious [c]	none	0/10 (0.0%)	1/10 (10.0%)	**RR 0.33** (0.02 to 7.32)	**67 fewer per 1,000** (from 98 fewer to 632 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (tachycardia)												
1	randomized trials	serious [g]	not serious	not serious	very serious [c]	none	4/73 (5.5%)	3/74 (4.1%)	**RR 1.35** (0.31 to 5.83)	**14 more per 1,000** (from 28 fewer to 196 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (dizziness)												
1	randomized trials	serious [g]	not serious	not serious	very serious [c]	none	3/73 (4.1%)	2/74 (2.7%)	**RR 1.52** (0.26 to 8.84)	**14 more per 1,000** (from 20 fewer to 212 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (chest pain)												
1	randomized trials	serious [g]	not serious	not serious	very serious [a]	none	0/73 (0.0%)	0/74 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (shortness of breath)												
1	randomized trials	serious [g]	not serious	not serious	very serious [a]	none	0/73 (0.0%)	0/74 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Postpartum haemorrhage: defined as blood loss of 500ml or more												
1	randomized trials	serious [g]	not serious	not serious	serious [h]	none	2/60 (3.3%)	15/60 (25.0%)	**RR 0.13** (0.03 to 0.56)	**218 fewer per 1,000** (from 110 fewer to 243 fewer)	⨁⨁◯◯ LOW	
Admission to intensive care												
1	randomized trials	not serious	not serious	not serious	very serious [c]	none	2/25 (8.0%)	0/25 (0.0%)	**RR 5.00** (0.25 to 99.16)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Perinatal death												
1	randomized trials	not serious	not serious	not serious	very serious [c]	none	2/30 (6.7%)	0/30 (0.0%)	**RR 5.00** (0.25 to 99.95)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Apgar score <7 at five minutes												
4	randomized trials	serious [b]	not serious	not serious	serious [i]	none	24/213 (11.3%)	25/214 (11.7%)	**RR 1.02** (0.40 to 2.62)	**2 more per 1,000** (from 70 fewer to 189 more)	⨁⨁◯◯ LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects associated with drug - FHR abnormality												
1	randomized trials	not serious	not serious	not serious	very serious [c]	none	3/50 (6.0%)	6/50 (12.0%)	**RR 0.50** (0.13 to 1.89)	**60 fewer per 1,000** (from 104 fewer to 107 more)	⨁⨁◯◯ LOW	
Admission to special care baby unit												
3	randomized trials	not serious	not serious	not serious	very serious [c]	none	11/105 (10.5%)	6/105 (5.7%)	**RR 1.83** (0.71 to 4.75)	**47 more per 1,000** (from 17 fewer to 214 more)	⨁⨁◯◯ LOW	

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

Explanations

a. No events and small sample size (-2)
b. Substantial proportion of pooled effect (>50%) from study with design limitations (-1)
c. Wide confidence interval crossing the line of no effect, small sample size and few events (-2)
d. Contributing studies have design limitations (-1)
e. No events (-2)
f. Wide confidence interval crossing the line of no effect, and small sample size (-2)
g. Single study with design limitations (-1)
h. Small sample size and few events (-1)
i. Wide 95% CI crossing line of no effect (-1)

Question: Labetalol compared to methyldopa for treatment of very high blood pressure during pregnancy

Setting: hospital in the United Kingdom.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Persistent high blood pressure												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	20/38 (52.6%)	15/34 (44.1%)	**RR 1.19** (0.74 to 1.94)	**84 more per 1,000** (from 115 fewer to 415 more)	⨁◯◯◯ VERY LOW	
Changed drugs due to side-effects												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	4/38 (10.5%)	0/34 (0.0%)	**RR 8.08** (0.45 to 144.73)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Fetal or neonatal death - Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [d]	none	0/38 (0.0%)	0/34 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Fetal or neonatal death - Neonatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	2/38 (5.3%)	0/34 (0.0%)	**RR 4.49** (0.22 to 90.30)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Methyldopa**	**Relative (95% CI)**	**Absolute (95% CI)**		
Admission to special care baby unit												
1	randomized trials	serious a	not serious	not serious	very serious b	none	19/38 (50.0%)	16/34 (47.1%)	**RR 1.06** (0.66 to 1.71)	**28 more per 1,000** (from 160 fewer to 334 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Wide 95% CI crossing the line of no effect, and small sample size (-2)
c. Wide 95% CI crossing the line of no effect, few events and small sample size (-2)
d. No events and small sample size (-2)

Question: Labetalol compared to diazoxide for treatment of very high blood pressure during pregnancy

Setting: hospital in Australia.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Diazoxide**	**Relative (95% CI)**	**Absolute (95% CI)**		
Persistent high blood pressure												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	3/45 (6.7%)	6/45 (13.3%)	**RR 0.50** (0.13 to 1.88)	**67 fewer per 1,000** (from 116 fewer to 117 more)	⨁◯◯◯ VERY LOW	
Hypotension												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	0/45 (0.0%)	8/45 (17.8%)	**RR 0.06** (0.00 to 0.99)	**167 fewer per 1,000** (from -- to 2 fewer)	⨁◯◯◯ VERY LOW	
Perinatal deaths												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/45 (0.0%)	3/45 (6.7%)	**RR 0.14** (0.01 to 2.69)	**57 fewer per 1,000** (from 66 fewer to 113 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Wide 95% CI crossing the line of no effect, few events and small sample size (-2)
c. Small sample size and few events (-1)

Question: Nitrates compared to magnesium sulfate for treatment of very high blood pressure during pregnancy

Setting: hospital in Mexico

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nitrates**	**Magnesium sulfate**	**Relative (95% CI)**	**Absolute (95% CI)**		
Eclampsia												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/18 (0.0%)	0/18 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Persistent high blood pressure												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	0/18 (0.0%)	3/18 (16.7%)	**RR 0.14** (0.01 to 2.58)	**143 fewer per 1,000** (from 165 fewer to 263 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. No events and small sample size (-2)
c. Wide 95% confidence interval crossing the line of no effect, small sample size and few events (-2)

Question: Nimodipine compared to magnesium sulfate for treatment of very high blood pressure during pregnancy

Setting: hospitals in Turkey, and eight countries in a multicentre trial.

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nimodipine**	**Magnesium sulfate**	**Relative (95% CI)**	**Absolute (95% CI)**		
Eclampsia												
2	randomized trials	serious [a]	not serious	not serious	serious [b]	none	21/837 (2.5%)	9/846 (1.1%)	**RR 1.03** (0.07 to 16.03)	**0 fewer per 1,000** (from 10 fewer to 160 more)	⨁⨁◯◯ LOW	
Stroke												
1	randomized trials	serious [c]	not serious	not serious	serious [d]	none	0/819 (0.0%)	0/831 (0.0%)	not estimable		⨁⨁◯◯ LOW	
Persistent high blood pressure												
1	randomized trials	serious [c]	not serious	not serious	not serious	none	374/819 (45.7%)	451/831 (54.3%)	**RR 0.84** (0.76 to 0.93)	**87 fewer per 1,000** (from 38 fewer to 130 fewer)	⨁⨁⨁◯ MODERATE	
Coagulopathy in women												
1	randomized trials	serious [c]	not serious	not serious	very serious [e]	none	5/819 (0.6%)	3/831 (0.4%)	**RR 1.69** (0.41 to 7.05)	**2 more per 1,000** (from 2 fewer to 22 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nimodipine**	**Magnesium sulfate**	**Relative (95% CI)**	**Absolute (95% CI)**		
Serious morbidity in women: Oliguria												
1	randomized trials	serious [c]	not serious	not serious	serious [b]	none	47/819 (5.7%)	55/831 (6.6%)	**RR 0.87** (0.59 to 1.26)	**9 fewer per 1,000** (from 17 more to 27 fewer)	⨁⨁◯◯ LOW	
Hypotension												
1	randomized trials	serious [c]	not serious	not serious	very serious [e]	none	5/819 (0.6%)	7/831 (0.8%)	**RR 0.72** (0.23 to 2.27)	**2 fewer per 1,000** (from 6 fewer to 11 more)	⨁◯◯◯ VERY LOW	
Postpartum haemorrhage												
1	randomized trials	serious [c]	not serious	not serious	serious [f]	none	8/819 (1.0%)	20/831 (2.4%)	**RR 0.41** (0.18 to 0.92)	**14 fewer per 1,000** (from 2 fewer to 20 fewer)	⨁⨁◯◯ LOW	
Placental abruption												
1	randomized trials	serious [c]	not serious	not serious	very serious [e]	none	6/819 (0.7%)	8/831 (1.0%)	**RR 0.76** (0.27 to 2.18)	**2 fewer per 1,000** (from 7 fewer to 11 more)	⨁◯◯◯ VERY LOW	
Respiratory difficulty in women												
1	randomized trials	serious [c]	not serious	not serious	serious [f]	none	3/819 (0.4%)	11/831 (1.3%)	**RR 0.28** (0.08 to 0.99)	**10 fewer per 1,000** (from 0 fewer to 12 fewer)	⨁⨁◯◯ LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nimodipine**	**Magnesium sulfate**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (all side-effects)												
1	randomized trials	serious [c]	not serious	not serious	not serious	none	109/819 (13.3%)	162/831 (19.5%)	**RR 0.68** (0.55 to 0.85)	**62 fewer per 1,000** (from 29 fewer to 88 fewer)	⨁⨁⨁◯ MODERATE	
Side-effects in women (headache)												
1	randomized trials	serious [c]	not serious	not serious	very serious [b]	none	47/819 (5.7%)	45/831 (5.4%)	**RR 1.06** (0.71 to 1.58)	**3 more per 1,000** (from 16 fewer to 31 more)	⨁◯◯◯ VERY LOW	
Side-effects in women (nausea and/or vomiting)												
1	randomized trials	serious [c]	not serious	not serious	serious [b]	none	49/819 (6.0%)	58/831 (7.0%)	**RR 0.86** (0.59 to 1.24)	**10 fewer per 1,000** (from 17 more to 29 fewer)	⨁⨁◯◯ LOW	
Side-effects in women (flushing)												
1	randomized trials	serious [c]	not serious	not serious	not serious	none	13/819 (1.6%)	59/831 (7.1%)	**RR 0.22** (0.12 to 0.40)	**55 fewer per 1,000** (from 43 fewer to 62 fewer)	⨁⨁⨁◯ MODERATE	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nimodipine**	**Magnesium sulfate**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects: Low blood pressure in babies												
1	randomized trials	serious [c]	not serious	not serious	very serious [e]	none	6/767 (0.8%)	2/797 (0.3%)	**RR 3.12** (0.63 to 15.40)	**5 more per 1,000** (from 1 fewer to 36 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Studies contributing data had design limitations (-1)
b. Wide 95% CI crossing the line of no effect (-1)
c. Single study with design limitations (-1)
d. No events (-2)
e. Wide 95% CI crossing the line of no effect, low event rate (-2)
f. Low event rate (-1)

Question: Nifedipine compared to prazosin for treatment of very high blood pressure during pregnancy

Setting: hospital in South Africa

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine**	**Prazosin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/74 (0.0%)	1/71 (1.4%)	**RR 0.32** (0.01 to 7.73)	**10 fewer per 1,000** (from 14 fewer to 95 more)	⨁◯◯◯ VERY LOW	
Eclampsia												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	0/74 (0.0%)	0/71 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
HELLP syndrome												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	6/74 (8.1%)	5/71 (7.0%)	**RR 1.15** (0.37 to 3.60)	**11 more per 1,000** (from 44 fewer to 183 more)	⨁◯◯◯ VERY LOW	
Renal failure												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/74 (1.4%)	2/71 (2.8%)	**RR 0.48** (0.04 to 5.17)	**15 fewer per 1,000** (from 27 fewer to 117 more)	⨁◯◯◯ VERY LOW	
Pulmonary oedema												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/74 (1.4%)	5/71 (7.0%)	**RR 0.19** (0.02 to 1.60)	**57 fewer per 1,000** (from 42 more to 69 fewer)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine**	**Prazosin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Placental abruption												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	9/74 (12.2%)	9/71 (12.7%)	**RR 0.96** (0.40 to 2.28)	**5 fewer per 1,000** (from 76 fewer to 162 more)	⨁◯◯◯ VERY LOW	
Admission to intensive care												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/74 (0.0%)	1/71 (1.4%)	**RR 0.32** (0.01 to 7.73)	**10 fewer per 1,000** (from 14 fewer to 95 more)	⨁◯◯◯ VERY LOW	
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	6/75 (8.0%)	13/74 (17.6%)	**RR 0.46** (0.18 to 1.13)	**95 fewer per 1,000** (from 23 more to 144 fewer)	⨁◯◯◯ VERY LOW	
Admission to special care baby unit												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	22/69 (31.9%)	25/61 (41.0%)	**RR 0.78** (0.49 to 1.23)	**90 fewer per 1,000** (from 94 more to 209 fewer)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)
c. No events and small sample size (-2)

Question: Nifedipine compared to chlorpromazine for treatment of very high blood pressure during pregnancy

Setting: hospital in Mexico

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine**	**Chlorpromazine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Eclampsia												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/30 (3.3%)	0/25 (0.0%)	**RR 2.52** (0.11 to 59.18)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Persistent high blood pressure												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/30 (0.0%)	5/30 (16.7%)	**RR 0.09** (0.01 to 1.57)	**152 fewer per 1,000** (from 95 more to 165 fewer)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)

Question: Hydralazine compared to diazoxide for treatment of very high blood pressure during pregnancy

Setting: hospital in Australia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydralazine**	**Diazoxide**	**Relative (95% CI)**	**Absolute (95% CI)**		
Perinatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	3/49 (6.1%)	0/52 (0.0%)	**RR 7.42** (0.39 to 140.06)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	2/49 (4.1%)	0/52 (0.0%)	**RR 5.30** (0.26 to 107.70)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Neonatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/49 (0.0%)	1/52 (1.9%)	**RR 0.35** (0.01 to 8.47)	**13 fewer per 1,000** (from 19 fewer to 144 more)	⨁◯◯◯ VERY LOW	
Apgar score < 7 at 5 minutes												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	4/49 (8.2%)	4/52 (7.7%)	**RR 1.06** (0.28 to 4.01)	**5 more per 1,000** (from 55 fewer to 232 more)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)

b. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)

Question: Methyldopa compared to atenolol for treatment of very high blood pressure during pregnancy

Setting: hospital in Argentina

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methyldopa**	**Atenolol**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (somnolence)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	10/30 (33.3%)	0/30 (0.0%)	**RR 21.00** (1.29 to 342.93)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	1/30 (3.3%)	1/30 (3.3%)	**RR 1.00** (0.07 to 15.26)	**0 fewer per 1,000** (from 31 fewer to 475 more)	⨁◯◯◯ VERY LOW	
Neonatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	1/30 (3.3%)	1/30 (3.3%)	**RR 1.00** (0.07 to 15.26)	**0 fewer per 1,000** (from 31 fewer to 475 more)	⨁◯◯◯ VERY LOW	
Side-effects in babies												
1	randomized trials	serious [a]	not serious	not serious	very serious [d]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Low event rate and small sample size (-1)
c. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)
d. No events and small sample size (-2)

Question: Methyldopa compared to ketanserin for treatment of very high blood pressure during pregnancy

Setting: hospital in Argentina

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Methyldopa**	**Ketanserin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (somnolence)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	10/30 (33.3%)	0/30 (0.0%)	**RR 21.00** (1.29 to 342.93)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	1/30 (3.3%)	0/30 (0.0%)	**RR 3.00** (0.13 to 70.83)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Neonatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	1/30 (3.3%)	3/30 (10.0%)	**RR 0.33** (0.04 to 3.03)	**67 fewer per 1,000** (from 96 fewer to 203 more)	⨁◯◯◯ VERY LOW	
Side-effects in babies												
1	randomized trials	serious [a]	not serious	not serious	very serious [d]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Low event rate and small sample size (-1)
c. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)
d. No events and small sample size (-2)

Question: Ketanserin compared to atenolol for treatment of very high blood pressure during pregnancy

Setting: hospital in Argentina

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketanserin**	**Atenolol**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women (somnolence)												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	0/30 (0.0%)	1/30 (3.3%)	**RR 0.33** (0.01 to 7.87)	**22 fewer per 1,000** (from 33 fewer to 229 more)	⨁◯◯◯ VERY LOW	
Neonatal death												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	3/30 (10.0%)	1/30 (3.3%)	**RR 3.00** (0.33 to 27.23)	**67 more per 1,000** (from 22 fewer to 874 more)	⨁◯◯◯ VERY LOW	
Side-effects in babies												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. No events and small sample size (-2)
c. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)

Question: Urapidil compared to calcium channel blockers for treatment of very high blood pressure during pregnancy

Setting: Hospital in France

Certainty assessment							№ of women		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Urapidil**	**Calcium channel blockers**	**Relative (95% CI)**	**Absolute (95% CI)**		
Side-effects in women												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/9 (11.1%)	6/9 (66.7%)	**RR 0.17** (0.02 to 1.12)	**553 fewer per 1,000** (from 80 more to 653 fewer)	⨁◯◯◯ VERY LOW	
Side-effects in babies												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	0/9 (0.0%)	0/9 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	

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

Explanations

a. Single study with design limitations (-1)
b. Wide 95% CI crossing the line of no effect, low event rate and small sample size (-2)
c. No events and small sample size (-2)

For more information, please contact the following departments:

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