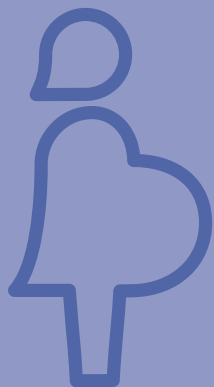WHO recommendations for
Prevention and treatment of pre-eclampsia and eclampsia

World Health Organization

WHO recommendations for

Prevention and treatment of pre-eclampsia and eclampsia

World Health Organization

Acknowledgements

Abbreviations

AGREE	Appraisal of Guidelines Research and Evaluation
CI	confidence interval
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (WHO project)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HELLP	haemolysis, elevated liver enzymes, low platelet count
MMR	maternal mortality ratio
PICO	population, interventions, comparisons, and outcomes
RCT	randomized controlled trial
REVMAN	Review Manager Software
RR	relative risk
OR	odds ratio
USAID	United States Agency for International Development

Contents

The standardized criteria used in grading the evidence and the GRADE tables are not included in this document (although table numbers – prefixed with 'EB' – are included for ease of reference). The tables have been published in a separate document entitled *WHO recommendations for pre-eclampsia and eclampsia: evidence base* and can be accessed online at the following link:

www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/index.html

Summary of recommendations

Introduction

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. In Africa and Asia, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy, whereas one quarter of maternal deaths in Latin America have been associated with those complications. Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. The majority of deaths due to pre-eclampsia and eclampsia are avoidable through the provision of timely and effective care to the women presenting with these complications. Optimizing health care to prevent and treat women with hypertensive disorders is a necessary step towards achieving the Millennium Development Goals. WHO has developed the present evidence-informed recommendations with a view to promoting the best possible clinical practices for the management of pre-eclampsia and eclampsia.

Guideline development methods

The procedures used in the development of these guidelines, which are outlined in the *WHO Handbook for guideline development[1]*, involved: (i) identification of questions related to clinical practice and health policy for which answers were needed; (ii) retrieval of up-to-date research-based evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations with inputs from a wide range of stakeholders; and (v) formulation of plans for dissemination, implementation, impact evaluation and updating.

The scientific evidence for the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. For each preselected critical question, evidence profiles were prepared based on 19 up-to-date systematic reviews. The final recommendations were formulated and approved by an international group of experts who participated in the WHO Technical Consultation on the Prevention and Treatment of Pre-eclampsia and Eclampsia, held in Geneva, Switzerland, on 7–8 April 2011. The experts also identified important knowledge gaps that need to be addressed through primary research and developed a list of priority research questions.

Recommendations

The WHO Technical Consultation made a total of 23 recommendations. For each recommendation, the quality of the supporting evidence was graded as very low, low, moderate or high. Then, taking into account the quality of the evidence and other factors (including the values and preferences, the magnitude of effect, the balance of benefits versus disadvantages, resource use and feasibility of each recommendation), the experts marked the recommendations as either weak or strong following the GRADE methodology. In addition, in order to ensure that each recommendation will be understood and used in practice in accordance with its intended meaning, the experts made several remarks, which are noted below the recommendations in the full document. For additional details on the recommendation, the reader is referred to the remarks in the full version of the guidelines. The 23 recommendations are presented below in two sets: interventions that are recommended and interventions that are not recommended.

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[1] *WHO Handbook for guideline development*. Geneva, World Health Organization, 2010.

Box 1: Interventions that are recommended for prevention or treatment of pre-eclampsia and eclampsia

Recommendation	Quality of evidence	Strength of recommendation
In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of pre-eclampsia in all women, but especially those at high risk of developing pre-eclampsia.	Moderate	Strong
Low-dose acetylsalicylic acid (aspirin, 75 mg) is recommended for the prevention of pre-eclampsia in women at high risk of developing the condition.	Moderate	Strong
Low-dose acetylsalicylic acid (aspirin, 75 mg) for the prevention of pre-eclampsia and its related complications should be initiated before 20 weeks of pregnancy.	Low	Weak
Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.	Very low	Strong
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.	Very low	Weak
Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants.	High	Strong
Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants.	Moderate	Strong
The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia.	Moderate	Strong
For settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe pre-eclampsia and eclampsia.	Very low	Weak
Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks.	Very low	Strong
In women with severe pre-eclampsia, a viable fetus and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.	Very low	Weak
In women with severe pre-eclampsia, a viable fetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.	Very low	Weak
In women with severe pre-eclampsia at term, early delivery is recommended.	Low	Strong
In women with mild pre-eclampsia or mild gestational hypertension at term, induction of labour is recommended.	Moderate	Weak
In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended.	Very low	Strong
Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.	Very low	Strong

Box 2: Interventions that are *not* recommended for prevention or treatment of pre-eclampsia and eclampsia

Recommendation	Quality of evidence	Strength of recommendation
Advice to rest at home is not recommended as an intervention for the primary prevention of pre-eclampsia and hypertensive disorders of pregnancy in women considered to be at risk of developing those conditions.	Low	Weak
Strict bedrest is not recommended for improving pregnancy outcomes in women with hypertension (with or without proteinuria) in pregnancy.	Low	Weak
Restriction in dietary salt intake during pregnancy with the aim of preventing the development of pre-eclampsia and its complications is not recommended.	Moderate	Weak
Vitamin D supplementation during pregnancy is not recommended to prevent the development of pre-eclampsia and its complications.	Very low	Strong
Individual or combined vitamin C and vitamin E supplementation during pregnancy is not recommended to prevent the development of pre-eclampsia and its complications.	High	Strong
Diuretics, particularly thiazides, are not recommended for the prevention of pre-eclampsia and its complications.	Low	Strong
The use of corticosteroids for the specific purpose of treating women with HELLP syndrome is not recommended.	Very low	Weak

1. Background

Hypertensive disorders of pregnancy affect about 10% of all pregnant women around the world (*1, 2*). This group of diseases and conditions includes pre-eclampsia and eclampsia, gestational hypertension and chronic hypertension (*2*). Hypertensive disorders of pregnancy are an important cause of severe acute morbidity, long-term disability and death among mothers and babies (*1–3*). In Asia and Africa, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy, whereas one quarter of all maternal deaths in Latin America have been associated with those complications (*3*). The majority of deaths related to hypertensive disorders can be avoided by providing timely and effective care to women presenting with such complications (*4*). Thus, optimization of health care for women during pregnancy to prevent and treat hypertensive disorders of pregnancy is a necessary step towards achievement of the Millennium Development Goals.

Pre-eclampsia stands out among the hypertensive disorders for its impact on maternal and neonatal health. It is one of the leading causes of maternal and perinatal mortality and morbidity worldwide. However, the pathogenesis of pre-eclampsia is only partially understood and it is related to disturbances in placentation at the beginning of pregnancy, followed by generalized inflammation and progressive endothelial damage. There are other uncertainties too: the diagnosis, screening and management of pre-eclampsia remain controversial, as does the classification of its severity. However, it is generally accepted that the onset of a new episode of hypertension during pregnancy (with persistent diastolic blood pressure >90 mm Hg) with the occurrence of substantial proteinuria (>0.3 g/24 h) can be used as criteria for identifying pre-eclampsia. Although pathophysiological changes (e.g. inadequate placentation) exist from very early stages of the pregnancy, hypertension and proteinuria usually become apparent in the second half of pregnancy and are present in 2%–8% of all pregnancies overall (*2*).

Obesity, chronic hypertension and diabetes are among the risk factors for pre-eclampsia, which also include nulliparity, adolescent pregnancy and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy). Pre-eclampsia is usually classified as mild or severe. In most settings, pre-eclampsia is classified as severe when any of the following conditions is present: severe hypertension, heavy proteinuria or substantial maternal organ dysfunction. Early onset (before 32–34 weeks of pregnancy) of pre-eclampsia and fetal morbidity are used as independent criteria to classify pre-eclampsia as severe in some parts of the world. Maternal deaths can occur among severe cases, but the progression from mild to severe can be rapid, unexpected, and occasionally fulminant. Primary prevention of pre-eclampsia is controversial and subject of active research, particularly with regard to the use of anti-inflammatory agents and micronutrients including calcium, vitamin D and antioxidant vitamins C and E supplements. The only definitive treatment for pre-eclampsia is termination of pregnancy/delivery of the fetus and placenta, though some women with pre-eclampsia also present a transient aggravation of the disease in the postpartum period. Management of women with pre-eclampsia aims at minimizing further pregnancy-related complications, avoiding unnecessary prematurity and maximizing maternal and infant survival (*2*).

Delaying the interruption of pregnancy may lead to progression of pre-eclampsia, eventually resulting in placental insufficiency and maternal organ dysfunction. These conditions are clearly associated with increased risk of maternal and perinatal mortality. Maternal organ dysfunction associated with pre-eclampsia may present with varied clinical features, including eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count). Eclampsia is characterized by the occurrence of generalized seizures in women with pre-eclampsia, provided that the tonic–clonic seizures are not attributable to other causes (e.g. epilepsy). As with pre-eclampsia, the pathogenesis of eclampsia remains largely unknown and 5%–8% of women with pre-eclampsia present this condition in developing countries (*2, 5*). HELLP syndrome

occurs in 10%–20% of women with severe pre-eclampsia and is associated with substantial, widespread endothelial damage. Eclampsia and HELLP syndrome are important predictors of further organ dysfunctions and mortality (*2, 6*).

The primary goal of the present guidelines is to improve the quality of care and outcomes for pregnant women presenting with pre-eclampsia and its main complications (e.g. eclampsia). The target audience of these guidelines includes obstetricians, midwives, general medical practitioners, health-care managers and public health policy-makers, particularly those in under-resourced settings. The guidance provided is evidence-informed and covers selected topics related to the management of pre-eclampsia and eclampsia that were regarded as critical questions by an international, multidisciplinary group of health-care workers, consumers and other stakeholders. These guidelines are not intended as a comprehensive guide on the management of pre-eclampsia and eclampsia.

2. Methods

The present guidelines represent WHO's normative work to support the use of evidence-informed policies and practices in all countries. They form part of the knowledge-to-action project entitled GREAT (Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge) (*7*) and were developed through standardized operating procedures in accordance with the process described in the *WHO Handbook for guideline development (8).* In summary, the process included: (i) identification of critical questions and critical outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of

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

First, a guideline steering group was constituted, which included staff of the WHO Departments of Reproductive Health and Research, Making Pregnancy Safer, and Nutrition for Health and Development, and two external experts (see Annex 1). This group drafted a list of questions and outcomes related to the prevention and treatment of pre-eclampsia and eclampsia. Next, via an online survey, WHO consulted a group of international stakeholders (midwives, obstetricians, neonatologists, researchers, experts in research synthesis, experts in health-care programmes, and consumer representatives) to review and prioritize the draft questions and outcomes (first online consultation). The international stakeholders commented on the importance of the drafted questions and outcomes and rated them on a scale of 1 to 9. In this context, a 'critical question or outcome' was defined as a question or outcome that received an average score of 7 or more. Questions and outcomes that scored between 4 and 6 were considered 'important but not critical', while those that scored less than 4 were not considered to be important for the purposes of these guidelines. The international stakeholders were encouraged to revise the questions or suggest new questions and outcomes. The responses to the online survey were reviewed by the guideline steering group. The questions and outcomes rated as critical were included in the scope of this document for evidence grading and formulation of recommendations and were further refined in order to make them conform to the PICO format (population, interventions, comparisons, and outcomes). The average scores given to outcomes by international stakeholders and external experts during the online consultation are presented in Annex 2.

Cochrane systematic reviews of randomized controlled trials (RCTs) were the primary source of evidence for the recommendations.[2] Based on the list of selected questions and outcomes, the guideline steering group identified the relevant Cochrane systematic reviews and determined whether they needed to be updated. Relevant and possibly relevant Cochrane systematic reviews were updated using their specific standard search strategies. A review was considered to be outdated if the last date of search for new trials was two years old, or if there were relevant studies awaiting assessment, as identified by the standard search procedures of the Cochrane Pregnancy and Childbirth Group. For the outdated reviews, the corresponding review authors were invited to update them. Not all authors were in a position to do that within the set deadline. Hence, the review authors who could comply with the deadline and members of the guideline steering group updated the systematic reviews. The search strategies employed to identify the trials and the specific criteria for inclusion and exclusion of the trials are described in the individual systematic reviews.

The following procedures were used to process in a consistent manner each systematic review used to extract the evidence for these guidelines. First, the up-to-date Review Manager software (RevMan) file was retrieved from the Cochrane Pregnancy and Childbirth Cochrane Group. Next, the RevMan file was customized in order to reflect the critical comparisons and outcomes (comparisons and outcomes not relevant to the guidelines were excluded). The next step was to export the RevMan file to the GRADE profiler

software and apply the GRADE criteria for critical appraisal to the retrieved scientific evidence. As a final step, evidence profiles (GRADE tables) were prepared for each comparison. An online content management system, the GREAT project *Guideline Production System,* was used to handle and share the electronic files.

The standardized criteria used in grading the evidence and the GRADE tables **are not included in this document** (although table numbers – prefixed with 'EB'– are included for ease of reference): they are being published online separately in a document entitled *WHO recommendations for pre-eclampsia and eclampsia: evidence base* (www.who.int/reproductivehealth/publications/maternal_perinatal_ health/9789241548335/en/index.html). Each GRADE table relates to one specific question or comparison. The evidence presented in the GRADE tables was derived from a larger body of data extracted primarily from Cochrane reviews, which in many cases contained multiple comparisons (EB Tables 1 to 53). In some GRADE tables data are not presented for all critical outcomes. This is because data for those outcomes were not available in the Cochrane reviews. The raw data which constitute the basis of the GRADE tables are also not included in this document, but can be made available upon request to researchers interested in finding out how the GRADE tables were constructed. The guideline steering group used the information presented in the GRADE tables to draft the recommendations. Balance worksheets were used to summarize the values, preferences and judgements made with regard to the strength of the recommendations. Those balance worksheets are presented in the evidence base document (EB Tables 54–59).

In order to review and finalize the draft recommendations and the supporting evidence (including GRADE tables), a preliminary online consultation was held. The draft document and recommendations were made available to a

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[2] As part of the Cochrane prepublication editorial process, reviews are commented on by three peers (an editor, and two refe-rees who are external to the editorial team) and the Group's Statistical Adviser. (http://www.cochrane.org/cochrane-reviews). The Cochrane Handbook for Systematic Reviews of Interventions describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

large number of international stakeholders; their opinion was collected via e-mail and through an online survey. This preliminary online consultation was followed by a meeting held in Geneva, Switzerland, on 7–8 April 2011 (WHO Technical Consultation on the Prevention and Treatment of Pre-eclampsia and Eclampsia). A subset of the international group of experts that had participated in the online consultations and other experts were invited to participate in this technical meeting (see Annex 1 for the list of participants). The draft recommendations and supporting documents were provided to the Technical Consultation participants in advance of the meeting.

Declaration of interest by participants in the WHO Technical Consultation

According to the WHO rules, all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. All guideline group members and participants of meeting completed a Declaration of Interest Form before the meeting. These declarations of interest forms were reviewed by the WHO steering group in consultation with the WHO Legal Department before finalization of the group composition and invitation to attend the guideline group meeting. Box 1 (Annex 1) summarizes relevant declarations of interest. In addition, the external advisers verbally declared potential conflicts of interest at the beginning of the meeting. The procedures for management of conflicts of interests strictly followed WHO *Guidelines for declaration of interest (WHO experts)*. Full participation of all experts was deemed appropriate.

Decision-making during the technical consultation

It was planned that the participants in the Technical Consultation would discuss each of the recommendations drafted by the guideline steering group and arrived at a consensus,

which was defined as agreement by the large majority of the participants (three quarters of participants), provided that those who disagreed did not feel strongly about their position. Strong disagreements would be recorded as such in the guidelines. The participants had been unable to reach a consensus, the disputed recommendation, or any other decision, would be put to a vote. The recommendation or decision would stand if a simple majority (more than half) of the participants voted for it, unless the disagreement related to a safety concern, in which case the WHO Secretariat would choose not to issue a recommendation at all. WHO staff present at the meeting and other external technical experts involved in the collection and grading of the evidence were not allowed to vote. If the issue to be voted upon involved primary research or systematic reviews conducted by any of the participants who have declared an academic conflict of interest, the participants in question were allowed to participate in the discussion, but were not allowed to vote on it. In addition to the scientific evidence and its quality, applicability issues, costs and other judgements were taken into consideration in the formulation of the final recommendations.

The strength of each recommendation was determined during the Technical Consultation using GRADE methodology. By default, the strength of the recommendations was initially aligned with the quality of the evidence (i.e. moderate and high quality of evidence prompted strong recommendations while low and very low quality of evidence prompted week recommendations). During the meeting, the participants' values and preferences, the magnitude of effect, balance of benefits versus disadvantages, resource use and feasibility of each recommendation were considered. Balance worksheets were used to note and synthesize these considerations (EB Tables 54–59) and whenever the default strength of the recommendation was changed due to values and preferences, the reasons were recorded in the balance worksheets.

Document preparation and peer review

A template for guideline reporting was developed for the WHO GREAT project series of guidelines. That guideline template was used in the preparation of this document. Prior to the Technical Consultation, the guideline steering group prepared a preliminary version of this document, including draft recommendations. The participants of the Technical Consultation meeting held in Geneva received the draft guidelines and supporting documents 10 days before the meeting. The draft guidelines were also sent to a large number of international stakeholders for peer review together with an online questionnaire about the draft recommendations (preliminary online consultation). Inputs received from the peer reviewers were carefully evaluated by the guideline steering group and the suggestions considered as relevant were included in the document or highlighted for further discussion during the meeting. The guideline steering group refrained from making any substantive changes to the scoping (e.g. further expansion of the guideline scoping) of the guidelines. The comments and feedback received during the preliminary online consultation were discussed during the meeting and incorporated into the document as appropriate. During the meeting, the draft guidelines were modified in line with the participants' deliberations and considering the input of received during the online preliminary consultation. After the meeting, members of the guideline steering group worked on the preliminary version to ensure that a revised version reflected accurately the deliberations and decisions of the participants. The revised version was sent electronically back to the participants in the Technical Consultation for their approval.

3. Results

A total of 50 stakeholders from all six WHO regions responded to the first online scoping survey. Feedback from the surveyed experts was then used to modify the scoping questions and outcomes. Annex 2, Table 1 shows the average scores given to the scoping outcomes by the external experts. A total of 19 systematic reviews (including 17 Cochrane systematic reviews) were identified for providing the evidence related to the selected priority questions. A total of 54 GRADE tables was prepared and are presented in the document *WHO recommendations for pre-eclampsia and eclampsia: evidence base.* The following section contains the narrative summaries and the evidence-informed recommendations. A total of 173 stakeholders participated in the online preliminary consultation (from all WHO regions) and 25 experts participated in the WHO Technical Consultation.

4. Evidence and recommendations

Rest for prevention and treatment of pre-eclampsia

Rest for prevention of pre-eclampsia and its complications

Evidence related to the effect of rest or advice to reduce physical activity for the prevention of pre-eclampsia and its complications came from a Cochrane review of two small trials involving a total of 106 normotensive women at moderate risk of developing pre-eclampsia (*9*). One of the trials (32 women) compared 4-hour daily rest at home in a left lateral position with unrestricted activity while the other (74 women) compared 15 minutes twice daily rest at home plus nutritional supplementation with unrestricted activity plus placebo.

None of the critical outcomes was assessed in either of the trials. Gestational hypertension and pre-eclampsia were reported in both trials and were selected as proxy outcomes for this recommendation. When daily rest at home was compared with unrestricted activity, there was a significant reduction in the risk of pre-eclampsia [one trial, 32 women; relative risk (RR) 0.05, 95% confidence interval (CI) 0.00–0.83], but no statistical difference was observed in the risk of gestational hypertension (one trial, 32 women; RR 0.25, 95% CI 0.03–2.00) (EB Table 1). Compared with unrestricted activity plus placebo, rest at home plus nutritional supplementation resulted in significant reduction of both proxy outcomes (gestational hypertension: one trial, 74 women; RR 0.15, 95% CI 0.04–0.63 and pre-eclampsia: one trial, 74 women; RR 0.12, 95% CI 0.03–0.51) (EB Table 2). The findings for these proxy outcomes were considered imprecise because of the very small sample size and scarce data.

Bedrest for treatment of hypertension in pregnancy

Evidence related to different degrees of bedrest for improving pregnancy outcomes in women with hypertension in pregnancy was extracted from one Cochrane systematic review of four RCT (*10*). The trials were relatively small, with a total of 449 women. Three of the trials were assessed by the Cochrane review authors to be of good quality. Two trials (145 women) compared strict bedrest with some rest in hospital for women with pre-eclampsia, while the other two (304 women) compared some bedrest in hospital with routine activity at home for nonproteinuric hypertension. When strict bedrest was compared with some rest in hospitalized women, there were no statistically significant differences in the critical outcomes of eclampsia (one trial, 105 women; RR 0.33, 95% CI 0.01–7.85), perinatal death (two trials, 145 women; RR 1.07, 95% CI 0.52–2.19) and admission to intensive care nursery

(one trial, 105 women; RR 0.75, 95% CI 0.49–1.17) (EB Table 3). For the comparison between some rest in hospital and routine activity at home, there were also no statistically significant differences in the critical outcomes of perinatal death (one trial, 218 women; RR 1.96, 95% CI 0.18–21.34), admission to intensive care nursery (one trial, 218 women; RR 0.82, 95% CI 0.37–1.81) and pre-eclampsia (one trial, 218 women; RR 0.98, 95% CI 0.80–1.20) (EB Table 4).

Recommendations

1. Advice to rest at home is not recommended as an intervention for the primary prevention of pre-eclampsia and hypertensive disorders of pregnancy in women considered to be at risk of developing those conditions.

   • (Low-quality evidence. Weak recommendation.)

2. Strict bedrest is not recommended for improving pregnancy outcomes in women with hypertension (with or without proteinuria) in pregnancy.

   • (Low-quality evidence. Weak recommendation.)

Remarks

a. The guideline development group acknowledged that there may be situations in which different levels of rest, either at home or in hospital, may be indicated for individual women. The above recommendations do not cover advice regarding overall physical activity and manual or office work.

b. Women may need to be hospitalized for reasons other than bedrest, such as for maternal and fetal surveillance. The guideline development group agreed that hospitalization for maternal and fetal surveillance is resource intensive and should be considered as a priority for research and future recommendations.

Dietary salt restriction for prevention of pre-eclampsia

Evidence on the differential effects of altered dietary salt intake on the development of pre-eclampsia and its complications came from a Cochrane systematic review of two RCTs involving 603 women in the Netherlands (*11*). Participants in both trials were nulliparous women with normal blood pressure at trial entry. The two trials compared restricted dietary salt intake (20 mmol/day or 50 mmol/day) with advice to continue with normal diet. There were no statistically significant differences for the critical (and proxy) outcomes addressed in the trials: pre-eclampsia (two trials, 603 women; RR 1.11 95% CI 0.49–1.94), perinatal death (two trials, 409 women; RR 1.92, 95% CI 0.18–21.03), admission to intensive care unit (one trial, 361 women; RR 0.98, 95% CI 0.69–1.40) and Apgar score less than seven at 5 minutes (one trial, 361 women; RR 1.37, 95% CI 0.53–3.53) (EB Table 5). Although there were no serious limitations in the quality of the studies included in the review, the relatively small number of participants and few events yielded generally imprecise estimates.

Recommendation

3. Restriction in dietary salt intake during pregnancy with the aim of preventing the development of pre-eclampsia and its complications is not recommended.

   - (Moderate-quality evidence. Weak recommendation.)

Remarks

a. The guideline development group agreed that healthy dietary practices should be promoted in the general population, including among pregnant women.

b. The group considered the avoidance of excessive dietary salt intake as a healthy dietary practice.

Calcium supplementation during pregnancy to prevent pre-eclampsia and its complications

A Cochrane systematic review of 13 RCTs, involving a total of 15 730 women, investigated the effects of routine (daily) supplementation with at least 1 g of calcium when used for preventing pre-eclampsia and related problems (*12*). As many as 96.2% of the women recruited were at a low risk of developing pre-eclampsia and over 70% had low baseline dietary calcium intake (less than 900 mg per day). All the trials in the review compared calcium supplementation with placebo or with no treatment. Supplemental calcium dose used ranged between 1.5 g and 2.0 g per day in all trials.

For all women, irrespective of the baseline risk of developing pre-eclampsia and calcium intake status, calcium supplementation more than halved the risk of pre-eclampsia when compared with placebo (13 trials, 15 730 women; RR 0.45 95% CI 0.31–0.65). This risk reduction was 41% for women at low risk of developing pre-eclampsia (eight trials, 15 143 women; RR 0.59, 95% CI 0.41–0.83) whereas the largest risk reduction (78%) was recorded among those at high risk of hypertensive disorders (five trials, 587 women; RR 0.22, 95% CI 0.12–0.42) (EB Table 6). Significant heterogeneity was observed among trials providing the estimate for low-risk women, probably as a result of variations in baseline dietary calcium intake or the smaller sample size. A considerable risk reduction for pre-eclampsia (64%) was found in eight trials that involved women or populations with low baseline dietary calcium intake (10 678 women; RR 0.36, 95% CI 0.20–0.65) while four trials showed no statistically significant reduction in the risk of pre-eclampsia for women or populations with adequate dietary calcium intake (5022 women; RR 0.62, 95% CI 0.32–1.20) (EB Table 7).

In women or populations with low calcium intake, there was a modest reduction in risk for the composite outcome of maternal death or

serious morbidity among women who received calcium compared with placebo (four trials, 9732 women, RR 0.80, 95% CI 0.65–0.97). Overall, a statistically significant increase in the risk ratio for HELLP syndrome was observed among women who received calcium supplementation compared with placebo (two trials, 12 901 women; RR 2.67, 95% CI 1.05–6.82). There were no statistically significant differences between the two groups for other critical (and proxy) outcomes addressed by the review: eclampsia (three trials, 13 425 women; RR 0.73, 95% CI 0.41–1.27); maternal death (one trial, 8312 women; RR 0.17, 95% CI 0.02–1.39); maternal intensive care unit admission (one trial, 8312 women; RR 0.84, 95% CI 0.66–1.07); stillbirth or death before discharge from hospital (11 trials, 15 665 women, RR 0.90, 95% CI 0.74–1.09); and admission to neonatal intensive care unit (four trials, 13 406 women, RR 1.05, 95% CI 0.94–1.18) (EB Tables 6 and 7).

Recommendation

4. In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of pre-eclampsia in all women, but especially in those at high risk of developing pre-eclampsia.

    • (Moderate-quality evidence. Strong recommendation.)

Remarks

a. The guideline development group agreed that healthy dietary practices should be promoted in the general population, among pregnant women.

b. The group considered appropriate dietary calcium intake as a healthy dietary practice. Available evidence supports the theory that calcium supplementation reduces the risk of development of pre-eclampsia by filling a dietary gap in calcium intake; calcium supplementation does not act as a therapeutic agent. In some populations, barriers to increasing

dietary calcium intake may be greater than those against providing calcium supplementation to pregnant women. The guideline development group noted that determining the dietary calcium intake on an individual basis is complex. In this context, the guideline group targeted this recommendation at populations living in geographical areas where low dietary calcium intake is commonly observed.

c. Women are regarded as being at high risk of developing pre-eclampsia if they have one or more of the following risk factors: previous pre-eclampsia; diabetes; chronic hypertension; renal disease; autoimmune disease; and multiple pregnancies. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

d. The guideline development group considered that in populations with adequate calcium intake, additional calcium supplementation does not improve outcomes related to pre-eclampsia and hypertensive disorders of pregnancy.

e. The group also considered the issue of interaction between iron supplements and calcium supplements. In this regard the group noted that concomitant administration of the two should be avoided. Ideally, the two supplements should be administered several hours apart (e.g. morning and evening). With regard to the timing of initiation of calcium supplementation, in most of the trials included in the Cochrane review it was started around 20 weeks of gestation.

f. Additional questions related to calcium and other pregnancy-related complications will be addressed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG).

Note

One participant in the guideline development group (Dr Peter von Dadelszen) wished to record his dissent with the above recommendation.

He believed that, while the current evidence supports the view that calcium supplementation in women from populations with low intake of calcium reduces the risk of diagnosis of pre-eclampsia, in these women calcium may function as an antihypertensive agent, reducing the incidence of hypertension and, because of that, the diagnosis of 'pre-eclampsia' (i.e., proteinuric hypertension in pregnancy). In other words, Dr Peter von Dadelszen was concerned that calcium supplementation could mask the development of pre-eclampsia. He was also concerned that the antihypertensive effect of calcium would not reduce the incidence of complications of pre-eclampsia if "heavy proteinuria" is excluded from the diagnosis of 'severe pre-eclampsia'.

Vitamin D supplementation

A Cochrane systematic review of 6 RCTs, involving a total of 1023 women, investigated the effects on pregnancy outcomes of vitamin D supplementation alone or in combination with other vitamins and minerals, including calcium, for women during pregnancy (*13*). Five trials involving 623 women compared the effects of vitamin D alone versus no supplementation/placebo and one trial involving 400 women compared the effects of vitamin D and calcium versus no supplementation. The dose of vitamin D used in routine daily supplementation ranged from 800 IU to 1200 IU. One trial provided 800 IU, three trials used a regimen dose of 1000 IU, and one trial used 1200 IU daily. Only one trial (400 women) reported on pre-eclampsia: women who received 1200 IU vitamin D along with 375 mg of elemental calcium per day were as likely to develop pre-eclampsia as women who received no supplementation (RR 0.67; 95% CI 0.33–1.35). In terms of other conditions, there were no significant differences between groups in terms of side-effects/nephritic syndrome (one trial, 400 women; RR 0.17, 95% CI 0.01–4.06); stillbirths (one trial, 400 women; RR 0.17, 95% CI 0.01–4.06) or neonatal deaths (one trial, 400 women; RR 0.17 95% CI 0.01–4.06) in women who received vitamin D supplements in comparison with no treatment or placebo. No studies reported on maternal death, admission to neonatal intensive care unit/special nursery or Apgar scores (EB Table 8).

Recommendation

5. Vitamin D supplementation during pregnancy is not recommended to prevent the development of pre-eclampsia and its complications.

    *   (Very-low-quality evidence. Strong recommendation.)

Remark

a. The guideline development group noted that several studies were still in progress on this topic which may change the evidence base in the future. The group was concerned about the limited evidence on safety of vitamin D supplementation during pregnancy and therefore made a strong recommendation against the use of vitamin D supplementation for prevention of pre-eclampsia during pregnancy.

Antioxidants for prevention of pre-eclampsia and its complications

Evidence related to the differential effects of antioxidants in the prevention of pre-eclampsia and its complications was extracted from a Cochrane systematic review of 15 RCTs involving a total of 22 359 women (*14*). Most of the trials had compared one or more vitamins, particularly combined vitamins C and E regimens, with placebo. When antioxidants were compared with placebo, there were no statistically significant differences in the critical (and proxy) maternal outcomes of pre-eclampsia (15 trials, 20 748 women; RR 0.94, 95% CI 0.82–1.07), severe pre-eclampsia (six trials, 16 341 women; RR 1.01, 95% CI 0.85–1.19), maternal death (eight trials, 19 586 women; RR 0.60, 95% CI 0.14– 2.51), serious maternal morbidity (three

trials, 4523 women; RR 1.22, 95% CI 0.39–3.81), gestational hypertension (10 trials, 1028 women; RR 1.02, 95% CI 0.85–1.23), and severe hypertension (four trials, 7990 women; RR 1.02, 95% CI 0.80–1.31). There was an increase in the risk ratio for use of intravenous antihypertensive medication among women allocated antioxidants compared with placebo (one trial, 2395 women; RR 1.94, 95% CI 1.07–3.53). No statistical differences were observed for any of the infant-related critical (and proxy) outcomes addressed in the trials: any baby death (eight trials, 19 782 women; RR 0.97, 95% CI 0.82–1.13); admission to special care nursery (four trials, 14 926 women; RR 1.02, 95% CI 0.95–1.10); and 5-minute Apgar score lower than seven (two trials, 3492 women; RR 1.25, 95% CI 0.79–2.00). Consideration of various risk levels of developing pre-eclampsia and gestational age at entry to the studies for these outcomes did not demonstrate any beneficial effects of antioxidants over placebo (EB Table 9).

Recommendation

6. Individual or combined vitamin C and vitamin E supplementation during pregnancy is not recommended to prevent the development of pre-eclampsia and its complications.

   • (High-quality evidence.
     Strong recommendation.)

Antiplatelets for prevention of pre-eclampsia

Evidence related to the effects of antiplatelet agents, such as aspirin and dipyridamole, when used for the prevention of pre-eclampsia and its complications came from a Cochrane systematic review of 60 RCTs involving 37 720 women (*15*). Most of the trials were relatively small and only nine recruited 1000 or more women. Participants were pregnant women considered to be at moderate or high risk of developing pre-eclampsia. Women were regarded as being at high risk if they were normotensive or had chronic hypertension in addition to one or more of the following risk factors: previous severe pre-eclampsia; diabetes; chronic hypertension;

renal disease; or autoimmune disease. Those at moderate risk were those with any other known risk factors for pre-eclampsia, in particular, primi-gravity. Aspirin alone was compared with placebo or no treatment in majority of the trials.

Antiplatelet agents versus placebo or no antiplatelet for primary prevention

When any antiplatelet agent, regardless of the dose, duration of therapy and time of initiating treatment, was compared with placebo in women with normal blood pressure at trial entry, there was no statistically significant difference in the risk of gestational hypertension (33 trials, 20 701 women; RR 0.95, 95% CI 0.88–1.03). This finding remains consistent for women at moderate risk of pre-eclampsia, whereas for those at high risk the use of antiplatelet agents was associated with a significant reduction in the risk of gestational hypertension (moderate risk: 22 trials, 19 863 women; RR 1.00, 95% CI 0.92–1.08; high risk: 12 trials, 838 women; RR 0.54, 95% CI 0.41–0.70). There was a statistically significant risk reduction in the development of pre-eclampsia among women who received antiplatelet agents compared with placebo (44 trials, 32 750 women; RR 0.82, 95% CI 0.76–0.89). This risk reduction remains consistent across risk groups for pre-eclampsia although it was more marked among high-risk women (moderate risk: 26 trials, 28 629 women; RR 0.86, 95% CI 0.78–0.94; high risk: 18 trials, 4121 women; RR 0.75, 95% CI 0.66–0.85).

No statistically significant differences were observed between the two comparison groups for any other critical (or proxy) outcomes addressed in the trials: eclampsia (nine trials, 22 584 women; RR 0.94, 95% CI 0.59–1.48); maternal death (three trials, 12 709 women; RR 2.57, 95% CI 0.39–17.06); placental abruption (16 trials, 24 982 women; RR 1.10, 95% CI 0.89–1.37); perinatal death (15 trials, 16 550 women; RR 0.89, 95% CI 0.74–1.08); and admission to special care baby unit (15 trials, 28 298 women; RR 0.95, 95% CI 0.90–1.01) (EB Table 10).

In trials in which the gestational age at recruitment was specified, the above findings were consistent between women who commenced treatment before and after 20 weeks of pregnancy for gestational hypertension, pre-eclampsia and placental abruption. For fetal, neonatal or infant death, the use of antiplatelet agents was associated with statistically significant reduction in risk among women who commenced treatment before 20 weeks, although the reduction in risk remained stattistically insignificant for those initiating treatment after 20 weeks (<20 weeks: 19 trials, 17 666 women, RR 0.82, 95% CI 0.69–0.98; >20 weeks: 19 trials, 11 057 women, RR 0.91, 95% CI 0.73–1.13) (EB Table 11).

Treatment effects of antiplatelet agents compared with placebo were evaluated across three dosage categories [low-dose aspirin (acetylsalicylic acid): 75 mg/day or lower; higher-dose aspirin: more than 75 mg/day; and aspirin more than 75 mg/day + dipyridamole] for the following critical (or proxy) outcomes: gestational hypertension; pre-eclampsia; placental abruption and fetal; and neonatal or infant death. While no statistically significant effect was demonstrated with low-dose aspirin, higher doses of aspirin and more than 75 mg/day aspirin plus dipyridamole were associated with statistically significant reduction in the risk of gestational hypertension. The risk reduction effect of antiplatelet agent compared with placebo for pre-eclampsia was consistent across the three dosage categories and tend to increase with increasing dose (12% reduction with aspirin 75 mg/d or lower to 70% reduction with aspirin more than 75 mg/day + dipyridamole). Similar pattern was observed for fetal, neonatal or infant death across the three dosage categories. No statistically significant effect was demonstrated in any of the dosage categories for placental abruption (EB Table 12).

Antiplatelet agents versus placebo or no antiplatelet for women with gestational hypertension

Comparison of any antiplatelet agent with placebo in women with gestational hypertension at trial entry showed a statistically significant reduction in the risks of pre-eclampsia (five trials, 1643 women; RR 0.60, 95% CI 0.45–0.78) and severe pre-eclampsia (one trial, 94 women; RR 0.33, 95% CI 0.14–0.75). No statistically significant differences were observed for any other critical (or proxy) outcomes addressed: eclampsia (three trials, 354 women; RR 0.25, 95% CI 0.03–2.24); placenta abruption (one trial, 94 women; RR 0.35, 95% CI 0.01–8.32); fetal, neonatal or infant death (four trials, 1728 women; RR 1.02, 95% CI 0.72–1.45); and admission to special care baby unit (one trial, 94 women; RR 0.52, 95% CI 0.05–5.56). Most of the trials providing these outcomes were small and at moderate risk of bias, thereby generating very-low- to low-quality evidence (EB Table 13).

Recommendations

7. Low-dose acetylsalicylic acid (aspirin, 75 mg/day) is recommended for the prevention of pre-eclampsia in women at high risk of developing the condition.

   - (Moderate-quality evidence. Strong recommendation.)

8. Low-dose acetylsalicylic acid (aspirin, 75 mg/day) for the prevention of pre-eclampsia and its related complications should be initiated before 20 weeks of pregnancy.

   - (Low-quality evidence. Weak recommendation.)

Remarks

a. Women are regarded as being at high risk of developing pre-eclampsia if they have one or more of the following risk factors: previous pre-eclampsia; diabetes; chronic hypertension; renal disease; autoimmune disease; and multiple pregnancies. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

b. The guideline development group acknowledged that in settings where 75 mg aspirin tablets are not available, the available dose nearest to 75 mg should be used.

c. While low-dose aspirin has been shown to be beneficial in women at high risk of pre-eclampsia, there is a paucity of evidence to suggest that any subset of women within the high-risk group would benefit from aspirin therapy.

d. The guideline development group noted that it may be appropriate to initiate antiplatelet agents before 20 weeks of gestation, and, if possible, as early as 12 weeks of gestation.

Antihypertensive drugs and diuretics

Antihypertensive drug treatment for mild to moderate hypertension during pregnancy

A Cochrane systematic review of 46 RCTs involving a total of 4282 women evaluated the potential benefits, risks and side-effects of antihypertensive drug treatment for women with mild to moderate hypertension in pregnancy (*16*). The trials compared antihypertensive drugs with placebo (28 trials, 3200 women) or another anti-hypertensive drug (19 trials, 1282 women). Thirty four of these trials (3480 women) were conducted in high-income countries and the others in low- and middle-income countries. The trials were generally small, with the largest recruiting 300 women. The class of antihypertensive drugs evaluated included alpha agonists, beta blockers, calcium channel blockers, vasodilators, ketan-serin and glyceryl trinitrate. All but glyceryl trini-trate were administered orally in the trials. In most trials, mild to moderate hypertension was defined as a diastolic blood pressure of 90 mm Hg or more, but not exceeding 110 mm Hg.

Any antihypertensive drug versus placebo or no antihypertensive

Comparison of any antihypertensive drug with placebo or no antihypertensive drug showed no statistically significant differences in the overall risk ratio for critical (and proxy) outcomes of pre-eclampsia (22 trials, 2702 women; RR 0.97,

95% CI 0.83–1.13), severe pre-eclampsia (two trials, 267 women; RR 0.61, 95% CI 0.25–1.48), eclampsia (five trials, 578 women; RR 0.34, 95% CI 0.01–8.15), HELLP syndrome (one trial, 197 women; RR 2.02, 95% CI 0.38–10.78), pulmonary oedema (one trial, 176 women; RR 5.23, 95% CI 0.25–107.39), maternal death (four trials, 376 women; RR 2.85, 95% CI 0.30–27.00), perinatal death (20 trials, 2382 women; RR 0.96, 95% CI 0.60–1.54) and admission to special care baby unit (eight trials, 1321 women; RR 1.11, 95% CI 0.93–1.32). Maternal adverse events as reflected by stopping or changing drugs due to side-effects were, however, significantly more common among women treated with an anti-hypertensive drug compared with those who received placebo (15 trials, 1403 women; RR 2.59, 95% CI 1.33–5.04) (EB Table 14).

For critical outcomes of pre-eclampsia, the lack of benefits with the use of antihypertensive drug over placebo was consistent across types of hypertensive disorders (hypertension alone, hypertension plus proteinuria or chronic hyperten-sion). Four small trials involving 725 women given calcium channel blockers showed an increase in the risk ratio for pre-eclampsia (RR 1.40, 95% CI 1.06–1.86) while eight trials involving 883 women treated with beta blockers showed statis-tically significant decrease in the risk ratio for pre-eclampsia (RR 0.73, 95% CI 0.57–0.94). For the proxy outcome of total fetal or neonatal death (including miscarriage), the similarity between the two comparison groups was consistent across the types of hypertensive disorders and gesta-tional age at trial entry (EB Table 15).

Any antihypertensive drug versus methyldopa

When any antihypertensive drug (essentially beta blockers, calcium channel blockers and/or ketanserin) was compared with methyldopa, no statistically significant differences were observed for the critical (or proxy) outcomes addressed: pre-eclampsia (nine trials, 804 women; RR 0.81, 95% CI 0.57–1.16); total fetal or neonatal death (17 trials, 1130 women; RR 0.67, 95% CI 0.37–1.21); admission to special care baby

unit (three trials, 379 women; RR 0.94, 95% CI 0.68–1.29); and maternal adverse events (four trials, 272 women; RR 2.80, 95% CI 0.12–67.91) (EB Table 16).

Any antihypertensive drug versus calcium channel blockers

Comparison of any antihypertensive drug (essentially beta blockers and glyceryl trinitrate) with calcium channel blockers showed similarity in the overall risks for the critical (or proxy) outcomes addressed: pre-eclampsia (two trials, 128 women; RR 2.15, 95% CI 0.73–6.38); HELLP syndrome (one trial, 100 women; RR 1.50, 95% CI 0.26–8.60); total fetal or neonatal death including miscarriage (two trials, 136 women; RR 1.00, 95% CI 0.06–15.55); admission to special care baby unit (one trial, 99 women; RR 1.47, 95% CI 0.44–4.89); and maternal adverse events (two trials, 136 women; RR 2.60, 95% CI 0.13–50.25) (EB Table 17).

Antihypertensive drug treatment for severe hypertension during pregnancy

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 29 RCTs involving 3351 women (*17*). Most of the trials were relatively small and only five of them recruited more than 100 women. Most of the trials participants recruited had diastolic blood pressure of 100 mmHg or higher at trial entry. 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 and isosorbide. Hydralazine was compared with another drug in 5 out of the 13 comparisons in the review. There were considerable variations between the studies regarding antihypertensive drug dosages.

Labetalol versus hydralazine

When labetalol was compared with hydralazine in women with very high blood pressure, no statistically significant differences were observed for any of the critical (or proxy) outcomes addressed in the trials: persistent high blood pressure (two trials, 217 women; RR 1.58, 95% CI 0.66–3.77); maternal pulmonary oedema (one trial, 197 women; RR 3.03, 95% CI 0.12–73.49); HELLP syndrome (one trial, 197 women; RR 1.01, 95% CI 0.15–7.03); oliguria (one trial, 197 women; RR 0.51, 95% CI 0.09–2.69); fetal or neonatal death (four trials, 274 women; RR 0.75, 95% CI 0.17–3.21); Apgar score <7 at 5 minutes (two trials, 224 women; RR 0.81, 95% CI 0.25–2.61); and hypotension (three trials, 247 women; RR 0.20, 95% CI 0.10–4.15). No events were recorded in both arms of the studies that reported eclampsia, maternal death and disseminated intravascular coagulation. The trials providing these results had moderate risk of bias, relatively small sample sizes and very sparse events, thus generating generally very-low-quality of evidence for the critical outcomes (EB Table 18).

Calcium channel blockers versus hydralazine

Compared with hydralazine, calcium channel blockers (nifedipine and isradipine) showed a statistically significant reduction in the risk of persistent high blood pressure (five trials, 263 women; RR 0.33, 95% CI 0.15–0.70). No statistically significant differences were observed for any other critical (or proxy) outcomes addressed: further episode(s) of very high blood pressure (two trials, 163 women; RR 0.85, 95% CI 0.65–1.11); fetal or neonatal death (four trials, 161women; RR 1.36, 95% CI 0.42–4.41); low blood pressure for the woman (three trials, 199 women; RR 2.83, 95% CI 0.12–64.89); and side-effects for the woman (four trials, 236 women; RR 0.79, 95% CI 0.50–1.24). Most of the trials providing these critical outcomes were small and at moderate or high risk of bias, thus generating very-low-quality evidence for the outcomes (EB Table 19).

Prostacyclin versus hydralazine

One trial (47 women) comparing prostacyclin with hydralazine showed no statistically significant differences between the comparison groups for the critical outcomes addressed: persistent high blood pressure (RR 0.23, 95% CI 0.01–4.47); neonatal death (RR 1.14, 95% CI 0.08–17.11); and side-effects for the woman (RR 1.14, 95% CI 0.08–17.11). This trial had moderate risk of bias and yielded generally imprecise estimates due to the very small sample size and few events (EB Table 20).

Ketanserin versus hydralazine

Compared with hydralazine, ketanserin was more likely to be associated with persistent high blood pressure (three trials, 180 women; RR 4.79, 95% CI 1.95–11.73), but fewer side-effects for the women (three trials, 120 women; RR 0.32, 95% CI 0.19–0.53). No statistically significant differences were observed in the effects of the two drugs for other critical (or proxy) outcomes addressed: eclampsia (two trials, 64 women; RR 0.60, 95% CI 0.08–4.24); severe maternal morbidity (one trial, 56 women; RR 0.32, 95% CI 0.09–1.12); maternal death (two trials, 124 women; RR 0.32, 95% CI 0.03–2.96); perinatal death (two trials, 116 women; RR 0.27, 95% CI 0.05–1.64); and hypotension (two trials, 76 women; RR 0.26, 95% CI 0.07–1.03) (EB Table 21).

Uradipil versus hydralazine

Two small trials (59 women) compared uradipil with hydralazine. There were no differences between the comparison groups for the critical outcomes addressed: persistent high blood pressure (two trials, 59 women; RR 1.38, 95% CI 0.06–31.14); neonatal death (two trials, 59 women; RR 0.66, 95% CI 0.08–5.25); hypotension (one trial, 33 women; RR 0.22, 95% CI 0.02–2.13); and side-effects for the women (two trials, 59 women; RR 0.59, 95% CI 0.10–3.58). No case of eclampsia or stillbirth was recorded in either arm of both trials. The moderate risk of bias in the trials providing these results, in addition to the

very small sample size and few events, generated evidence of very-low-quality for the critical outcomes (EB Table 22).

Labetalol versus calcium channel blockers

Two small trials (80 women) that compared labetalol with calcium channel blockers showed no statistical differences between the two drugs for any of the critical outcomes: eclampsia (one trial, 20 women, RR 0.20, 95% CI 0.01–3.70); persistent high blood pressure (one trial, 60 women; RR 1.22, 95% CI 0.59–2.51); and specific side-effects such as nausea and/or vomiting (one trial, 60 women; RR 1.00, 95% CI 0.07–15.26); and palpitations (one trial, 60 women; RR 0.14, 95% CI 0.01–2.65). No case of hypotension was recorded in either of the two arms of the trials (EB Table 23).

Labetalol versus methyldopa

One small trial (72 women) comparing labetalol with methyldopa showed no statistical differences between the two drugs for any of the critical outcomes addressed: persistent high blood pressure (RR 1.19, 95% CI 0.74–1.94); neonatal death (RR 4.49, 95% CI 0.22–90.30); total stillbirths and neonatal deaths (RR 4.49, 95% CI 0.22–90.30); admission to special care baby unit (RR 1.06, 95% CI 0.66–1.71); and side-effects resulting in changing of drugs (RR 8.08, 95% CI 0.45–144.73). The trial providing these results had moderate risk of bias and few events, thus yielding generally very-low-quality evidence for the reported critical outcomes (EB Table 24).

Labetalol versus diazoxide

One small trial (90 women) showed that labetalol was less likely to cause hypotension requiring treatment compared with diazoxide, although the confidence interval was borderline for statistical significance (RR 0.06, 95% CI 0.00–0.99). There were no statistical differences observed for the other critical outcomes addressed: persistent high blood pressure (RR 0.50, 95% CI 0.13–1.88); and perinatal deaths (RR 0.14, 95% CI 0.01–2.69) (EB Table 25).

Nitrates versus magnesium sulfate

A small trial (36 women) comparing isosorbide with magnesium sulfate reported no case of eclampsia in association with either drug and showed no statistically significant differences between them for the proxy outcome of persistent high blood pressure (RR 0.14, 95% CI 0.01–2.58) (EB Table 26).

Nimodipine versus magnesium sulfate

Compared with magnesium sulfate, nimodipine was statistically significantly more likely to be associated with eclampsia (two trials, 1683 women; RR 2.24, 95% CI 1.06–4.73), but there was less risk of persistent high blood pressure (one trial, 1650 women; RR 0.84, 95% CI 0.76–0.93) and flushing as a side-effect (one trial, 1650 women; RR 0.22, 95% CI 0.12–0.40). No statistical differences were observed for any other critical (or proxy) outcomes addressed: coagulopathy (one trial, 1650 women; RR 1.69, 95% CI 0.41–7.05); oliguria (one trial, 1650 women; RR 0.87, 95% CI 0.59–1.26); and hypotension (one trial 1650 women; RR 0.72, 95% CI 0.23–2.27). The quality of evidence for these outcomes ranges between very-low- to low-quality, mainly because the principal study (1650 women) was at high risk of bias (EB Table 27).

Nifedipine versus chlorpromazine

One small trial (60 women) comparing nifedipine with chlorpromazine showed no statistically significant differences for the critical (and proxy) outcomes addressed: eclampsia (55 women; RR 2.52, 95% CI 0.11–59.18), persistent high blood pressure (60 women; RR 0.09, 95% CI 0.01–1.57) (EB Table 28).

Nifedipine versus prasozin

One trial (150 women) comparing nifedipine with prasozin showed no statistically significant differences for any of the critical (or proxy) outcomes addressed: HELLP syndrome (one trial, 145 women; RR 1.15, 95% CI 0.37–3.60); renal failure (one trial, 145 women; RR 0.48, 95% 0.04–5.17); pulmonary oedema (one trial, 145 women; RR 0.19, 95% CI 0.02–1.60); admission to intensive care (one trial, 145 women; RR 0.32, 95% CI 0.01–7.73); maternal death (one trial, 145 women; RR 0.32, 95% CI 0.01–7.73); stillbirth (one trial, 149 women; RR 0.46, 95% CI 0.18–1.13); and admission to special care baby unit (one trial, 130 women; RR 0.78, 95% CI 0.49–1.23). No case of eclampsia was recorded in either arms of the trial. This trial had moderate risk of bias, few events in addition to its small sample size and thus yielded generally very-low-quality evidence for the critical (and proxy) outcomes (EB Table 29).

Nitroglycerine versus nifedipine

One small trial (32 women) compared nitroglycerine administered as an infusion with sublingual nifedipine. The risk of critical (and proxy) outcomes addressed were similar for both drugs: Apgar <8 at 5 minutes (RR 3.00, 95% CI 0.13–68.57); and specific side-effects such as flushing (RR 0.67, 95% CI 0.23–1.92), headache (RR 1.50, 95% CI 0.29–7.81) and palpitations (RR 0.33, 95% CI 0.01–7.62). No case of maternal or perinatal death was recorded in the trial. Although this trial had little or no risk of bias, the very small sample size and few events resulted in generally low-quality evidence for the reported critical outcomes (EB Table 30).

In summary, the analysis of the evidence related to the multiple comparisons of antihypertensive drugs for very high hypertension during pregnancy is complicated by its low quality which is due primarily to the small samples used in the trials, rare events as outcomes and variations in the adminsterred 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.

Diuretics for preventing pre-eclampsia

Evidence related to the effects of diuretics on the prevention of pre-eclampsia came from a Cochrane systematic review of five RCTs involving 1836 women in the USA (*18*). Both primiparous and multiparous women with gestations from first to the third trimester were recruited into the trials. Two trials (347 women) recruited only women with normal blood pressure, one trial (20 women) recruited only those with chronic hypertension while the other two trials (1658 women) did not report on blood pressure status at trial entry. In all trials thiazide diuretics were compared with placebo or no treatment.

When diuretics were compared with placebo or no treatment, there were no statistically significant differences in the critical (or proxy) outcomes: new or worsening hypertension (two trials, 1475 women; RR 0.85, 95% CI 0.68–1.08), pre-eclampsia (four trials, 1391 women; RR 0.68, 95% CI 0.45–1.03), severe pre-eclampsia (two trials, 1297 women; RR 1.56, 95% CI 0.26–9.17), use of antihypertensive drugs (one trial, 20 women; RR 2.00, 95% CI 0.21–18.69), adverse events (two trials, 1217 women; RR 1.85, 95% CI 0.81–4.22), perinatal death (five trials, 1836 women; RR 0.72, 95% CI 0.40–1.27) and 5-minute Apgar score less than seven (one trial, 20 women; RR 3.00, 95% CI 0.14–65.90). There was no case of eclampsia in both the intervention and control arms of one trial that reported it as an outcome measure. All the trials providing this evidence had moderate risk of bias, relatively small sample sizes and sparse events resulting in generally low overall quality of evidence for the critical outcomes (EB Table 31).

Recommendations

9. Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.

   - (Very-low-quality evidence.
     Strong recommendation.)

10. 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.

    - (Very-low-quality evidence.
      Weak recommendation.)

11. Diuretics, particularly thiazides, are not recommended for the prevention of pre-eclampsia and its complications.

    - (Low-quality evidence.
      Strong recommendation.)

Remarks

a. The guideline development group considered that there is absence of 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 acute hypertension.

b. With regard to the treatment of mild/moderate hypertension in pre-eclampsia, a formal evidence review was conducted. The guideline development group considered the available evidence controversial, as there are potential harms and benefits associated with both lines of action. The group was aware of ongoing trials that might provide more robust data in the near future for guidance. Hence, they decided not to issue a recommendation on the treatment of mild/moderate hypertension until further evidence becomes available.

c. In terms of the choice and route of adminis-
tration 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.

d. In not recommending diuretics, particularly
thiazides, for the for the prevention of pre-
eclampsia and its complications, the group
noted that this recommendation applies
only to women at risk of developing pre-
eclampsia who are not currently under treat-
ment with diuretics. It does not apply to the
use of diuretics for non-pre-eclampsia-related
indications.

Magnesium sulfate for prevention and treatment of eclampsia

Prevention of pre-eclampsia

A Cochrane systematic review of 15 RCTs inves-
tigated the relative effects of magnesium sulfate
and other anticonvulsants when used for preven-
tion of eclampsia (*19*). Notable comparisons in
this review were between magnesium sulfate
and placebo or no anticonvulsants (six trials,
11 444 women); phenytoin (four trials, 2345
women); diazepam (two trials, 66 women); and
nimodipine (one trial, 1750 women). One small
trial (36 women) compared magnesium sulfate
with isosorbide, and another trial (33 women)
compared magnesium chloride with methyldopa.

*Magnesium sulfate versus placebo or no
anticonvulsant*

Six RCTs (11 444 women), including the large
multicentre Magpie Trial (*20*) involving 10 141
participants, provided the evidence for this
comparison. About half of the women recruited
into the trial had received the maintenance
regimen of magnesium sulfate through the intra-
venous route (1 g/h) and the other half through
the intramuscular route. The maintenance dose
was administered strictly by the intravenous
route in four trials and the intramuscular route in
one trial. For most trials, clinical monitoring for
potential adverse effects was reported and none
of the six trials reported using serum monitoring
of magnesium sulfate.

When compared with placebo or no anticonvul-
sant, magnesium sulfate was associated with
statistically and clinically significant reduction in
the risk of eclampsia by 59% (six trials, 11 444
women; RR 0.41, 95% CI 0.29–0.58) (EB Table
32). This effect was consistent for women who
were antepartum at trial entry (six trials, 10 109
women; RR 0.40, 95% CI 0.27–0.57) but nonsig-
nificant for those who were postpartum at trial
entry (one trial, 1335, RR 0.54, 95% CI 0.16–1.80)
(EB Table 33). The effect was also consistent
and more pronounced among women who were
34 or more weeks pregnant (two trials, 6498
women; RR 0.37, 95% CI 0.24–0.59) and those
who had received no anticonvulsants prior to
trial entry (three trials, 10 086 women; RR 0.33,
95% CI 0.22–0.48) (EB Tables 34 and 35). It was
consistent regardless of the route of administra-
tion for the maintenance of magnesium sulfate
(EB Table 36).

No statistically significant differences were
observed between magnesium sulfate and
placebo regarding the risks of maternal death
(two trials, 10 795 women; RR 0.54, 95%
CI 0.26–1.10), any serious maternal morbidity (two
trials 10 332 women; RR 1.08, 95% CI 0.89–1.32),
respiratory arrest (one trial, 10 110 women; RR
2.50, 95% CI 0.49–12.88) and toxicity as shown
by respiratory depression and absent tendon

reflexes (three trials, 10 899 women; RR 5.96, 95% CI 0.72–49.40) and calcium gluconate administration (two trials, 10 795 women; RR 1.35, 95% CI 0.63–2.88). Any reported side-effects were significantly more common among women treated with magnesium sulfate rather than placebo (one trial, 9992 women; RR 5.26, 95% CI 4.59–6.03).

For the baby, no clear difference were observed in the risks of stillbirth or neonatal death (three trials, 9961 babies; RR 1.04, 95% CI 0.93–1.15), admission to special care baby unit (RR 1.01, 95% CI 0.96–1.06) and Apgar score less than seven at 5 minutes (one trial, 8260 women; RR 1.02, 95% CI 0.85–1.22).

Magnesium sulfate versus phenytoin

Magnesium sulfate was compared with phenytoin for the prevention of eclampsia in four RCTs (2343 women). Compared with phenytoin, magnesium sulfate significantly reduced the risk of eclampsia (three trials, 2291 women; RR 0.08, 95% CI 0.01–0.60). No statistically significant differences were observed between the two groups in terms of stillbirth (RR 0.62, 95% CI 0.27–1.41), neonatal death (RR 0.26, 95% CI 0.03–2.31), Apgar score less than seven at 5 minutes (RR 0.58, 95% CI 0.26–1.30) and admission to neonatal care (RR 1.00, 95% CI 0.63–1.59) (EB Table 37).

Magnesium sulfate versus diazepam

A small trial involving 66 women compared magnesium sulfate and diazepam for the prevention of eclampsia. The sample size and the events recorded were too small to draw any reliable conclusions (EB Table 38).

Magnesium sulfate versus nimodipine

Magnesium sulfate was compared with nimodipine in one trial (1650 women). There were fewer cases of eclampsia among women allocated magnesium sulfate compared with nimodipine (RR 0.33, 95% CI 0.14–0.77) (EB Table 39).

Treatment of eclampsia

Magnesium sulfate versus diazepam for women with eclampsia

A Cochrane systematic review of seven RCTs involving 1396 women provided the evidence on the differential effects of magnesium sulfate when compared with diazepam for the care of women with eclampsia (*21*). Most women in the trials had eclampsia either before or after delivery and about half of them received an anticonvulsant before trial entry. All regimens used in the trials for both magnesium sulfate and diazepam included loading and maintenance doses.

Magnesium sulfate fared better than diazepam regarding critical maternal outcomes of death (seven trials; 1396 women; RR 0.59, 95% CI 0.38–0.92) and recurrence of convulsions (seven trials; 1390 women; RR 0.43, 95% CI 0.33–0.55). There were no statistical differences between the two drugs for any serious maternal morbidity (two trials, 956 women; RR 0.88, 95% CI 0.64–1.19) or any of its proxies addressed in this comparison. Regarding fetal outcomes, no clear difference was demonstrated between the comparison groups for perinatal death (four trials, 788 infants; RR 1.04, 95% CI 0.81–1.34) and admission to intensive care unit (three trials, 634 infants; RR 0.92, 95% CI 0.79–1.06). Magnesium sulfate was associated with fewer cases of babies born with Apgar scores lower than seven at 5 minutes (three trials, 643 infants; RR 0.70, 95% CI 0.54–0.90) (EB Table 40).

Comparison of the two treatment groups according to route of administration of magnesium sulfate maintenance showed that intramuscular maintenance significantly reduced the risks of maternal respiratory depression (two trials, 120 women; RR 0.30, 95% CI 0.10–0.93) and maternal ventilation (two trials, 120 women; RR 0.20, 95% CI 0.05–0.88), but there was no statistically significant difference for maternal cardiac arrest (two trials, 120 women; RR 0.52, 95% CI 0.10–2.66) (EB Table 41). The two trials from which these findings were derived had a moderate risk of bias, small sample sizes and few events, resulting in inadequate quality of data.

Magnesium sulfate versus phenytoin for women with eclampsia

Evidence related to the effects of magnesium sulfate compared with phenytoin for the care of women with eclampsia came from a Cochrane systematic review of six RCTs involving a total of 972 women (*22*). Most of the women had eclampsia before delivery and had received anticonvulsants prior to trial entry. Eighty per cent of the women in the review had participated in the relatively large Collaborative Eclampsia Trial (*23*), which had a low risk of bias. The other five trials were all small and at a moderate risk of bias.

Compared with those treated with phenytoin, women treated with magnesium sulfate were at reduced risk of recurrence of convulsions (six trials, 972 women; RR 0.34, 95% CI 0.24–0.49), admission to intensive care unit (one trial, 775 women; RR 0.67, 95% CI 0.50–0.89) and need for ventilatory support (two trials, 825 women; RR 0.68, 95% CI 0.50–0.91). There were no statistically significant differences between the two treatment groups for maternal death (three trials, 847 women; RR 0.50, 95% CI 0.24–1.05), any serious maternal morbidity (one trial, 775 women; RR 0.94, 95% CI 0.73–1.20) and the reported proxy outcomes for severe maternal morbidity (EB Table 42).

Babies born to women treated with magnesium sulfate, rather than phenytoin, were less likely to be admitted for special care (one trial, 518 infants, RR 0.73, 95% CI 0.58–0.91) but no clear differences were observed between the two treatment groups with regard to the risks of perinatal death (two trials, 665 infants; RR 0.85, 95% CI 0.67–1.09) and Apgar score less than seven at 5 minutes (one trial, 518 infants; RR 0.86, 95% CI 0.52–1.43).

Magnesium sulfate versus lytic cocktail for women with eclampsia

The evidence on the differential effects of magnesium sulfate compared with the so-called "lytic cocktail" (usually a combination of chlorproma-

zine, promethazine and pethidine) was derived from a Cochrane systematic review of three small trials involving a total of 397 women (*24*). Compared with lytic cocktail, magnesium sulfate was associated with significantly fewer cases of maternal death (three trials, 397 women; RR 0.14, 95% CI 0.03–0.59), recurrence of convulsions (three trials, 397 women; RR 0.06, 95% CI 0.03–0.12), coma for more than 24 hours (one trial, 108 women; RR 0.04, 95% CI 0.00–0.74) and respiratory depression (two trials, 198 women; RR 0.12, 95% CI 0.02–0.91). No clear differences were observed between the two treatment groups for any other proxy outcome for severe maternal morbidity. The risks of stillbirth and neonatal mortality were also similar between the two treatment groups (EB Table 43).

Alternative regimens of magnesium sulfate for treatment of pre-eclampsia and eclampsia

Evidence related to the comparative effects of alternative magnesium sulfate regimens for the treatment of pre-eclampsia and eclampsia came from a Cochrane systematic review of six RCTs involving 866 women (*25*). Two of the trials (451 women) had compared regimens for eclampsia while the other four (415 women) had compared regimens for pre-eclampsia. None of the trials had used dosages shown to be effective in large RCTs demonstrating the effectiveness of magnesium sulfate.

When loading dose alone was compared with loading dose plus maintenance regimen for women with eclampsia, one trial (401 women) showed no statistically significant differences in the critical outcomes of recurrent convulsions (RR 1.13, 95% CI 0.42–3.05) and maternal death (RR 0.89, 95% CI 0.37–2.14) and the proxy outcome for perinatal death, stillbirth (RR 1.13, 95% CI 0.66–1.92) (EB Table 44). The loading dose employed in this trial was 4 g intravenous (IV) plus 6 g intramuscular (IM), while the maintenance was 2.5 g IM every 4 hours for 24 hours. The trial had very serious limitations with regard to its quality and the resulting data were gener-

ally imprecise. A small trial (50 women) compared low-dose regimen (similar to the regimen above) with the "standard" regimen (4 g IV + 8 g IM as loading dose, then 4 g IM every 4 hours for 24 hours) for women with eclampsia. The only case of recurrent convulsion in the trial was reported among women treated with the low-dose regimen, thus generating a highly imprecise and unreliable data for this critical outcome. No statistically significant differences were observed between the two treatment groups for admission to neonatal special care unit (RR 2.36, 95% CI 0.53–10.58) and proxy outcomes of oliguria (RR 0.20, 95% CI 0.03–1.59) and any baby death (RR 0.89, 95% CI 0.41–1.93) (EB Table 45).

One small trial (17 women) had compared intravenous (2 g hourly for 24 hours) and intramuscular (5 g 4-hourly for 24 hours) maintenance regimens for women with pre-eclampsia. There was no case of eclampsia in either of the two arms of the trials. The trial was too small to yield any reliable conclusions regarding other critical and proxy outcomes reported [magnesium sulfate toxicity (RR 3.33, 95% CI 0.15– 71.90); renal failure (RR 3.33, 95% CI 0.15–71.90); stillbirth (RR 1.25, 95% CI 0.09–17.02) (EB Table 46).

Three trials involving 398 women evaluated short versus 24-hour postpartum magnesium sufate regimens for women with mild and severe pre-eclampsia or imminent eclampsia. Two of these trials, accounting for approximately two thirds of the participants, were at a low or no risk of bias while one was at a moderate risk of bias. None of the women in these trials developed any of the critical outcomes addressed: eclampsia (two trials, 394 women); magnesium sulfate toxicity (one trial, 196 women) (EB Table 47).

Recommendations

12. Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants.

    - (High-quality evidence. Strong recommendation.)

13. Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants.

    - (Moderate-quality evidence. Strong recommendation.)

14. The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia.

    - (Moderate-quality evidence. Strong recommendation.)

15. For settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe pre-eclampsia and eclampsia.

    - (Very-low-quality evidence. Weak recommendation.)

Remarks

a. Magnesium sulfate is a lifesaving drug and should be available in all health-care facilities throughout the health system. The guideline development group believed that capacity for clinical surveillance of women and administration of calcium gluconate were essential components of the package of services for the delivery of magnesium sulfate.

b. Clinical evidence supports the use of magnesium sulfate in all pre-eclampsia patients. In settings where there are resource constraints to manage the administration of magnesium sulfate safely in all women with pre-eclampsia, there may be a need to accord greater priority to the more severe cases. Magnesium sulfate is effective in preventing seizures in both mild and severe pre-eclampsia. However, the guideline development group noted that a higher number of women need to be treated to prevent one seizure. The group agreed on the need to treat women with severe pre-

eclampsia, but the group members were divided on the use of magnesium sulfate as a prophylaxis for mild pre-eclampsia.

c. Large trials have evaluated and demonstrated the effectiveness of full regimens of magnesium sulfate, which include a loading dose followed by 24-hour maintenance therapy. Specific guidance on how to administer magnesium sulfate can be found in the WHO manual entitled *Managing complications in pregnancy and childbirth: a guide for midwives and doctors* (*26*).

d. The guideline development group deliberated on the best course of action in settings in which it is not possible to administer the full magnesium sulfate regimen. The group debated the possible (but yet unproven) benefits of administering only the loading dose versus transferring women with severe pre-eclampsia and eclampsia without any magnesium sulfate. The group felt that that, even in cases where immediate transfer of the woman to a higher-level facility was not possible, the patient was likely to be better off with only the loading dose than without it. The group felt that since this was a common scenario in many low-income countries, it should be given high priority for further research.

Corticosteroids for HELLP syndrome

Evidence related to the use of corticosteroids for improving pregnancy outcomes in women with HELLP syndrome was extracted from one Cochrane systematic review of 13 RCTs (*27*), all of which were relatively small (total of 626 women). Participants in these trials were women with clinical and biochemical diagnosis of HELLP syndrome during pregnancy or shortly after delivery. Eleven trials (550 women) compared corticosteroid therapy (dexamethasone, bethamethasone or prednisolone) with placebo or no treatment while two trials (76 women) compared dexamethasone with bethamethasone.

When a corticosteroid was compared with placebo or no treatment for women with HELLP syndrome, there were no statistical differences in the critical (or proxy) outcomes: eclampsia (one trial, 132 women; RR 0.80, 95% CI 0.34–1.90); maternal death (five trials, 362 women; RR 0.95, 95% CI 0.28–3.21), maternal death or severe morbidity (one trial, 31 women; RR 0.27, 95% CI 0.03–2.12), maternal liver haematoma, rupture or failure (two trials, 91 women; RR 0.22, 95% CI 0.03–1.83), maternal pulmonary oedema (three trials, 297 women; RR 0.77, 95% CI 0.24–2.48), renal failure (three trials, 297 women; RR 0.69, 95% CI 0.39–1.22), need for dialysis (one trial, 60 women; RR 3.00, 95% CI 0.13–70.83), perinatal/infant death (two trials, 58 women; RR 0.64, 95% CI 0.21–1.97) and 5-minute Apgar score less than seven (two trials, 58 women; RR 0.89, 95% CI 0.27–2.95). These findings were consistent when treatment was commenced antenatally, postnatally or mixed (EB Table 48). The findings for all these outcomes were generally imprecise because of very small sample sizes in the trials and sparse data.

Comparison of dexamethasone with bethamethasone for treatment of HELLP syndrome showed no statistically significant differences in the two critical outcomes addressed: perinatal/infant death (one trial, 43 infants; RR 0.95, 95% CI 0.15–6.17); and 5-minutes Apgar score less than seven (one trial, 43 infants; RR 0.95, 95% CI 0.22–4.21) (EB Table 49).

Recommendation

16. The use of corticosteroids for the specific purpose of treating women with HELLP syndrome is not recommended.

    • (Very-low-quality evidence. Weak recommendation.)

Remarks

a. The guideline development group noted that, in addition to the existing evidence, three small trials addressing this research question had been registered in the WHO International

Clinical Trials Registry Platform (*28*). In one trial (66 women) recruitment had been completed, in the second trial it was still ongoing (160 women) and in the third recruitment was yet to begin. In view of the very low quality of the evidence base on this topic and relative ease of use and availability/affordability of corticosteroids, the group accorded corticosteroids for the treatment of HELLP syndrome high priority for further research.

b. The guideline development group emphasized that the use of corticosteroids for other indications, such as fetal lung maturation, are not included in the above recommendation.

Interventionist versus expectant care for severe pre-eclampsia before term

Evidence related to the differential effects of a policy of interventionist care and early delivery compared with a policy of expectant care and delayed delivery for women with early onset severe pre-eclampsia was extracted from a Cochrane systematic review (*29*). The review included three small trials that recruited a total of 163 women with severe pre-eclampsia at less than 34 weeks' gestation. The policy of interventionist care in these trials included 24–48 hours of stabilization followed by delivery just after stabilization. During the stabilization period steroids, magnesium sulfate and antihypertensive drugs were administered as necessary. When the policy of interventionist care was compared with that of expectant care and delayed delivery, there were no statistically significant differences in any of the critical (or proxy) outcomes of eclampsia, renal failure, pulmonary oedema, HELLP syndrome, perinatal death and admission to neonatal intensive care unit. Adverse critical outcomes for the mother were generally rare in both comparison groups (EB Table 50). The findings for reported critical outcomes in RCTs were considered imprecise because of very small sample sizes and sparse data in the comparisons. Another systematic review including observational data (39 cohorts, 4650 women, very low quality) found

similar results, though all four cohorts relevant to women with pre-eclampsia before 24 weeks went in favour interventionist care due to very high perinatal mortality and morbidity with either policy (*30*).

Recommendations

17. Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks.

    • (Very-low-quality evidence. Strong recommendation.)

18. In women with severe pre-eclampsia, a viable fetus, and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.

    • (Very-low-quality evidence. Weak recommendation.)

19. In women with severe pre-eclampsia, a viable fetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.

    • (Very-low-quality evidence. Weak recommendation.)

Remarks

a. A policy of expectant management usually includes intra-hospital care with steroids for fetal lung maturation, magnesium sulfate (as necessary), antihypertensive drugs (as necessary), and close maternal and fetal monitoring to identify indications for delivery (e.g. uncontrolled hypertension, deterioration in the condition of the mother and the fetus, including organ dysfunction and fetal distress). As part

of expectant management, in-utero transfer to a tertiary-level centre with neonatal intensive care capacity should be considered. The decision on the route of delivery should be made on a case-by-case basis, taking into account, among other factors, gestational age, fetal and cervical status, and urgency.

b. The guideline development group considered that the gestational age threshold for using expectant management in very preterm fetuses depends on the fetal viability status and on the anticipated prolongation of gestation with expectant management. The guideline development group acknowledged that the gestational age threshold of fetal viability should be locally agreed. In establishing this, the local context, the availability of resources, and the local newborn survival rates by gestational age, should be considered (*2,19*). The average gain in terms of prolongation of gestation with expectant management ranges from 1 week to 2 weeks. Hence, fetuses at a gestational age 1–2 weeks below the fetal viability threshold may benefit from expectant management.

c. The guideline development group considered that there was not enough evidence to make a clear-cut recommendation for women with severe pre-eclampsia between 34 and 36 (plus 6 days) weeks of gestation. However, considering the long-term adverse consequences of late preterm birth, the group put more emphasis on expectant management than early delivery.

Induction of labour for pre-eclampsia at term

In order to assess the differential effects of a policy of induction of labour versus expectant management for pre-eclampsia at term, a systematic review of literature was conducted. This review identified one multicentre RCT conducted in the Netherlands that had recruited a total of 756 women with mild pre-eclampsia or gestational hypertension after 36 weeks' gestation (*31*). When a policy of induction of

labour (aim within 24 hours) was compared with expectant management, there was no case of eclampsia, maternal death or perinatal death recorded in both arms of the trial. There were also no statistically significant differences between the two comparison groups for the other critical (or proxy) outcomes addressed in the trial: pulmonary oedema (RR 0.20, 95% CI 0.01–4.17), HELLP syndrome (RR 0.37, 95% CI 0.12–1.14), admission of the mother to intensive care unit (RR 0.43, 95% CI 0.17–1.11), admission of the newborn to neonatal intensive care unit (RR 1.26, 95% CI 0.50–3.15) and 5-minute Apgar score less than seven (RR 0.78, 95% CI 0.29–2.08) Nevertheless, a reduced risk of systolic and diastolic severe hypertension (respectively, $\geq$ 170 mmHg and $\geq$ 110 mmHg) was observed among women with mild pre-eclampsia submitted to expectant management at term (respectively, RR 0.60, 95% CI 0.38–0.95 and RR 0.56, 95% CI 0.36–0.87) (EB Table 51). This evidence is indirectly applied to women with severe pre-eclampsia, at term for supporting a policy of early delivery.

Recommendations

20. In women with severe pre-eclampsia at term, a policy of early delivery is recommended.

    - (Low-quality evidence.
      Strong recommendation.)

21. In women with mild pre-eclampsia or gestational hypertension at term, induction of labour is recommended.

    - (Moderate-quality evidence.
      Weak recommendation.)

Remarks

a. The guideline development group considered that there is absence of clinical uncertainty over whether termination of pregnancy in women with severe pre-eclampsia at term is beneficial. Quality of evidence provided by the Hypitat trial (*31*) further downgraded for indirectness.

b. The guideline development group considered that, in women with pre-eclampsia at term, expectant management is associated with a substantial risk of further maternal and fetal complications and absence of substantial maternal and fetal benefits.

c. In settings where gestational age is difficult to determine accurately, special attention should be paid to avoid iatrogenic prematurity in infants.

d. The guideline development group considered that, if induction of labour is contraindicated due to maternal or fetal conditions, early delivery by caesarean section is recommended (as opposed to expectant management).

Prevention and treatment of postpartum hypertension

Evidence related to the effects of routine post-natal antihypertensive drug therapy compared with no treatment for the prevention of postpartum hypertension in women with antenatal pre-eclampsia and for improving outcomes in women with mild to moderate hypertension was obtained from a Cochrane review of eight RCTs (*32*). The trials were relatively small, with a total of only 622 women. Three trials (313 women) compared a policy of routine administration of oral antihypertensive drugs (furosemide or nifedipine) with an approach that used antihypertensive drugs only for severe postpartum hypertension in women with antenatal pre-eclampsia. The relative risks were not estimable for the reported critical (and proxy) outcomes (namely maternal death, maternal organ failure, maternal side-effects necessitating changing of drug and severe hypotension) as no events were recorded in either of the two arms of each trial (EB Table 52).

The Cochrane review identified no trial that compared antihypertensive drug therapy with placebo for women with mild to moderate postpartum hypertension. Three trials (189 women),

however, compared timolol, hydralazine and nifedipine with methyldopa for the treatment of mild to moderate postpartum hypertension. Two of these trials (106 women) recorded no case of maternal death in the two groups. There was also no significant difference between the two groups in terms of the risk of medication being changed due to maternal side-effects (two trials, 106 women; RR 0.50, 95% CI 0.05–5.30). Two trials (120 women) compared intravenous hydrala-zine with either sublingual nifedipine or labetalol for the treatment of women with severe post-partum hypertension. No case of maternal death or maternal hypotension was reported for this comparison (EB Table 53).

The trials providing evidence for critical outcomes in the above comparisons were all at a moderate risk of bias. This level of bias in addition to their generally small sample size and sparse events resulted in very low overall quality of evidence.

Recommendations

22. In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended.

    • (Very-low-quality evidence. Strong recommendation.)

23. Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.

    • (Very-low-quality evidence. Strong recommendation.)

Remarks

a. The guideline development group recognized the need for discharge instructions, including education concerning the signs and symptoms associated with postpartum hypertension.

b. In women receiving postpartum antihyper-tensive treatment, at the present time it is not known at what point the treatment and

monitoring of hypertension could be stopped. Hence, the group highlighted this topic as a research priority.

c. The guideline development group put more emphasis on the frequency of postpartum deaths related to stroke and recognized that the maximum increase in blood pressure usually occurs towards the end of the first postpartum week (when, in most settings, women have been already discharged from facility care).

d. In women diagnosed with mild pre-eclampsia antenatally, but not treated with antihypertensive drugs, the initiation of antihypertensive treatment postpartum should be considered for minimizing the risk of complications of severe high blood pressure (see remark 'c' above). That remark was made based on expert opinion and considering the evidence related to the treatment of mild/moderate hypertension during pregnancy. In the postpartum period, the maternal risk of a complication of hypertension is not counterbalanced by the risk of an adverse fetal effect produced by maternal hypotension.

e. The guideline development group considered that there is little clinical uncertainty over whether treatment of severe postpartum hypertension is beneficial. This recommendation was made based on expert opinion and the guideline development group considered that most maternal deaths related to hypertensive disorders are associated with complications of uncontrolled severe high blood pressure. Based on that, the guideline development group agreed that antihypertensive treatment should be recommended in all cases of severe acute hypertension.

5. Research implications

The guideline development group identified important knowledge gaps that need to be addressed through primary research. In general, in these guidelines, the weak recommendations are based on evidence that has been labelled 'very low quality' or 'low quality', indicating that further research is needed. Conversely, strong recommendations are based on 'moderate-quality' or 'high-quality' evidence, suggesting that further research is not a priority.

The group noted that for some research priorities there is planned or ongoing research. Since there is no certainty that the planned or ongoing research would give conclusive results, the research topics are listed as research priorities in this document. The evidence base for making recommendations on the dosages of pharmaceutical products remains limited. Since appropriate dose-finding studies may require large sample sizes (which may not be feasible), an indirect meta-analysis technique was suggested as a secondary research approach to see whether it can be helpful in the evaluation of dosages. Examples include acetylsalicylic acid dose (<75 mg vs ≥ 75 mg), calcium dose (<1 g vs $1.5–2$ g) and magnesium sulfate regimens (standard regimens vs low-dose regimens).

Research priorities based on guideline questions

1. The benefits and potential harms of advice to rest at home or bedrest under clinical observation at a health-care facility to prevent or treat hypertensive disorders of pregnancy.

2. Calcium supplementation:

a. It is unclear whether calcium supplementation corrects the pathological processes that underpin pre-eclampsia/eclampsia. A pilot RCT will be conducted in South Africa to assess the feasibility of pre-conceptional calcium supplementation and such a trial, if effective, could provide more information on this question.

b. Most calcium supplementation trials to date have used fairly high doses of daily calcium (1.5–2.0 g/day). While recommending those doses the guideline development group agreed that lower doses of calcium supplementation should be evaluated. This is important in view of the logistic and financial challenges of implementing large-scale calcium supplementation programmes.

c. Calcium supplementation programme implementation should be monitored and evaluated carefully to assess their successes and failures in terms of integration of the programmes into the overall antenatal care package

d. Evidence is weak on the effects of calcium supplementation in populations that are high risk of hypertensive disorders of pregnancy but have adequate intake of dietary calcium. It is unclear whether the observed effectiveness of calcium supplementation is the result of filling a dietary gap or whether calcium acts as a therapeutic agent.

3. Vitamin D supplementation alone should be evaluated for the prevention of hypertensive disorders of pregnancy.

4. For mild to moderate high blood pressure, there is a need to determine whether treatment is better than no treatment.

5. Further research is needed on the relative effectiveness of available drugs for severe acute hypertension.

6. Magnesium sulfate:

a. There is a need to assess the safety and efficacy of the loading dose magnesium sulfate at the primary care level flowed by transfer to higher level facility.

b. Implementation research is needed to increase utilization of magnesium sulfate therapy.

7. The benefits and potential harms of corticosteroids for treatment of HELLP syndrome need to be elucidated.

8. The effectiveness of interventionist versus expectant management approaches need to be evaluated for women with severe pre-eclampsia at 34–36 weeks gestation.

9. More research is needed on the benefits and potential harms of a policy of labour induction for mild pre-eclampsia or gestational hypertension at term in settings where accurate gestational age assessment is difficult due to late initiation of antenatal care.

10. Treatment schedules for women with postpartum hypertension (including timing of stopping treatment) need to be studies further.

Other research questions

1. What educational interventions can be targeted at women and health-care providers to improve knowledge of signs and symptoms of hypertensive disorders of pregnancy to promote appropriate and timely care?

2. How can the use of practices recommended in guideline be increases through implementation research.

3. The effectiveness of diagnostic screening tools for community health workers

6. Dissemination and implementation of the guidelines

The ultimate goal of these guidelines is to improve the quality of care and health outcomes related to hypertensive disorders of pregnancy. Hence, dissemination and implementation of these guidelines are crucial steps to be undertaken by the international community and local health-care services. The WHO Department of Reproductive Health and Research has adopted a formal knowledge-to-action framework for the dissemination, adaptation and implementation of guidelines (7). In addition to this framework, during the WHO Technical Consultation, a list of priority

actions was established which will be used by WHO and other partners to foster the dissemination and implementation of these guidelines (EB Box 2).

Guideline dissemination

The recommendations in these guidelines will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and nongovernmental organizations. They will also be published on the WHO web site and in The WHO Reproductive Health Library (33), where it will be accompanied by an independent critical appraisal based on the AGREE (Appraisal of Guidelines Research and Evaluation, http://www.agreecollaboration.org/instrument/) instrument. In addition, a policy brief aimed at a wide range of policy-makers, programme managers and clinicians will be developed and disseminated through WHO country offices.

Guideline implementation

The successful introduction into national programmes and health-care services of evidence-based policies related to the prevention and management of pre-eclampsia and eclampsia 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 based on this document.

The recommendations contained in the present guidelines should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. In this context, modifications to the recommendations may be limited to weak recommendations and justification for any changes should be made in an explicit and transparent manner.

In addition to that, 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 magnesium sulfate), and that the behaviour of the health-care practitioner changes towards the use evidence-based practices. In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged. The WHO Department of Reproductive Health and Research has published specific guidance on the introduction of WHO's reproductive health guidelines and tools into national programmes (*34*).

7. Applicability issues

Anticipated impact on the organization of care and resources

Evidence-based management of pre-eclampsia and eclampsia can be achieved with the use of relatively inexpensive drugs. However, the guideline development group noted that the following issues should be considered before applying the recommendations made in the present guidelines:

1. Women receiving magnesium sulfate should never be left alone and resources to monitor the well-being of both the woman and her fetus should be made available.

2. When IV magnesium sulfate is used for the treatment or prevention of eclampsia, the infusion rate of magnesium sulfate should be closely monitored.

3. Health-care facilities using magnesium sulfate should have calcium gluconate available in case of magnesium sulfate toxicity.

Monitoring and evaluating the guideline implementation

Ideally, implementation of the recommendations should be monitored at the health-service level. Interrupted time series clinical audits or criterion-based clinical audits could be used to obtain

relevant data related to the management of pre-eclampsia and eclampsia. Clearly defined review criteria and indicators are needed and could be associated with locally agreed targets. In this context, one basic indicator is suggested:

- Proportion of women with eclampsia receiving magnesium sulfate as the first option method of anticonvulsive therapy (calculated as the number of women with eclampsia receiving magnesium sulfate as the first option method of anticonvulsive therapy divided by the total number of women presenting with eclampsia).

This indicator provides an overall assessment of the use of magnesium sulfate as the first option therapy for eclampsia. The use of other locally agreed process indicators is recommended, particularly for the assessment of the preventive use of magnesium sulfate and local protocol compliance during loading and maintenance phases. WHO has developed specific guidance for evaluating the quality of care for severe maternal complications (including pre-eclampsia and eclampsia) based on the near-miss and criterion-based clinical audit concepts (available at http://www.who.int/reproductivehealth/publications/monitoring/9789241502221/en

8. Updating of the guidelines

This guideline will be updated after five years, or following the identification of new evidence showing a need to change the recommendations. WHO welcomes suggestions regarding additional questions for inclusion in the guidelines when they come up for updating. Please e-mail your suggestions to reproductivehealth@who.int and mncah@who.int.

References

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Seminars in Perinatol*ogy, 2009 Jun;33(3):130–137.

2. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*, 2010, 21;376(9741):631–44.

3. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet,* 2006 Apr 1;367(9516):1066–1074.

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): 1284–1299.

5. *World Health Organization Multicountry survey on maternal and newborn health.* Geneva, World Health Organization (available at www. who.int/reproductivehealth).

6. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A Review. *BMC Pregnancy and Childbirth,* 2009, 9:8.

7. *Knowledge to action framework and the G.R.E.A.T. project.* Geneva, World Health Organization, 2010 (http://www.who.int/ reproductivehealth/topics/best_practices/ greatproject_KTAframework/en/index.html, accessed 16 August 2011).

8. *WHO Handbook for guideline development.* Geneva, World Health Organization, 2010.

9. Meher S, Duley L. Rest during pregnancy for preventing pre-eclampsia and its complications in women with normal blood pressure. *Cochrane Database of Systematic Reviews,* 2006, (2):CD005939.*

10. Meher S, Abalos E, Carroli G. Bed rest with or without hospitalisation for hypertension during pregnancy. *Cochrane Database of Systematic Reviews,* 2005, (4):CD003514.*

11. Duley L, Henderson-Smart D, Meher S. Altered dietary salt for preventing pre-eclampsia, and its complications. *Cochrane Database of Systematic Review,* 2005, (4):CD005548.*

12. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews*, 2010, (8):CD001059.

13. De Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews*, 2011 (in press).

14. Rumbold A, Duley L, Crowther CA, Haslam RR. Antioxidants for preventing pre-eclampsia. *Cochrane Database of Systematic Reviews*, 2008, (1):CD004227.*

15. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews,* 2007, (2): CD004659.*

16. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews*, 2007, (1):CD002252.*

17. *Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database of Systematic Reviews, 2006, (3):CD001449.*

18. Churchill D, Beevers GDG, Meher S, Rhodes C. Diuretics for preventing pre-eclampsia. *Cochrane Database of Systematic Reviews,* 2007, (1):CD004451.*

19. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulfate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database of Systematic Reviews*, 2010, (11):CD000025.

20. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D; Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet,* 2002, 359(9321):1877–1890.

21. Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database of Systematic Reviews*, 2010, (12):CD000127.

22. Duley L, Henderson-Smart DJ, Chou D. Magnesium sulfate versus phenytoin for eclampsia. *Cochrane Database of Systematic Reviews*, 2010, (10):CD000128.

23. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet,* 1995, 345(8963):1455–1463.

24. Duley L, Gülmezoglu AM, Chou D. Magnesium sulfate versus lytic cocktail for eclampsia. *Cochrane Database of Systematic Reviews,* 2010 (9):CD002960.

25. Duley L, Matar HE, Almerie MQ, Hall DR. Alternative magnesium sulfate regimens for women with pre-eclampsia and eclampsia. *Cochrane Database of Systematic Reviews,* 2010, (8):CD007388.

26. *Managing complication in pregnancy and childbirth: a guide for midwives and doctors.* Geneva, World Health Organization, 2000 (available at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9241545879/en/index.html).

27. Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD008148. DOI: 10.1002/14651858.CD008148.pub2.

28. *International Clinical Trials Registry Platform*. Geneva, World Health Organization (http://www.who.int/ictrp/en/, accessed 16 August 2011).

29. Churchill D, Duley L. Interventionist versus expectant care for severe pre-eclampsia before term. *Cochrane Database of Systematic Reviews*, 2002, (3):CD003106.*

30. Magee LA, Yong PJ, Espinosa V, Côté AM, Chen I, von Dadelszen P. Expectant management of severe pre-eclampsia remote from term: a structured systematic review. *Hypertension in Pregnancy*, 2009, (3):312–347.

31. Koopmans CM, Bijlenga D, Groen H et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomized controlled trial. *Lancet*, 2009; 374: 979–988.

32. Magee L, Sadeghi S, von Dadelszen P. Prevention and treatment of postpartum hypertension. *Cochrane Database of Systematic Reviews,* 2005, (1):CD004351.*

33. *The WHO Reproductive Health Library.* Geneva, World Health Organization (www.who.int/rhl, accessed 16 August 2011).

34. *Introducing WHO's sexual and reproductive health guidelines and tools into national programmes: principles and process of adaptation and implementation.* Geneva, World Health Organization, 2007 (http://www.who.int/reproductivehealth/publications/general/RHR_07_09/en/index.html, accessed 16 August 2011)

NOTE:

Systematic reviews identified with an asterisk have been updated during the preparation of this guideline. Hence, data used in the GRADE tables may differ from the existing published version.

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Box 1: Summary of relevant declarations of interest from external advisers participating in the technical consultation

External adviser	Type of interest	Description of the interest	Amount of income or value of interest
P von Dadelszen	Private/commercial	PD acted as a paid consultant for a company which develops point-of-care diagnostic tests for pre-eclampsia and other pre-eclampsia complications.	USD 2000.00
JM Smith	Academic/ programmatic	JMS is employee of Johns Hopkins University and works in pre-eclampsia related public health programmes.	Salary
J Moodley	Academic/ programmatic	JM is the chair of the National Committee on Confidential Enquiries into Maternal Deaths. JM has also functioned as technical adviser and researcher in the field of pre-eclampsia and has been involved in the development of guidelines on Hypertension for the South Africa Department of Health.	Support from the South Africa Department of Health. JM has also received research grants and nonmonetary support for activities related with pre-eclampsia in South Africa.
S Lewin	Academic/ programmatic	The participation of SL in the consultation (travel costs and per diem) was covered by the University of British Columbia.	Travel costs and per diem

The WHO Legal Department has reviewed the Declarations of Interest of the participants listed in this table. Full participation in the consultation was considered as appropriate for all of them. All other participants did not present any potentially conflicting interest.

None of the recommendations developed during the Technical Consultation deal with diagnostic tests.

Annex 2. Prioritization of the outcomes

Table 1. Average scores given to outcomes by international stakeholders and external experts (1= not important; 9 = critical)

	Outcomes	Average score
1.	Maternal death	8.8
2.	Eclampsia	8.6
3.	Recurrent seizures	8.3
4.	Severe maternal morbidity	8.8
5.	Perinatal deaths	8.5
6.	Adverse effects of interventions	7.8
7.	Admission to neonatal intensive care unit / special nursery	7.9
8.	Apgar scores	6.9

World Health Organization