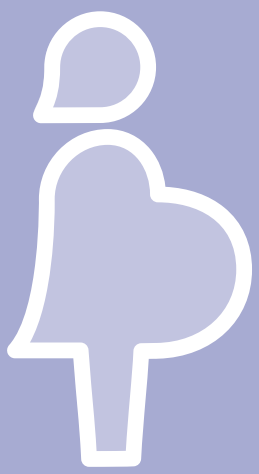
WHO recommendations

Policy of interventionist versus expectant management of severe pre-eclampsia before term



World Health Organization

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

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Acronyms and abbreviations

BMGF	Bill & Melinda Gates Foundation
CI	Confidence interval
CS	Caesarean section
DOI	Declaration of Interest
FIGO	International Federation of Gynaecology and Obstetrics
FWC	Family, Women's and Children's Health (a WHO cluster)
GDG	Guideline Development Group
GRC	Guideline Review Committee
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (a WHO project)
GSG	Executive Guideline Steering Group
HELLP	Haemolysis, elevated liver enzymes, low platelet
ICM	International Confederation of Midwives
IOL	Induction of labour
LMIC	Low and middle-income country
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health
MPA	Maternal and Perinatal Health and Preventing Unsafe Abortion (a team in WHO's Department of Reproductive Health and Research)
MPH	Maternal and perinatal health
NICU	Neonatal Intensive Care Unit
NNT	Number needed to treat
PICO	Population (P), intervention (I), comparison (C), outcome (O)
RHR	[WHO Department of] Reproductive Health and Research
RR	Relative risk
SDG	Sustainable Development Goals
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization

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Executive Summary

Introduction

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

In 2017, the Executive Guideline Steering Group (GSG) on the World Health Organization's (WHO) maternal and perinatal health recommendations prioritized the updating of the existing three WHO recommendations on the management of severe pre-eclampsia before term in response to important new evidence on these questions. These recommendations are a revalidation of the previous recommendations issued in 2011 in the *WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia.*

Target audience

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

Guideline development methods

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

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

(ii) retrieval of evidence;

(iii) assessment and synthesis of evidence;

(iv) formulation of the recommendation; and

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

The scientific evidence supporting these recommendations was synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The systematic review was used to prepare evidence profiles for the prioritized question. WHO convened an online meeting on 2 May 2018 where an international group of experts – the Guideline Development Group (GDG) – reviewed and approved these recommendations.

The recommendations

The GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG revalidated the WHO recommendations published in 2011 with minor revisions to the remarks and implementation considerations.

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

Table 1: WHO recommendations: policy of interventionist versus expectant management of severe pre-eclampsia before term.

Recommendations:

1. **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. (*strong recommendation, very low certainty evidence*)**
2. **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. (*conditional recommendation, very low certainty evidence*)**
3. **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. (*conditional recommendation, very low certainty evidence*)**

Remarks

- 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.

- 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 threshold, the local context, the availability of resources, and the local newborn survival rates by gestational age should be considered. 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.

1. Background

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

There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications *(4)*. Almost two-thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings *(5)*. To provide good quality care, healthcare providers at all levels of maternal healthcare services (particularly in low and middle-income countries) need to have access to appropriate medications and training in relevant procedures. Healthcare providers, health managers, policymakers and other stakeholders also need up-to-date, evidence-based recommendations to inform clinical policies and practices, in order to optimize quality of care, and enable improved healthcare outcomes. Efforts to prevent and reduce morbidity and mortality in pregnancy and childbirth could reduce the profound inequities in maternal and perinatal health globally.

Pre-eclampsia and eclampsia

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths *(6)*. 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 remains controversial, as does the classification of its severity.

The 11th revision of the International Classification of Diseases (ICD-11) describes pre-eclampsia as a condition characterized by systolic blood pressure greater than 140 mmHg, and/or diastolic greater or equal to 90 mmHg on two occasions 4 hours or more apart, in the presence of either proteinuria or other new onset maternal organ dysfunction characterized by one thrombocytopenia, elevated serum creatinine or liver transaminases, or neurological conditions or fetal growth restriction *(7)*. Although patho-physiological changes (e.g. inadequate placentation) exist from the 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.

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 in severe cases, but the progression from mild to severe can be rapid, unexpected and occasionally fulminant. The only definitive treatment for pre-eclampsia is termination of pregnancy or 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.

In 2011, the World Health Organization (WHO) published 22 recommendations for the prevention and treatment of pre-eclampsia and eclampsia, including three recommendations on the management of severe pre-eclampsia before term *(8)*. These recommendations were developed according to the WHO guideline development standards, including synthesis of available research evidence, use of the GRADE methodology, and formulation of recommendations by a guideline panel of international experts.

Rationale and objectives

In 2017, WHO established a new process for prioritizing and updating maternal and perinatal health recommendations whereby an Executive Guideline Steering Group (GSG) oversaw a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating *(9)*. Recommendations were prioritized on the basis of changes or important, new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized the updating of the three existing WHO recommendations on the management of severe pre-eclampsia before term in response to new, potentially important evidence on the subject.

The primary goal of these recommendations is to improve the quality of care and outcomes for pregnant women, particularly related to the treatment of hypertensive disorders of pregnancy. These recommendations provide a foundation for the sustainable implementation of the intervention globally.

Target audience

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

The recommendations will also be of interest to professional societies involved in the care of pregnant women, nongovernmental organizations and implementing partners concerned with promoting people-centred maternal care, and implementers of maternal and child health programmes.

Scope of the recommendations

Framed using the population (P), intervention (I), comparison (C), outcome (O) (PICO) format, the question directing these recommendations was:

- In women with severe pre-eclampsia before term (P), does interventionist care (I) compared to expectant management (C), improve maternal or perinatal outcomes (O)?

Persons affected by the recommendations

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

2. Methods

The recommendations were first developed using standardized operating procedures in accordance with the process described in the WHO handbook for guideline development *(10)*. In summary, the process included:

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

(ii) retrieval of evidence;

(iii) assessment and synthesis of evidence;

(iv) formulation of the recommendations; and

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

The three WHO recommendations on the management of severe pre-eclampsia before term were identified by the Executive GSG as a high priority for updating in response to new, potentially important evidence on this question. Six main groups were involved in this process, with their specific roles described in the following sections.

Contributors to the guideline

Executive Guideline Steering Group (Executive GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating *(11)*.

WHO Steering Group

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

Guideline Development Group

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

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

The GDG members for these recommendations were also selected in a way that ensured

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

External Review Group

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

Systematic review team and guideline methodologists

A Cochrane systematic review on this question was updated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Representatives of the Cochrane Pregnancy and Childbirth Group attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

External partners and observers

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

Identification of critical outcomes

The critical and important outcomes were aligned with the prioritized outcomes from the *WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (8)*. These outcomes were initially identified through a search of key sources of relevant, published, systematic reviews and a prioritization of outcomes by the 2011 GDG panel. All outcomes were included in the scope of this document for evidence searching, retrieval, grading and formulation of the recommendations. The list of outcomes is provided in Annex 2.

Evidence identification and retrieval

A Cochrane systematic review was updated by the Cochrane Pregnancy and Childbirth Group *(12)*. This systematic review was the primary source of evidence for these recommendations.

Randomized controlled trials (RCT) relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were fed into Review Manager (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not

relevant to the recommendations were excluded). Then the RevMan file was exported to GRADE profiler software (GRADEpro) and GRADE criteria were used to critically appraise the retrieved scientific evidence.

Finally, evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach *(13)*. Using the GRADE approach, the certainty of evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

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

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the direction of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

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

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

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

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

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Formulation of recommendations

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

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

Declaration of interests by external contributors

According to WHO regulations, all experts must declare their relevant interests prior to participation in WHO guideline development processes and meetings. All GDG members were therefore required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and before participating in the guideline-related meeting. The WHO Steering Group reviewed each declaration before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the Steering Group determined whether such conflicts were serious enough to affect the expert's objective judgement of the guideline and recommendation development process. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO Handbook for Guideline Development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting, and no further actions were taken.

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

Decision-making during the Guideline Development Group meeting

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

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

Table 1: WHO recommendation: policy of interventionist versus expectant management of severe pre-eclampsia before term.

Recommendations:

1. **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. (*strong recommendation, very low certainty evidence*)**
2. **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. (*conditional recommendation, very low certainty evidence*)**
3. **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. (*conditional recommendation, very low certainty evidence*)**

Remarks

- 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.

- 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 threshold, the local context, the availability of resources, and the local newborn survival rates by gestational age should be considered. 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.

Document preparation

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

Peer review

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

3. Recommendations and supporting evidence

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

The following recommendations were adopted by the GDG. Evidence on the effectiveness of the intervention was derived from one systematic review and was summarized in GRADE tables (Annex 5). The certainty of the supporting evidence was rated as 'very low' for most critical outcomes. To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional 'remarks' reflecting the summary of the discussion by GDG are included under the recommendations.

4. Dissemination and implementation of the recommendations

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

Recommendation dissemination and evaluation

A shorter document containing the recommendations, remarks, implementation considerations and research priorities will be formulated for public dissemination. This document will have annexes (also made publicly

available) containing all the information in this document, including methods, evidence-to-decision frameworks and GRADE tables.

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

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

Implementation considerations

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

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

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

- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged;

- Healthcare providers should discuss with women the risks, benefits and treatment options in the management of severe pre-eclampsia, to facilitate informed consent and shared decision-making *(19)*;

- Other WHO resources (such as the clinical handbook *Managing Complications of Pregnancy and Childbirth*) provide further guidance on applying these recommendations in clinical settings *(19)*.

5. Research implications

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

- Relative effectiveness of available drugs for severe acute hypertension, including effects on the fetus and newborn;

- Further research to understand the relative importance that women with pre-eclampsia during pregnancy place on treatment options and health outcomes, and their preferences; and

- Evaluating communication interventions and tools (such as visual aids) to assist women with pre-eclampsia to make informed decisions.

6. Applicability issues

Anticipated impact on the organization of care and resources

Implementing these evidence-based recommendations will require resources to ensure implementation is done safely, including staff time for monitoring of women undergoing induction of labour. The GDG noted that updating training curricula and providing training would increase impact and facilitate implementation. Standardization of care by including recommendations into existing maternity care packages and protocols could encourage healthcare provider behaviour change.

Monitoring and evaluating guideline implementation

Implementation should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of maternal and newborn care. For example, interrupted time series, clinical audits or criterion-based clinical audits can be used to obtain relevant data related to induction of labour. Clearly defined review criteria and indicators are needed and these could be associated with locally agreed targets. These could be aligned with the standards and indicators described in the WHO document *Standards for improving quality of maternal and newborn care in health facilities (20)*.

7. Updating the recommendations

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

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

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

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Annex 2. Priority outcomes for decision-making

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

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

Name		Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Edgardo	**ABALOS**	Content expert and end-user	None declared	Not applicable
Ebun	**ADEJUYIGBE**	Content expert and end-user	None declared	Not applicable
Shabina	**ARIFF**	Content expert and end-user	None declared	Not applicable
Jemima	**DENNIS-ANTWI**	Content expert and end-user	None declared	Not applicable
Luz Maria	**DE-REGIL**	Content expert and end-user	Global Affairs Canada awarded a grant to Dr De-Regil's institution to implement nutrition interventions in low and middle-income countries. Some of the funded work included support for implementation research on calcium supplementation in pregnancy in Kenya and Ethiopia. The work was sub-granted to Cornell University, and Dr De-Regil was not part of the research team. As a former WHO staff member, she supported the development of a guideline on calcium supplementation in pregnancy (led by NHD).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation
Christine	**EAST**	Content expert and end-user	None declared	Not applicable
Lynn	**FREEDMAN**	Content expert and end-user	None declared	Not applicable
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Name		Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Rachel	**PLACHCINSKI**	Consumer representative	None declared	Not applicable
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Eleni	**TSIGAS**	Consumer representative	Ms Tsigas represents patient experiences around preeclampsia and other hypertensive disorders of pregnancy to organizations, committees, and other multidisciplinary bodies. She is also a voting member on the Council for Patient Safety in Women's Healthcare (USA).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation

Annex 4. Evidence-to-decision framework

A) QUESTION

In women with severe pre-eclampsia before term (P), does interventionist care (I) compared to expectant management (C), improve maternal or fetal outcomes (O)?

Problem: Severe pre-eclampsia before term
Perspective: Clinical practice recommendation – population perspective
Population: Pregnant women with severe pre-eclampsia before term
Intervention: Interventionist care (i.e. immediate delivery by caesarean section or induction)
Comparison: Expectant management/no treatment
Main outcomes: [1]

Maternal

- Eclampsia
- Recurrent seizures
- Severe maternal morbidity (including renal failure, pulmonary oedema, haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome or other severe maternal conditions)
- Maternal death
- Adverse effects of interventions

Fetal/Neonatal

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

B) ASSESSMENT

1. EFFECTS OF INTERVENTIONS

Research evidence

Summary of the evidence

Evidence on the effects of interventionist care versus expectant management for severe pre-eclampsia between 24 and 34 weeks' gestation is from a Cochrane systematic review including six trials with 748 women *(12)*. All the studies were carried out in hospital settings. Three trials were multi-centre trials: one was UK based and involved 69 hospitals in 13 European countries; the second was based in Latin America and was carried out in eight tertiary hospitals in Latin America; and the third was conducted across 10 hospital sites in the Netherlands. The other three trials were single-centre trials, based in Egypt, South Africa, and the USA. In the UK-based multi-centre trial only a subset of women within this trial had severe pre-eclampsia (262 out of 547 women). Individual participant data (IPD) meta-analyses were available for this subset of women, and the data for this subset were included in the Cochrane review. The most recent study, from Latin America, was the largest, with 267 women randomized. This trial only recruited women between 28 and 33 weeks' gestation. Participants below 28 weeks were

[1] These outcomes reflect the prioritized outcomes used for this recommendation, in the WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (2011).

excluded, because it was felt that the neonatal care provided was too poor due to limited resources in some units.

All of the women had severe pre-eclampsia. Their gestation period ranged from less than or equal to 34 weeks' (one trial), between 28 and 32 weeks' gestation (one trial), between 28 and 34 weeks' gestation (two trials) and between 28 and 33 weeks' gestation (two trials). In five trials, women had a 24- to 48-hour period during which they were given steroids to accelerate fetal lung maturity and if necessary magnesium sulfate to prevent seizures and antihypertensives to lower blood pressure. At the end of this period, if they continued to meet the eligibility criteria, they were then randomized. They were randomized either to an interventionist group, for immediate delivery by caesarean section or induction, or to an expectant management group, who were managed with hospitalisation and intensive maternal and fetal monitoring. Earlier delivery in the expectant group was implemented if either the maternal or fetal condition deteriorated, as determined by pre-specified criteria.

Effects of interventions

Maternal outcomes

Maternal death: Two studies reported on this outcome, and there were no maternal deaths in either study (two studies, 320 women; 0/159 vs 0/161; effect not estimable; low certainty evidence).

Eclampsia: It is uncertain whether interventionist care reduces eclampsia because the certainty of this evidence is very low.

HELLP syndrome: Low-certainty evidence from two studies suggests little or no clear difference between the interventionist and expectant care groups (two studies, 359 women; 22/179 vs 20/180; RR 1.09, 95% CI 0.62 to 1.91).

Pulmonary oedema: It is uncertain whether interventionist care reduces pulmonary oedema because the certainty of this evidence is very low.

Renal failure: It is uncertain whether interventionist care reduces renal failure because the certainty of this evidence is very low.

Infant outcomes

Perinatal mortality: Low-certainty evidence from three studies suggests little or no clear difference between the interventionist and expectant care groups (three studies, 343 infants; 20/172 vs 18/171; RR 1.11, 95% CI 0.62 to 1.99).

Admission to neonatal intensive care unit: Low-certainty evidence from three studies suggests little or no clear difference between the interventionist and expectant care groups (three studies, 400 infants; 156/198 vs 149/202; RR 1.19, 95% CI 0.89 to 1.60).

Low Apgar score at five minutes (< 7 at 5 minutes): Low-certainty evidence from one small study suggests little or no clear difference between the interventionist and expectant care groups (one study, 262 infants; 31/141 vs 18/121; RR 1.48, 95% CI 0.87 to 2.50).

There were no data reported for the prioritized maternal outcome: **recurrent seizures.**

Desirable effects

How substantial are the desirable anticipated effects of interventionist care for severe pre-eclampsia before term?

Judgement

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

Undesirable effects

How substantial are the undesirable anticipated effects of interventionist care for severe pre- eclampsia before term?

Judgement

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

Certainty of the evidence

What is the overall certainty of the evidence of effects?

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

Additional considerations

For the main comparison, there was evidence of harm to the baby in the interventionist group for some outcomes that were not pre-specified, namely: intraventricular haemorrhage or hypoxic ischaemic encephalopathy (HIE), hyaline membrane disease and newborns requiring ventilation.

Values

Is there important uncertainty about, or variability in, how much women value the main outcomes associated with interventionist care for severe pre-eclampsia before term?

Research evidence

We did not identify any reviews or studies that directly addressed this question.

Additional considerations

Evidence from a qualitative systematic review found that while women place a high value on a physiological labour and birth experience, they also acknowledge that birth can be unpredictable. Even where an intervention (such as interventionist care) is needed or wanted, women usually wish to retain a sense of personal achievement and control by being involved in decision-making *(14)*.

The GDG considered it likely that women in different settings with a pregnancy of viable gestational age would highly value perinatal morbidity and mortality outcomes.

Judgement

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

Balance of effects

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

Judgement

☐	☑	☐	☐	☐	☐	☐
Don't know	Varies	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention

2. RESOURCES

How large are the resource requirements (costs) of interventionist care for severe pre-eclampsia before term?

Research evidence

The Cochrane review did not pre-specify outcomes related to economic costs. No cost- effectiveness studies that directly addressed this question were identified.

Main resource requirements

Resource	Description
Staff training	• Training in recognition and management of severe pre- eclampsia (including surveillance of maternal organ dysfunction) • Training in performance and monitoring of labour induction and caesarean section • Training in fetal surveillance
Supplies	• Induction agent (e.g. Foley catheter, misoprostol or prostaglandin E2) • Dipstick for proteinuria • Magnesium sulfate (neuroprotection) • Antenatal corticosteroids (dexamethasone or betamethasone) • Antihypertensive drugs
Equipment	• Equipment for vaginal birth • IV and IM injection equipment for magnesium sulfate and antenatal corticosteroids • Ultrasound or other means for fetal surveillance • Laboratory resources for maternal surveillance (e.g. assessment of blood cell count, platelet count, serum creatinine, liver enzymes, proteinuria, coagulation studies)
Infrastructure	• Capacity to perform caesarean section • Maternal high-risk units, or capacity for adequate referral to higher-level care
Staff time	• Assessment by skilled birth attendant, monitoring after induction • Assessment of fetal well-being

Additional considerations

None.

Resources required

Judgement

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

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement

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

Cost-effectiveness

Judgement

☑ Don't know	☐ Varies	☐ Favours the comparison	☐ Probably favours the comparison	☐ Does not favour either the intervention or the comparison	☐ Probably favours the intervention	☐ Favours the intervention

3. EQUITY

What would be the impact of interventionist care on severe pre-eclampsia before term on health equity?

Research evidence

No direct evidence identified.

Additional considerations

In low to middle-income countries (LMICS), women who are poor, least educated, and residing in rural areas have lower health intervention coverage and worse health outcomes than the more advantaged women. In the 2015 WHO State of Inequalities Report, antenatal care coverage of at least four visits differed by at least 25% between the most and least educated, and the richest and poorest in half the LMICs studied *(15)*. It is therefore likely that adverse consequences of hypertensive disorders of pregnancy are worse in women living in disadvantaged circumstances.

Judgement

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

4. ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

Research evidence

We did not identify any studies directly addressing this question.

Additional considerations

None

Judgement

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

5. FEASIBILITY

Is the intervention feasible to implement?

Research evidence

We did not identify any studies directly addressing this question.

Additional considerations

Communicating with women about healthcare decision-making: Indirect evidence from a qualitative systematic review of healthy, low-risk women found that while women place a high value on a physiological labour and birth experience, they also acknowledge that birth can be unpredictable. Even where an intervention is needed or wanted, women usually wish to retain a sense of personal achievement and control by being involved in decision-making *(16)*. Other reviews have also identified the importance of clear, open communication in healthcare decision-making during pregnancy and childbirth *(14, 17)*, hence the intervention will likely be easier to implement in the context of effective communication between women and healthcare providers.

Factors affecting implementation: A mixed-methods study of multi-stakeholder groups in Uganda and Tanzania on the implementation of the WHO pre-eclampsia and eclampsia guidelines *(18)* identified key factors affecting implementation: at the health system level (access to resources, drugs, equipment and supplies, and adequate drug procurement, distribution and management mechanisms); health provider level (the need for buy-in, improving knowledge and skills through training and mentorship); and woman and community level (including traditional beliefs and perceptions of healthcare services, knowledge and awareness of illnesses and interventions, and engaging community healthcare workers).

Judgement

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

C) SUMMARY OF JUDGEMENTS

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

Annex 5. GRADE Tables

Question: Interventionist care compared to expectant (delayed delivery) care for severe pre-eclampsia between 24 and 34 weeks' gestation

Setting: Six studies with 748 women conducted in hospital settings in the USA, South Africa, Egypt, The Netherlands, Latin America (Panama, Pennsylvania, Mexico, Venezuela, Guatemala, Peru, Ecuador) and Europe (Belgium, Cyprus, Czech Republic, Germany, Hungary, Greece, Italy, Netherlands, Poland, Portugal, Saudi Arabia, Slovenia, UK)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventionist care**	**Expectant (delayed delivery) care for severe pre-eclampsia**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal deaths												
2	randomized trials	serious [a]	not serious	not serious	serious [b]	none	0/159	0/161	not estimable		⨁⨁◯◯ LOW	CRITICAL
Eclampsia												
2	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	1/179 (0.6%)	1/180 (0.6%)	**RR 0.98** (0.06 to 15.58)	**0 fewer per 1,000** (from 5 fewer to 81 more)	⨁◯◯◯ VERY LOW	CRITICAL
HELLP syndrome												
4	randomized trials	serious [a]	not serious	not serious	serious [d]	none	22/179 (12.3%)	20/180 (11.1%)	**RR 1.09** (0.62 to 1.91)	**10 more per 1,000** (from 42 fewer to 101 more)	⨁⨁◯◯ LOW	CRITICAL
Pulmonary oedema												
2	randomized trials	serious [a]	not serious	not serious	very serious	none	1/205 (0.5%) (0.6%)	3/210 (1.4%) 2/180 (1.1%)	**RR 0.45** (0.07 to 3.00)	**8 fewer per 1,000** (from 13 fewer to 29 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventionist care**	**Expectant (delayed delivery) care for severe pre-eclampsia**	**Relative (95% CI)**	**Absolute (95% CI)**		
Renal failure												
3	randomized trials	serious [f]	not serious	not serious	very serious	none	1/199 (0.5%)	4/198 (2.0%)	**RR 0.32** (0.05 to 1.99)	**14 fewer per 1,000** (from 19 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Perinatal mortality - Perinatal death												
2	randomized trials	serious [f]	not serious	not serious	very serious [d]	none	20/172 (11.6%)	18/171 (10.5%)	**RR 1.11** (0.62 to 1.99)	**12 more per 1,000** (from 40 fewer to 104 more)	⨁⨁◯◯ LOW	CRITICAL
Intraventricular haemorrhage or hypoxic ischaemic encephalopathy												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	38/278 (13.7%)	17/259 (6.6%)	**RR 1.94** (1.15 to 3.29)	**62 more per 1,000** (from 10 more to 150 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Admission to neonatal intensive care unit												
3	randomized trials	serious [f]	not serious	not serious	serious [d]	none	156/198 (78.8%)	149/202 (73.8%)	**RR 1.19** (0.89 to 1.60)	**140 more per 1,000** (from 81 fewer to 443 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventionist care**	**Expectant (delayed delivery) care for severe pre-eclampsia**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low Apgar score at five minutes (< 7 at five minutes)												
1	randomized trials	not serious	not serious	not serious	very serious	none	31/141 (22.0%)	18/121 (14.9%)	**RR 1.48** (0.87 to 2.50)	**71 more per 1,000** (from 19 fewer to 223 more)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Limitations in study design (no blinding) (-1)
b. No events (-1)
c. Low event rate and wide CI crossing the line of no effect (-2)
d. Wide CI crossing the line of no effect (-1)
e. Small number of events and wide CI crossing the line of no effect (-2)
f. Limitations in study design (-1)
g. Small sample size and wide CI crossing the line of no effect (-2)

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