WHO recommendations on
antiplatelet agents for the prevention of pre-eclampsia

World Health Organization

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ISBN 978-92-4-003754-0 (electronic version)
ISBN 978-92-4-003755-7 (print version)

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Acknowledgements

The World Health Organization (WHO) Department of Sexual and Reproductive Health and Research, and the Department of Maternal, Newborn, Child and Adolescent Health, and Ageing gratefully acknowledge the contribution of many individuals and organizations to the updating of these recommendations. The work on this update was coordinated by Doris Chou, Olufemi Oladapo and Joshua Vogel of the Department of Sexual and Reproductive Health and Research and Maurice Bucagu of the Department of Maternal, Newborn, Child and Adolescent Health, and Ageing.

WHO extends its sincere thanks to Edgardo Abalos, Sabina Ariff, Jemima Dennis-Antiwi, Christine East, Shireen Meher, James Neilson, Hiromi Obara, Rachel Plachciniski, Zahida Quereshi, and Kathleen Rasmussen who served as members of the Guideline Development Group (GDG), and to Zahida Quereshi (Chair) James Neilson (co-Chair) for leading the meeting. WHO also thanks the members of the External Review Group (ERG). WHO also gratefully acknowledges the contribution of the members of the Executive Guideline Steering Group (GSG).

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 the evidence. Doris Chou, Olufemi Oladapo and Joshua Vogel revised the narrative summaries and double-checked the corresponding GRADE tables and prepared the Evidence to Decision (EtD) frameworks. The ERG peer reviewed the final document prior to its receiving executive clearance by WHO and its publication.

WHO acknowledges the various organizations that were represented by observers, including Deborah Armbruster (United States Agency for International Development [USAID]), Emma Clark (USAID), Kathleen Hill (JHPIEGO), Ingela Wiklund (International Confederation of Midwives [ICM]), Bo Jacobsson and Gerry Vissler (International Federation of Gynecology and Obstetrics [FIGO]), Jeffrey Smith (Bill & Melinda Gates Foundation) and Charlotte Warren (Population Council).

WHO also appreciates the contributions of staff at the WHO regional offices, including Bremen de Mucio (PAHO), Karima Gholbzouri (EMRO), Chandani Anoma Jayathilaka (SEARO), Oleg Kuzmenko (EURO), Leopold Ouedraogo (AFRO), Howard Sobel (WPRO) and Claudio Sosa (PAHO).

WHO acknowledges the financial support for this work received from USAID and the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research. WHO would like to emphasize that donors do not participate in any decision related to the guideline development process, including the composition of research questions, membership of the guideline development groups, conducting and interpretation of systematic reviews, or formulation of the recommendations. The views of the funding bodies have not influenced the content of these recommendations.

Abbreviations

CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
DOI	declaration of interest
ERG	Evidence Review Group
ESG	Evidence Synthesis Group
EtD	Evidence to Decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSG	Guideline Steering Group
HELLP	hemolysis, elevated liver enzymes, low platelets
HRP	UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
ICU	intensive care unit
IU	international units
MPH	maternal and perinatal health
NICU	neonatal intensive care unit
NNT	number needed to treat
NNH	number needed to harm
PICO	population (P), intervention (I), comparator (C), outcome (O)
SDG	Sustainable Development Goals
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

In 2019, the Executive Guideline Steering Group (GSG) for the World Health Organization (WHO) maternal and perinatal health recommendations prioritized updating the then current WHO recommendations on antiplatelet agents for the prevention of pre-eclampsia. This decision was based on new evidence on the subject that had become available. The recommendation in this document thus supersedes the previous WHO recommendations on antiplatelet agents for the prevention of pre-eclampsia as published in the 2011 guidelines, *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia.*

Target audience

The primary audience for these recommendations includes health professionals who are responsible for developing national and local health-care guidelines and protocols and those involved in the provision of care to women and their newborns during pregnancy, labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians. The primary audience also includes managers of maternal and child health programmes, and relevant staff in ministries of health and educational and training institutions, in all settings.

Guideline development methods

Updating these recommendations was guided by standardized operating procedures in accordance with the process outlined in the *WHO handbook for guideline development.* The recommendations were developed and updated using the following steps:

(i) identification of priority questions and 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 future updating of the recommendations.

The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. An updated systematic review was used to prepare the evidence profiles for the prioritized question. WHO convened a meeting on 23-24 November 2020 at which the Guideline Development Group (GDG) members reviewed, deliberated and achieved consensus on the strength and direction of the recommendations presented herein. Through a structured process, the GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity.

Recommendations

Following the review, the GDG approved the recommendations. To ensure that the recommendations are correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation that follow each recommendation.

Table 1.

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

Remarks

- Evidence from the systematic review supports the use of aspirin in all at-risk groups (low, moderate and high). However, the GDG noted that a much larger number of women at low risk of developing pre-eclampsia would need to be treated to prevent one case of pre-eclampsia compared with women at moderate or high risk. Based on the risk-benefit assessment of the use of aspirin among women at low risk of pre-eclampsia, additional resource constraints on a health system, and the impact on equity, the GDG recommends restricting treatment to only women at moderate or high risk of pre-eclampsia.

- For the purpose of this recommendation, women are regarded as being at moderate risk of developing pre-eclampsia if they have any two of the following risk factors: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy; and at high risk of developing pre-eclampsia if they have one or more of the following risk factors: diabetes, chronic or gestational hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal or neonatal death associated with pre-eclampsia. This is not an exhaustive list of factors for moderate- or high-risk stratification for pre-eclampsia and can be adapted or complemented based on the local epidemiology of pre-eclampsia.

- The GDG acknowledged that in settings where 75 mg aspirin tablets are not available, the dose nearest to 75 mg that is available should be used.

- Although there is evidence to suggest that a daily dose of aspirin of 75 mg and above (up to 150 mg) may be more beneficial compared to an aspirin dose less than 75 mg in terms of reduction of pre-eclampsia, the GDG was concerned about the potential for increased risk of postpartum haemorrhage and the plausibility that the risk could be increased with higher doses of aspirin. Therefore, the GDG selected 75 mg as the optimal dose in terms of risk-benefit considerations (details described in the Evidence to Decision framework). In making this decision, the GDG acknowledged the lack of evidence on the comparative risk of postpartum haemorrhage among women who received 75 mg compared with those who received 150 mg of aspirin for pre-eclampsia prevention and noted it as a research priority.

- In view of the potential for a small increase in risk for postpartum haemorrhage among women treated with aspirin it is important to counsel women who are eligible for aspirin for the prevention of pre-eclampsia on the potential risks to encourage informed decision-making by the women and their families.

- Aspirin should not be used by women for whom it is contraindicated.

- The GDG emphasized that this recommendation applies to the use of aspirin in women with gestational hypertension as a secondary preventive measure against developing pre-eclampsia.

- This recommendation supersedes recommendation No. 7 in the *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia (2011)*.

Table 2.

Low-dose acetylsalicylic acid (aspirin, 75 mg per day) for the prevention of pre-eclampsia and its related complications should be initiated by 20 weeks' gestation or as soon as antenatal care is started. ***(Context-specific recommendation)***

Remarks

- Evidence from the systematic review shows that women appeared to have a decreased risk of developing pre-eclampsia and its complications with the use of antiplatelet agents whether they began the intervention before or after 20 weeks' gestation. However, in view of the pathophysiology of pre-eclampsia, the GDG supports the initiation of treatment early in a pregnancy. The GDG noted that in most of the trials providing evidence on the benefit of aspirin in early pregnancy, treatment was initiated at 12 weeks' gestation and therefore consider this an appropriate time to initiate aspirin treatment.
- While antenatal care is ideally initiated by 12 weeks' gestation, in situations where antenatal care is started later than 20 weeks in pregnancy, GDG suggests initiating treatment at the time it begins.
- Irrespective of when treatment is initiated, appropriate counselling on the risks and benefits of preventative treatment is paramount - both to improve adherence and to inform the woman of warning signs that should be reported (such as bleeding or abdominal pain).
- There is scant evidence on the optimal time to discontinue aspirin treatment for the prevention of pre-eclampsia. In addition, the GDG is aware that, in some settings, the use of aspirin around the time of birth may preclude the use of epidural or spinal anaesthesia at the time of delivery. The GDG suggests that aspirin should be discontinued in line with local practice on the use of anticoagulants in pregnancy. The GDG notes the need for research in this area to clarify the benefits of prevention of pre-eclampsia with the potential risks of postpartum and neuroaxial haemorrhage with the use of low-dose aspirin late in pregnancy.
- This recommendation supersedes recommendation No. 8 in the *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia (2011).*

1. Introduction

Background

An estimated 295 000 women and adolescent girls died as a result of pregnancy and childbirth related complications in 2017. Around 99% of these deaths 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 health-care for women is a necessary step towards the achievement of the health targets agreed in the Sustainable Development Goals (SDGs) and the targets and indicators of The World Health Organization's (WHO) Thirteenth General Programme of Work, particularly those for achieving universal health coverage. *(2)* 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. *(3)* The World Health Organization (WHO) envisions a world where "every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and postnatal period". *(4)* There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications. *(5)* Almost two thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings. *(6)* To provide good quality care, health-care providers at all levels of maternal health-care services, particularly in low- and middle-income countries must have access to appropriate medicines and health products and to training in relevant medical procedures. Health-care providers, health managers, policy-makers and other stakeholders also require up-to-date, evidence-informed recommendations to guide clinical policies and practices in order to optimize quality of care and enable improved health-care outcomes.

The prevention of morbidity and mortality in pregnancy and childbirth could reduce the profound inequities in maternal and perinatal health globally. Hypertensive disorders of pregnancy are a significant 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. *(7)* Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as significant causes of maternal and perinatal mortality and morbidity. The majority of deaths due to pre-eclampsia and eclampsia could be avoided through the provision of timely and effective care to women presenting with these complications.

Rationale and objectives

The Executive GSG prioritized updating the existing WHO recommendations on the use of aspirin to prevent pre-eclampsia. *(8)* WHO has established a new process for prioritizing and updating maternal and perinatal health recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of maternal and perinatal health (MPH) recommendations in most urgent need of updating. *(8)* Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence base on the benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation.

These updated recommendations were developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including the synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1] and GRADE Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CerQUAL)[2] methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders. *(9, 10,11)* The recommendations in this document thus supersede the previous WHO recommendations for the use of antiplatelets for the prevention of pre-eclampsia as published

[1] Further information is available at: http://www.gradeworkinggroup.org/.

[2] Further information is available at: https://www.cerqual.org/.

in the 2011 guidelines, *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia*. *(12)* The primary aim of these recommendations is to improve the quality of care and outcomes for women giving birth as related to the prevention and management of pre-eclampsia.

Target audience

The primary audience includes health professionals who are responsible for developing national and local health-care guidelines and protocols and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians. The primary audience also includes managers of maternal and child health programmes, and relevant staff in ministries of health and educational and training institutions, in all settings.

These recommendations will also be of interest to pregnant women, as well as members of professional societies involved in the care of pregnant women, staff of nongovernmental organizations concerned with promoting people-centred maternal care and implementers of maternal and perinatal health programmes.

Scope of the recommendations

These recommendations were framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format. The questions for these recommendations were:

- For women at risk of pre-eclampsia (P), does the use of antiplatelet agents (I), compared with the use of placebo or no antiplatelet agent (C), improve maternal and perinatal outcomes (O)?
- For women with gestational hypertension (P), does the use of antiplatelet agents (I), compared with the use of a placebo or no antiplatelet agent (C), improve maternal and perinatal outcomes (O)?

Persons affected by the recommendations

The population affected by the recommendations includes all pregnant women.

2. Methods

The recommendations were developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. *(13)* 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.

In 2019, updating recommendations on the use of antiplatelet agents for the prevention of pre-eclampsia was identified by the Executive GSG as a high priority in response to new evidence on this subject. Six main groups of experts and satkeholders were involved in this process, with their specific roles described below.

Contributors to the guidelines

Executive Guideline Steering Group (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, Eastern Mediterranean Region, European Region, South-East Asia Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations. *(8)*

WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health, and Ageing, managed the process of updating the recommendations. The WHO Steering Group drafted the key recommendation questions in PICO format, engaged the systematic review teams and guideline methodologists (that is, the Evidence Synthesis Group [ESG]), as well as the members of the GDG and the External Review Group (ERG) (see below). In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, drafted and finalized the guideline document, and will also manage the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

Guideline Development Group (GDG)

The WHO Steering Group identified a pool of approximately 50 experts and stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool consists of a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-informed recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health, as well as a consumer representative. The members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and that there are no perceived or real conflicts of interest. The 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 participate as members of the GDG for updating these recommendations. Those selected were a diverse group with expertise in research, guideline development methods, gender, equity and rights, clinical practice, policy and programmes, and included consumer representatives relating to the prevention and treatment of peripartum infection.

The GDG members were also selected in a manner that ensured geographic representation and gender balance and that there were no significant conflicts of interest. The GDG appraised the evidence that was used to inform the recommendationss, advised on the interpretation of this evidence, formulated the final recommendation based on the draft prepared by the WHO Steering Group and reviewed and reached a unanimous consensus on the recommendations in the final document. The members of the GDG are listed in Annex 1.

Evidence Synthesis Group (ESG)

WHO convened an ESG composed of guideline methodologists and systematic review teams to conduct or update systematic reviews, appraise the evidence and develop the Evidence to Decision (EtD) frameworks. A systematic review on the effects of the intervention was updated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the updated protocol and worked closely with the Cochrane Pregnancy and Childbirth Group and the guideline methodologist to appraise the evidence using the GRADE methodology. Representatives of the Cochrane Pregnancy and Childbirth Group and the guideline methodologist attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

Evidence on values, acceptability and feasibility were obtained from a mixed-methods review on views on women's and providers' perspectives and experiences in pregnancy and childbirth. *(14)* The evidence for cost-effectiveness was derived from a literature review. *(19-24)* Evidence on equity was derived from a systematic review

of qualitative studies evaluating "what women want" from antenatal care. *(15)* The qualitative systematic review of what women want from antenatal care showed that healthy pregnant women from high-, medium- and low-resource settings valued having a positive pregnancy experience, the components of which included the provision of effective clinical practices (interventions, tests and medication), relevant and timely information and psychosocial and emotional support by knowledgeable, supportive and respectful health-care practitioners, to optimize maternal and newborn health (*high confidence in the evidence*). *(6)* No studies were identified on the values and preferences of pregnant women with regards to the use of antiplatelet agents specifically.

External partners and observers

Representatives of the United States Agency for International Development (USAID), the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) and the Bill and Melinda Gates Foundation participated in the GDG meetings as observers. These organizations, with their history of collaboration with WHO in maternal and perinatal health guidelines dissemination and implementation, were identified as potential implementers of the recommendations. The list of observers who participated in the GDG meetings is included in Annex 1.

External Review Group (ERG)

The ERG included five technical experts with interests and expertise in the prevention and treatment of pre-eclampsia. The group was geographically diverse and gender balanced and the members reported no significant conflicts of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendations, health-care professionals and policy makers. It was not within the remit of this group to change the recommendations that were formulated by the GDG. Members of the ERG are listed in Annex 1.

Identification of priority questions and outcomes

The priority outcomes were aligned with those from the 2011 *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. (12)* These outcomes were initially identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the guideline. In recognition of the importance of women's experiences of care, two additional outcomes – maternal well-being and maternal satisfaction – were included in this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women and to ensure that the final set of recommendations would be woman-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

Evidence identification and retrieval

Evidence to support this update was derived from several sources by the ESG working in collaboration with the WHO Steering Group.

Evidence on the recommendations for the use of low dose acetylsalicylic acid (aspirin, 75 mg per day) for the prevention of pre-eclampsia in women at moderate or high risk of developing the condition

An existing systematic review on antiplatelet agents for preventing pre-eclampsia and its complications was updated. *(16)* The objective of the review was to assess the effectiveness and safety of antiplatelet agents such as aspirin

when given to women at risk of developing the condition. In total, the review included 77 trials and assessed the outcomes of 40 249 women and their babies.

This systematic review was the primary source of evidence of effectiveness for these recommendations. Randomized controlled trials relevant to the key questions were screened by the review authors and data on their outcomes and comparisons were entered into Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). The RevMan file was then exported to GRADE profiler software (GRADEpro) and GRADE criteria were used to critically appraise the retrieved scientific evidence. *(17)* Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements of each outcome and the estimated risks.

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

A mixed-methods systematic review was the primary source of evidence on values, acceptability and feasibility as they relate to the EtD framework. *(15)* This review included women's and providers' views and experiences with complications during labour and childbirth. Additionally, a systematic review of qualitative studies evaluating "what women want" from antenatal care was used to further inform the values and equity domains. *(15)* The primary sources of evidence for resources and cost-effectiveness were individual papers that compared different schema for use of aspirin for prevention of pre-eclampsia.

Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence on effects for each outcome was performed using the GRADE approach. *(9, 10)* Using this approach, the certainty of evidence for each outcome was rated "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 each individual study and then across the 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 directions 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 recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

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

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

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

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

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual tool. *(18)* The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low and very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest. *(19-24)*

Formulation of the recommendation

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

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: “What are the desirable and undesirable effects of the intervention?” and “What is the certainty of the evidence on effects?” Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the intervention. Where the intervention showed evidence of potential harm and was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.
- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those

affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: "Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?" When the intervention resulted in benefits or outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the "effects" domain (see above), informed the "balance of effects" judgement.

- **Resources:** For this domain, the questions asked were: "What are the resources associated with the intervention?" and "Is the intervention cost-effective?" The resources required to implement the use of antiplatelet agents (specifically aspirin) primarily includes the costs of mainly training of skilled health personnel and monitoring and evaluation. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively.

- **Acceptability:** For this domain, the question was: "Is the intervention acceptable to women and health-care providers?". The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.

- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of health-care providers responsible for administering it. The question addressed was: "Is it feasible for the relevant stakeholders to implement the intervention?" Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.

- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: "What is the anticipated impact of the intervention on equity?". The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

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

The WHO Steering Group provided the EtD framework (including evidence summaries, summary of findings tables and other documents related to the recommendation) to GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments electronically on the documents before the virtual GDG meeting. During the GDG meeting (23-24 November 2020), which was conducted under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD framework, and any comments received through preliminary feedback, and formulated the recommendations. The purpose of the meeting was to reach consensus on the recommendations and the specific context, based on explicit consideration of the range of evidence presented in the EtD framework and the judgement of the GDG members. The GDG was asked to select one of the following categories for the recommendations:

- **Recommended:** This category indicates that the intervention should be implemented.

- **Not recommended:** This category indicates that the intervention should not be implemented.

- **Recommended only in specific contexts ("context-specific recommendation"):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation and should only be implemented in these contexts.

- **Recommended only in the context of rigorous research ("research-context recommendation"):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided it takes the form of research that addresses unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

Management of declarations of interests

WHO has a robust process to protect the integrity of its normative work, as well as to protect the integrity of the individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflict of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest (DOI) for WHO experts. *(25)* All GDG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development process. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflicts of interest as outlined in the *WHO handbook for guideline development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contribution of its experts is, actually and ostensibly, objective and independent. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

Decision-making during the GDG meetings

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

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

Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, the evidence summary and other documents relevant to the GDG's deliberation. 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 full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to the GDG and the ERG for their final review and approval.

Peer review

Following review and approval by GDG members, the final document was sent to five external independent experts (comprising the ERG) who were not involved in the GDG 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 the correction of factual errors and improving language to address any lack of clarity.

3. Recommendations and supporting evidence

Pre-eclampsia can increase the risk of adverse outcomes to a mother (placental abruption, renal failure, liver failure, cerebrovascular accident, HELLP syndrome, admission to the intensive care unit [ICU]) and to a baby (fetal or neonatal death, admission to the neonatal intensive care unit [NICU]), as well as increase the use of additional interventions and hospital admission. Amongst women with risk factors for pre-eclampsia who participated in trials of any antiplatelet agent versus placebo or no treatment, for those in the untreated (placebo or no treatment) arm:

- 9.4% of women experienced pre-eclampsia; and
- 3.4% of women experienced fetal death, neonatal death or death before hospital discharge.

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The EtD 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 by the GDG in determining the strength and direction of the recommendation, is presented in the EtD framework (Annex 4).

Considering these risks, the GDG considers it unlikely that there would be important variability in how women value this outcome. The GDG also considered that it is likely that adverse consequences of pre-eclampsia in pregnancy are worse in women living in disadvantaged circumstances – the poorest, least educated, those residing in rural areas and those with poor access to quality antenatal care. *(13)*

The availability of a health-care intervention enables the fulfilment of a person's human rights with regard to health when it is shown to decrease prevalence of a disease or death. In this case, aspirin may be an inexpensive and accessible drug but it is able to prevent pre-eclampsia (which is the first or second ranked among the top causes of maternal death in most countries).

The equity domain was discussed at length by the GDG as they formulated these recommendations. It was agreed that an important aspect regarding

equity is that in fact the women who may have the least access to tertiary care for management of pre-eclampsia and eclampsia may see the greatest improvement in outcomes, i.e. might benefit the most from preventative measures.

In summary, the GDG believe that this intervention responds to the Human Rights Council resolution 11/8, para. 2 which states that "understanding at the international and regional levels that reducing maternal mortality and morbidity is not solely an issue of development, but a matter of human rights… the Human Rights Council identifies a range of human rights directly implicated in maternal mortality and morbidity, namely, the 'rights to life, to be equal in dignity, to education, to be free to seek, receive and impart information, to enjoy the benefits of scientific progress, to freedom from discrimination, and to enjoy the highest attainable standard of physical and mental health, including sexual and reproductive health'. Therefore the GDG recommendation is for effective and equitable implementation of this intervention (aspirin) as it may reduce health inequities. However, assuring access to an inexpensive drug alone is not likely to achieve these desired benefits. More research on how access to antiplatelet agents can be truly assured is needed to fully understand the full breadth and depth of its human rights implications.

The external review group was also asked to determine if the recommendations made were aligned with stakeholder interests.

The following recommendations were adopted by the GDG. The evidence on the effectiveness of this intervention was derived from the updated systematic review and summarized in GRADE tables (Annex 4).

To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional remarks reflecting the summary of the discussion by the GDG are included under each recommendation.

Table 1.

Low-dose acetylsalicylic acid (aspirin, 75 mg per day) is recommended for the prevention of pre-eclampsia in women at moderate or high risk of developing the condition. *(Recommended)*
Remarks • Evidence from the systematic review supports the use of aspirin in all at-risk groups (low, moderate and high). However, the GDG noted that a much larger number of women at low risk of developing pre-eclampsia would need to be treated to prevent one case of pre-eclampsia compared with women at moderate or high risk. Based on the risk-benefit assessment of the use of aspirin among women at low risk of pre-eclampsia, additional resource constraints on a health system, and the impact on equity, the GDG recommends restricting treatment to only women at moderate or high risk of pre-eclampsia. • For the purpose of this recommendation, women are regarded as being at moderate risk of developing pre-eclampsia if they have any two of the following risk factors: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy; and at high risk of developing pre-eclampsia if they have one or more of the following risk factors: diabetes, chronic or gestational hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal or neonatal death associated with pre-eclampsia. This is not an exhaustive list of factors for moderate- or high-risk stratification for pre-eclampsia and can be adapted or complemented based on the local epidemiology of pre-eclampsia.

Table 1. (continued)

Low-dose acetylsalicylic acid (aspirin, 75 mg per day) is recommended for the prevention of pre-eclampsia in women at moderate or high risk of developing the condition. *(Recommended)*
• The GDG acknowledged that in settings where 75 mg aspirin tablets are not available, the dose nearest to 75 mg that is available should be used. • Although there is evidence to suggest that a daily dose of aspirin of 75 mg and above (up to 150 mg) may be more beneficial compared to an aspirin dose less than 75 mg in terms of reduction of pre-eclampsia, the GDG was concerned about the potential for increased risk of postpartum haemorrhage and the plausibility that the risk could be increased with higher doses of aspirin. Therefore, the GDG selected 75 mg as the optimal dose in terms of risk-benefit considerations (details described in the Evidence to Decision framework). In making this decision, the GDG acknowledged the lack of evidence on the comparative risk of postpartum haemorrhage among women who received 75 mg compared with those who received 150 mg of aspirin for pre-eclampsia prevention and noted it as a research priority. In view of the potential for a small increase in risk for postpartum haemorrhage among women treated with aspirin it is important to counsel women who are eligible for aspirin for the prevention of pre-eclampsia on the potential risks to encourage informed decision-making by the women and their families. • Aspirin should not be used by women for whom it is contraindicated. • The GDG emphasized that this recommendation applies to the use of aspirin in women with gestational hypertension as a secondary preventive measure against developing pre-eclampsia. • This recommendation supersedes recommendation No. 7 in the *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia (2011)*.

Table 2.

Low-dose acetylsalicylic acid (aspirin, 75 mg per day) for the prevention of pre-eclampsia and its related complications should be initiated by 20 weeks' gestation or as soon as antenatal care is started. ***(Context-specific recommendation)***

Remarks

- Evidence from the systematic review shows that women appeared to have a decreased risk of developing pre-eclampsia and its complications with the use of antiplatelet agents whether they began the intervention before or after 20 weeks' gestation. However, in view of the pathophysiology of pre-eclampsia, the GDG supports the initiation of treatment early in a pregnancy. The GDG noted that in most of the trials providing evidence on the benefit of aspirin in early pregnancy, treatment was initiated at 12 weeks' gestation and therefore consider this an appropriate time to initiate aspirin treatment.

- While antenatal care is ideally initiated by 12 weeks' gestation, in situations where antenatal care is started later than 20 weeks in pregnancy, GDG suggests initiating treatment at the time it begins.

- Irrespective of when treatment is initiated, appropriate counselling on the risks and benefits of preventative treatment is paramount - both to improve adherence and to inform the woman of warning signs which should be reported (such as bleeding or abdominal pain).

- There is scant evidence on the optimal time to discontinue aspirin treatment for the prevention of pre-eclampsia. In addition, the GDG is aware that, in some settings, the use of aspirin around the time of birth may preclude the use of epidural or spinal anaesthesia at the time of delivery. The GDG suggests that aspirin should be discontinued in line with local practice on the use of anticoagulants in pregnancy. The GDG notes the need for research in this area to clarify the benefits of prevention of pre-eclampsia with the potential risks of postpartum and neuroaxial haemorrhage with the use of low-dose aspirin late in pregnancy.

- This recommendation supersedes recommendation No. 8 in the *WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia (2011).*

4. Dissemination, adaptation and implementation of the recommendations

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

Recommendation dissemination

The recommendations will be disseminated through WHO regional and country offices, WHO Advisory Groups, ministries of health, country and regional technical advisory groups, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. These recommendations will also be available on the WHO website and the WHO Reproductive Health Library.[3] Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO maternal and perinatal staff.

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

[3] Available at: www.who.int/rhl.

Adaptation

National and subnational subgroups may be established to adapt and implement these recommendations based on an existing strategy. This process may include the development or revision of existing national guidelines or protocols based on the updated recommendations.

The successful introduction of evidence-based policies (relating to the updated recommendations) depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national or local guidelines and protocols, often supported by ministries of health, United Nations agencies, local professional societies and other relevant leadership groups. An enabling environment should be created for the use of these recommendations, including changes in the behaviour of health-care practitioners to enable the use of evidence-based practices.

In the context of humanitarian emergencies, the adaptation of the current recommendations should consider integration and alignment with other response strategies. Additional considerations to the unique needs of women in emergency settings, including their values and preferences, should be made. Context-specific tools and toolkits may be required in addition to standard tools to support the implementation of the recommendations in humanitarian emergencies by stakeholders.

Implementation considerations

The successful introduction of these recommendations into national programmes and health-care 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

- These recommendations should be adapted into documents and tools that are appropriate for different locations and

contexts, to meet the specific needs of each country and health service. Modifications to the recommendations, where necessary, should be justified in an explicit and transparent manner.

- An enabling environment should be created for the implementation of these recommendations, including education to support behaviour change among skilled health personnel to facilitate the use of evidence-based practices.

- In order to implement these recommendations, policies concerning who may prescribe aspirin may need to be reviewed and possibly revised. Healthcare providers working in antenatal care settings require training and supportive supervision on how to prescribe aspirin for the prevention of pre-eclampsia appropriately and safely and how to inform and counsel women on the risks and benefits of the available options.

- Health professionals will require training to counsel women on the benefits and side-effects of aspirin therapy in the prevention of pre-eclampsia. In settings where this is newly introduced (or where recommended practices are changed), additional training and monitoring may be required.

- In settings where this intervention is being introduced for the first time, it is advised that policy-makers and health managers consider how to ensure reliable procurement of aspirin in 75 mg tablets (or the closest dose available).

- National health systems need to ensure reliable supply systems and sustain availability and equitable access to good-quality, affordable antibiotics for use in maternal and perinatal health-care listed in the WHO Model List of Essential Medicines. They also should ensure that the necessary equipment are available wherever maternity services are provided. This includes establishing robust and sustainable regulatory, procurement and logistics processes that can ensure good-quality medicines and equipment are obtained, transported and stored correctly.

- Women should be adequately counselled and engaged in shared decision-making around the use of aspirin for the prevention of pre-eclampsia.

- Guidance on blood pressure control and antenatal follow-up is available in the WHO handbook *Managing complications of pregnancy and childbirth*. *(27)*

5. Research implications

Research priorities

In addition to the priorities listed below, the GDG noted that while low-dose aspirin has been shown to be beneficial in women at moderate or high risk of pre-eclampsia, there is a paucity of evidence to suggest that any specific subset of women within these groups would benefit especially from aspirin treatment. The identification of which women (among moderate- and high-risk groups) will benefit most from aspirin treatment and the addition of evidence from lower resourced settings can provide robust evidence on the baseline incidence of pre-eclampsia per risk level to inform the number needed to treat (NNT) and number needed to harm (NNTH) calculations (tailored to the specific setting). In addition to traditional epidemiological means for identifying these women, alternative methods, such as the use of algorithms informed by clinical findings may also be explored. To improve and enhance generalizability, studies should include women at risk of developing pre-eclampsia from lower resourced setting.

The GDG acknowledges that there is planned or ongoing research for some research priorities. Since there is no certainty that the planned or

ongoing research will give conclusive results, the research topics are listed as research priorities in this document and potential PICO questions are also suggested.

6. **To determine the ideal dose of aspirin for the prevention of pre-eclampsia** – the GDG noted that a direct comparison of 75 vs 150 mg aspirin with regard to the benefits and risks of treatment would provide needed evidence.
   - DRAFT PICO question:
     For women at risk of pre-eclampsia (P), does the use of 150 mg aspirin (I), compared with the use of 75 mg aspirin (C), have greater benefit for maternal and perinatal outcomes (O)?

   - DRAFT PICO question:
     For women at risk of pre-eclampsia (P), does the administration of BMI or weight-adjusted dosing of aspirin treatment (I), compared with 75 mg of aspirin treatment (C), have greater benefit for maternal and perinatal outcomes (O)?

7. **The ideal timing of initiation** – the GDG noted that earlier than 12 weeks (e.g. pre-conception, pre-implantation) may be beneficial but there is little evidence to provide guidance on this currently. The GDG noted that outside of research settings, pharmacovigilance mechanisms must be in place in countries to document potential congenital anomalies due to aspirin exposure during organogenesis.
   - DRAFT PICO question:
     For women at risk of pre-eclampsia (P), does the initiation of aspirin earlier than 12 weeks' gestation (I), compared with the use of aspirin from 12-20 weeks' gestation (C), have greater benefit for maternal and perinatal outcomes (O)?

8. **The updated recommendations reflect clinical practice for discontinuing aspirin treatment** – to improve assessment of the risks and benefits of aspirin treatment for the prevention of pre-eclampsia later in pregnancy, direct evidence on ideal timing of cessation is needed. This would take into consideration the risk of developing pre-eclampsia in pregnancy and the early post-partum period with the risks of postpartum haemorrhage or bleeding associated with spinal or epidural anaesthesia.
   - DRAFT PICO question:
     For women at risk of pre-eclampsia and on aspirin preventative treatment (P), does the discontinuation of aspirin at 36 weeks' gestation (I), compared with the discontinuation at the time of delivery (C), reduce the adverse events in the mother or neonate (O)?

6. Applicability issues

Anticipated impact on the organization of care and resources

Implementing these evidence-based recommendations requires continued clinical monitoring of women at risk for pre-eclampsia. The GDG noted that updating training curricula and providing training would increase impact and facilitate implementation.

The evidence-based recommendations in these guidelines can be achieved with the use of relatively inexpensive practices and drugs. The GDG noted that the following issues should be considered to increase the impact and facilitate implementation of these recommendations:

- Health systems should ensure reliable supply systems and sustain availability and equitable access to the WHO Model List of Essential Medicines.

- Provide clear guidance for the timely transfer of women to specialized services.

A number of factors may hinder the effective implementation and scale-up of these recommendations. These factors may be related to the behaviours of patients (women or

families) or health-care professionals and to the organization of care or health service delivery. As part of efforts to implement these recommendations, health system stakeholders may wish to consider the following potential barriers to their application:

- concerns from skilled care personnel and system managers regarding the safety of aspirin in pregnancy; and
- lack of effective referral mechanisms and care pathways for women identified as needing additional care.

Monitoring and evaluating guideline implementation

The implementation and impact of these recommendations will be monitored at the health service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities (28)* provides a list of prioritized input, output and outcome measures that can be used to define quality of care criteria and indicators and that should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Sexual and Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child, Adolescent Health, and Ageing, data on country- and regional-level implementation of the recommendations can be collected and evaluated in the short to medium term to assess its impact on national policies of individual WHO Member States.

Information on recommended indicators can also be obtained at the local level by interrupted time series or clinical audits. In this context, the GDG suggests the following indicators be considered:

- the proportion of women who are assessed for risk of pre-eclampsia and the proportion of pregnant women at risk who develop pre-eclampsia or eclampsia, and have, or have adverse maternal and perinatal outcomes.

7. Updating the recommendations

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

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

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

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Annex 2. Priority outcomes used in decision-making

Priority outcomes (O):[4]
Maternal outcomes • Maternal death • Eclampsia • Pre-eclampsia • Gestational hypertension (primary prevention only) • Severe maternal morbidity (renal failure, liver failure, cerebrovascular accident, HELLP syndrome, placental abruption, intensive care unit (ICU) admission) • Severe hypertension (secondary prevention only)[5] • Adverse effects of interventions • Maternal well-being • Maternal satisfaction
Neonatal outcomes • Fetal or neonatal death • Admission to neonatal intensive care unit (NICU) or special nursery • Apgar scores (any assessment) • Adverse effects to the neonate as a result of maternal treatment interventions

[4] These outcomes reflect the prioritized outcomes used in the development of these recommendations, in the *WHO recommendations for prevention and treatment of pre-eclampsia,* 2011. The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

[5] For secondary prevention, all women had either gestational hypertension or intrauterine growth restriction at trial entry. For this update, the outcome 'severe hypertension' was therefore included for women receiving antiplatelet agents for secondary prevention.

Annex 3. Summary and management of declared interests from meeting participants

Name	Expertise contributed to guideline development process	Declared interest	Management of conflict of interest
Edgardo Abalos	Member GDG	None declared	Not applicable
Sabina Ariff	Member GDG	None declared	Not applicable
Jemima Dennis-Antiwi	Member GDG	None declared	Not applicable
Christine East	Member GDG	None declared	Not applicable
Shireen Meher	Member GDG	(1) received grant - on research related to pre-eclampsia (2) is an author of the Cochrane systematic review which underlies the evidence reviewed for this recommendation	The grant received funds for research related to the use of calcium for prevention of pre-eclampsia, there is no linkage to the use of aspirin. As a co-author of the systematic review, she has in-depth knowledge of the papers included but this would not have an impact on her objective participation.
James Neilson	Member GDG	None declared	Not applicable
Hiromi Obara	Member GDG	None declared	Not applicable
Rachel Plachciniski	Member GDG	None declared	Not applicable
Zahida Quereshi	Member GDG	None declared	Not applicable
Kathleen Rasmussen	Member GDG	None declared	Not applicable
Deborah Armbruster	Observers	None declared	Not applicable
Emma Clark	Observers	None declared	Not applicable
Kathleen Hill	Observers	None declared	Not applicable
Bo Jacobsson	Observers	Past history of receiving grants for research related to topic of meeting. No current funding.	Reviewed and agreed with the assessment that his declaration would not impact his objective participation
Jeffrey Smith	Observers	None declared	Not applicable
Gerry Visser	Observers	None declared	Not applicable
Charlotte Warren	Observers	None declared	Not applicable
Ingela Wiklund	Observers	None declared	Not applicable
Anna Cuthbert	Evidence synthesis group	None declared	Not applicable
Myfanwy Williams	Evidence synthesis group	None declared	Not applicable
Joshua Vogel	Consultant to secretariat	None declared	Not applicable

Annex 4. Evidence to Decision framework

BACKGROUND

- Antiplatelet agents are a class of drugs that decrease platelet aggregation and inhibit the formation of thrombi (blood clots).
- Aspirin (an irreversible cyclooxygenase inhibitor, also known as acetylsalicylic acid) is the most commonly used antiplatelet agent. Aspirin reduces platelet aggregation by inhibiting platelets from producing thromboxane A2. It also has antipyretic, analgesic and anti-inflammatory effects.
- Other antiplatelet agents include adenosine triphosphate receptor inhibitors (e.g. clopidogrel) and adenosine reuptake inhibitors (e.g. dipyridamole)

A) QUESTIONS

The following are the prioritized questions in PICO (population, intervention, comparator, outcome) format:

1. For women at risk of pre-eclampsia (P), does the use of antiplatelet agents (I), compared with the use of placebo or no antiplatelet agent (C), improve maternal and perinatal outcomes (O)?
2. For women with gestational hypertension (P), does the use of antiplatelet agents (I), compared with the use of placebo or no antiplatelet agent (C), improve maternal and perinatal outcomes (O)?

Problem: The onset of pre-eclampsia
Perspective: Clinical practice recommendation – population perspective
Population (P): Pregnant women at risk for developing pre-eclampsia
Intervention (I): Antiplatelet agents
Comparator (C): Placebo or no antiplatelet agent
Setting: Hospital or community setting
Subgroups: Level of maternal risk at trial entry; gestational age at trial entry; dose of antiplatelet agent
Priority outcomes (O):[6]

Maternal outcomes:

- Maternal death
- Eclampsia
- Pre-eclampsia
- Gestational hypertension (primary prevention only)
- Severe maternal morbidity (renal failure, liver failure, cerebrovascular accident, HELLP syndrome, placental abruption, intensive care unit (ICU) admission)
- Severe hypertension (secondary prevention only)[7]
- Adverse effects of interventions
- Maternal well-being
- Maternal satisfaction

Neonatal outcomes:

- Fetal or neonatal death
- Admission to neonatal intensive care unit (NICU) or special nursery
- Apgar scores (any assessment)
- Adverse effects to the neonate as a result of maternal treatment interventions

[6] These outcomes reflect the prioritized outcomes used in the development of these recommendations in the *WHO recommendations for prevention and treatment of pre-eclampsia,* 2011. The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

[7] For secondary prevention, all women had either gestational hypertension or intrauterine growth restriction at trial entry. For this update, the outcome 'severe hypertension' was therefore included for women receiving antiplatelet agents for secondary prevention.

B) ASSESSMENT

1. EFFECTS OF INTERVENTIONS:

What is the effect of antiplatelet agents on priority outcomes when used for the prevention of pre-eclampsia?

Summary of evidence

Source and characteristics of studies

Evidence on the effects of antiplatelet agents for the prevention of pre-eclampsia was derived from a Cochrane systematic review, which included 77 randomized trials involving 40 249 women and their babies (2). Two trials did not contribute data to the analyses in the review, because relevant outcome data were not included in the available reports.

Of the 75 trials (40 120 women) that contributed data, five were multicountry trials – ASPirin for PREeclampsia prevention (ASPRE: United Kingdom, Italy, Spain, Greece, Belgium, Israel), Collaborative Low dose Aspirin trial in Pregnancy (CLASP: Argentina, Australia, Belgium, Canada, Israel), Essai Regional Aspirine Mere-Enfant Study (ERASME: France and Belgium), Pergar (France and Belgium), Yu et al (identified in the review as United Kingdom plus others (United Kingdom, Brazil, Chile and South Africa). The remaining 70 trials took place in Algeria (one trial), Australia (seven trials), Austria (one trial), Barbados (one trial), Brazil (two trials), Canada (one trial), China (three trials), Egypt (one trial), Finland (five trials), France (three trials), Germany (two trials), India (five trials), Iran (Islamic Republic of) (four trials), Israel (three trials), Italy (four trials), Jamaica (one trial), Japan (one trial), Republic of Korea (one trial), Netherlands (four trials), Romania (one trial), Russian Federation (one trial), South Africa (one trial), Spain (four trials), United Republic of Tanzania (one trial), United Kingdom (four trials), USA (six trials), Venezuela (Bolivarian Republic of) (one trial), Zimbabwe (one trial). The trials were published between 1985 and 2018. Nine trials, accounting for 80% of the women in the review, recruited at least 1 000 women each, with the largest trial contributing 9 364 women. 34 trials had less than 100 women each.

All participants were pregnant women considered to be at risk of developing pre-eclampsia, though the specific risk factor or factors used and the level of risk varied between trials. The trials of antiplatelet agents for primary prevention recruited women without gestational hypertension, while trials investigating antiplatelet agents for secondary prevention recruited women who already had gestational hypertension, intrauterine growth restriction or both. 64 trials (27 897 women) administered antiplatelet agents for primary prevention of pre-eclampsia only; seven trials (544 women) for secondary prevention only; and four trials (11 679 women) included both primary and secondary prevention. The trials were largely conducted at maternity hospitals, or maternity units within hospitals. The women were usually recruited from antenatal clinics.

This review combined individual patient data (IPD) and aggregate data (AD).[8] Individual patient data were available for 38 trials, involving 34 514 women (86% of women in the review).

[8] Meta-analyses based upon individual patient data provide more powerful and uniformly consistent analyses while allowing better characterization of sub-groups and outcomes compared with analyses based on aggregate data alone (2, 3, 4). For example, individual patient data analyses in the systematic review help to classify the participants by characteristics such as maternal risk of developing pre-eclampsia. For the purpose of this evidence framework, analyses using data from all women are presented.

Primary prevention of pre-eclampsia

For the primary prevention of pre-eclampsia, the review presented subgroup analyses by level of maternal risk of pre-eclampsia at trial entry, gestational age at trial entry and dose of antiplatelet agent.

Maternal risk at trial entry

Women were categorized as:

- low risk (no identifiable risk factor or one of the following: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy);
- moderate risk (two of the following risk factors: primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy);
- high risk (woman had at least one of the following: diabetes, chronic hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal or neonatal death associated with pre-eclampsia); or
- unclear or unspecified risk.

Gestational age at trial entry

The timing of commencement of antiplatelet therapy in the trials varied. The systematic review grouped results by gestational age at commencement of therapy as < 20 weeks versus ³ 20 weeks. For trials focusing on women at risk of pre-eclampsia (primary prevention), one trial (54 women) started antiplatelet therapy pre-pregnancy, 46 trials (36 841 women) included women who began antiplatelet therapy before 20 weeks' gestation and 34 trials (33 982 women) included women who began at 20 weeks' gestation or later. In three trials (115 women), gestational age at trial entry was not described.

Dosing regimens in the trials

Results in the systematic review were presented grouped by women receiving doses of aspirin < 75 mg versus aspirin ³ 75 mg versus aspirin ³ 75 mg plus dipyridamole).

The included trials administered different doses of antiplatelet agents:

Aspirin

- 0.5 mg/kg per day (two trials, 180 women)[9]
- 50 mg per day (six trials, 1 726 women)
- 60 mg per day (16 trials, 23 526 women)
- 75 mg per day (nine trials, 4728 women)
- 80 mg per day (five trials, 593 women)
- 81 mg per day (four trials, 213 women)
- 100 mg per day (18 trials, 5 089 women)
- 150 mg per day (five trials, 2 798 women)

[9] This number describes the total number of women in the trials administering each dose, including women in the control arm and additional intervention arms where applicable.

Aspirin with dipyridamole

- 1.5 mg/kg aspirin plus 75 mg dipyridamole per day (1 trial, 200 women)
- 81 mg aspirin plus 200 mg dipyridamole per day (one trial, 44 women)
- 100 mg aspirin plus 300 dipyridamole per day (one trial, 91 women)
- 125 mg aspirin plus 150 to 225 mg dipyridamole per day (one trial, 76 women)
- 150 mg aspirin plus 225 mg dipyridamole per day (one trial, 230 women)
- 150 mg aspirin plus 300 mg dipyridamole per day (one trial, 102 women)

Aspirin plus other co-interventions

- 300 mg aspirin per week (split over three doses) plus 500 mg vitamin C per day, 400 IU vitamin E per day, and 1 g fish oil three times per day (one trial, 127 women)

Dipyridamole

- 225 mg per day (one trial, 300 women)

Dipyridamole with heparin

- 300 to 400 mg dipyridamole per day, split between four doses; plus 15 000 units subcutaneous heparin per day, split between two doses (one trial, 21 women)

Ozagrel hydrochloride

- 400 mg per day (one trial, 40 women)

Triazolopyrimidine

- 330 mg per day (one trial, 160 women)

In 53 trials (37 007 women) the control was placebo, in 17 trials (2 324 women) the control was no antiplatelet agent and in five trials (789 women) it was unclear whether or not a placebo was used.

Description of findings

Wherever both were available, the Cochrane review estimated the effects of antiplatelet agents based on the combined results of aggregate data and individual patient data (effect estimates from the combined results are provided in detail below and in the evidence tables). The review also reported effect estimates separately for aggregate data and individual patient data trials. In general, estimates of effect, regardless of data type, aligned with each other.

Where the effect estimates diverged substantially, or where only one of individual patient data or aggregate data were available for a particular outcome, it is specified within this summary.

Effects of antiplatelet agents compared with placebo or no antiplatelet agent for primary prevention of pre-eclampsia

Maternal outcomes:

Maternal death: It is unclear what effect antiplatelet agents have on maternal death - there were very few events (6/14 339 antiplatelet and 3/14 336 control) and the evidence was assessed as very low certainty (individual patient data only).

Eclampsia: When compared with placebo or no antiplatelet agent, antiplatelet agents may make little or no difference to the risk of eclampsia (low certainty evidence: 17 studies, 24 947 women; 38/12 496 vs 37/12 451; RR 1.03, 95% CI 0.66 to 1.60).

Pre-eclampsia: Antiplatelet agents probably reduce the risk of pre-eclampsia (moderate certainty evidence: 60 studies, 36 871 women; 1424/18 567 vs 1713/18 304; RR 0.82, 95% CI 0.77 to 0.88).

Gestational hypertension: antiplatelet agents probably make little or no difference to the risk of pregnant women developing gestational hypertension (moderate certainty evidence: 25 studies, 27 834 women; 1676/14 019 vs 1739/13 815; RR 0.95, 95% CI 0.90 to 1.01; IPD only).

Severe maternal morbidity: antiplatelet agents probably make little or no difference for pregnant women (regardless of level of risk at trial entry) developing or experiencing:

- **HELLP syndrome** (moderate certainty evidence: 16 studies, 20 130 women; 19/10 063 vs 25/10 067; RR 0.77, 95% CI 0.44 to 1.36) or
- **placental abruption** (moderate certainty evidence: 29 studies, 30 775 women; 145/15 442 vs 114/15 333; RR 1.21, 95% CI 0.95 to 1.54) or
- **pulmonary oedema** (low certainty evidence: 12 studies, 16 732 women; 10/8 407 vs 12/8 325; RR 0.84, 95% CI 0.37 to 1.89; individual patient data only).

It is unclear what effect antiplatelet agents have on the risk of **cerebrovascular accident**, **disseminated intravascular coagulation**, **liver failure** or **renal failure** (all individual patient data only); for all these outcomes the evidence was very low certainty. None of the included trials reported on **maternal intensive care unit admission**. No other severe maternal morbidity outcomes were reported in the Cochrane review.

Adverse effects of interventions:

Antiplatelet agents could slightly increase the risk of women experiencing **antepartum haemorrhage** however the confidence intervals cross the line of no effect (high certainty evidence: 25 trials, 30 513 women; 534/15 308 vs 206/15 205; RR 1.04, 95% CI 0.92 to 1.1; individual patient data only).

The review reported a small increase in women experiencing **postpartum haemorrhage but the confidence interval touches the line of no effect** (> 500ml; high certainty evidence: 19 trials, 23 769 women; 1795/11 893 vs 1691/11 876; RR 1.06, 95% CI 1.00 to 1.12).

The Cochrane review did not report on **maternal well-being** or **maternal satisfaction** with the intervention.

Neonatal outcomes:

Fetal or neonatal death: antiplatelet agents reduce the risk of the composite outcome **fetal death, neonatal death, or death before hospital discharge** (high certainty evidence: 52 studies, 35 391 babies; 509/17 777 vs 594/17 614; RR 0.85, 95% CI 0.76 to 0.95). However, antiplatelets make little or no difference to **fetal death** alone (high certainty evidence: 41 studies, 33 381 babies; 360/16 749 vs 392/16 632; RR 0.92, 95% CI 0.80 to 1.06) or **neonatal death in the first week of life** alone (moderate certainty evidence: 27 studies, 26 548 babies; 113/13296 vs 128/13 252; RR 0.88, 95% CI 0.68 to 1.13).

Admission to neonatal intensive care unit (NICU) or special nursery: antiplatelet agents make little or no difference to NICU admission (high certainty evidence: 29 studies, 32 808 women; 2468/16 441 vs 2562/16 367; RR 0.95, 95% CI 0.91 to 1.00).

The Cochrane review did not report on **Apgar scores**.

The review found that antiplatelet agents given to women during pregnancy probably do not have any effect on the risk of **intraventricular haemorrhage** (moderate certainty evidence: 20 studies, 32 224 babies; 73/16 094 vs 74/16 130; RR 0.99, 95%CI 0.72 to 1.36) **or other neonatal bleeds** (high certainty evidence: 20 studies, 30 715 babies; 203/15 357 vs 227/15 358; RR 0.9, 95%CI 0.75 to 1.08).

Subgroup analyses

The results of the Cochrane review were presented by three subgroups; level of maternal risk for pre-eclampsia at trial entry, gestational age at trial entry and dose of antiplatelet agent in the intervention group.

Only two priority outcomes had these subgroup analyses available (pre-eclampsia and fetal death, neonatal death or death before hospital discharge). Risks of adverse events (antepartum haemorrhage, postpartum haemorrhage, neonatal intraventricular haemorrhage or other neonatal bleed) were not described by sub-groups.

Effects of antiplatelet agents by level of risk of pre-eclampsia at trial entry (primary prevention for low, moderate, high risk women)

All women, regardless of level of risk at trial entry had lowered risk of developing pre-eclampsia:

- Low risk: moderate certainty evidence; 31 studies, 21 126 women; 419/10 623 vs 484/10 503; RR 0.85, 95% CI 0.75 to 0.97,
- Moderate risk: low certainty evidence; 20 studies, 1416 women: 70/734 vs 108/682; RR 0.64, 95% CI 0.49 to 0.83,
- High risk: moderate certainty evidence; 39 studies, 14 082 women; 927/7084 vs 1098/6998; RR 0.83, 95% CI 0.77 to 0.90.

Test for subgroup differences between low, moderate, and high risk groups: $Chi^2 = 3.89$, df = 2 (P = 0.14), $I^2 = 48.6\%$:

Unknown or unspecified risk: very low certainty evidence; 2 studies, 92 women; 1/46 vs 10/46, RR 0.14, 95% CI 0.03 to 0.76).

In high-risk women only, there was a reduction in the risk of fetal death, neonatal death or death before discharge (high certainty evidence; 37 studies, 13 399 babies; 188/6 731 vs 239/6668; RR 0.77, 95% CI 0.64 to 0.93). For other groups of women, maternal antiplatelet therapy did not affect mortality outcomes:

- Low risk: moderate certainty evidence, 28 studies, 20 961 babies; 281/10 536 vs 310/10 425; RR 0.90, 95% CI 0.77 to 1.05),
- Moderate risk: low certainty evidence, 16 studies, 884 babies; 29/437 vs 34/447; RR 0.94, 95% CI 0.60 to 1.48).

Test for subgroup differences between low, moderate, and high risk groups: $Chi^2 = 1.82$, df = 2 (P = 0.40), $I^2 = 0\%$

Unknown or unspecified risk: very low certainty evidence; 23 studies, 147 babies; 11/73 vs 11/74; RR 01.00, 95% CI 0.49 to 2.03)

Effects of antiplatelet agents by gestation at trial entry (primary prevention)

Women appeared to have a decreased risk for developing pre-eclampsia with the use of antiplatelet agents whether or not they began the intervention < 20 weeks' gestation or ≥ 20 weeks' gestation:

- Entered < 20 weeks' gestation: moderate certainty evidence; 46 studies, 22 510 women; 884/11 378 vs 1035/11 132; RR 0.80 95% CI 0.73 to 0.87),
- Entered > 20 weeks' gestation: moderate certainty evidence; 33 studies, 13 688 women; 547/6862 vs 614/6826; RR 0.88, 95% CI 0.79 to 0.99).

Test for subgroup differences: $Chi^2 = 2.07$, df = 1 (P = 0.15), $I^2 = 51.7\%$

There were fewer neonatal deaths (fetal death, neonatal death or death before hospital discharge) among babies born to women using antiplatelet agents, when therapy is initiated before 20 weeks' gestation:

- Entered < 20 weeks' gestation: high certainty evidence, 38 studies, 21 607 babies, 343/10 890 vs 402/10 717; RR 0.83 95% CI 0.72 to 0.95),
- Entered > 20 weeks' gestation: high certainty evidence, 32 studies, 13 523 babies, 164/6776 vs 180/6747; RR 0.92, 95% CI 0.75 to 1.13).

Test for subgroup differences: $Chi^2 = 0.68$, df = 1 (P = 0.41), $I^2 = 0\%$

Effects of antiplatelets agent by dose (primary prevention)

There was some evidence that higher doses of aspirin (≥ 75 mg: moderate certainty evidence; 35 trials, 12 612 women; 393/6 349 vs 560/6263; RR 0.69, 95% CI 0.61 to 0.78;) conferred a greater benefit than lower doses (< 75 mg: moderate certainty evidence; 17 trials, 23 204 women; 987/11 636 vs 1092/11 568; RR 0.90, 95% CI 0.83 to 0.98;) in terms of reducing the risk of developing pre-eclampsia (test for subgroup differences: $Chi^2 = 13.51$, df = 1 (P = 0.0002), $I^2 = 92.6\%$).

However, the evidence in this review did not indicate that the dose of aspirin made a difference to the risk of the composite outcome fetal death, neonatal death or death before hospital discharge:

- < 75 mg aspirin: high certainty evidence, RR 0.88, 95% CI 0.78 to 1.00,
- ≥ 75 mg aspirin: moderate certainty evidence, RR 0.69, 95% CI 0.51 to 0.93,
- ≥ 75 mg aspirin plus dipyridamole: moderate certainty evidence, RR 0.71, 95% CI 0.30 to 1.64.

Test for subgroup differences: $Chi^2 = 2.43$, df = 2 (P = 0.30), $I^2 = 17.8\%$

Effects of antiplatelet agents compared with placebo or no antiplatelet agent for women with gestational hypertension (secondary prevention of pre-eclampsia)

Maternal outcomes:

Maternal death: No studies included in the Cochrane review reported on this outcome.

Eclampsia: Among women with gestational hypertension, intrauterine growth restriction or both, the effect of antiplatelets compared to a placebo or no antiplatelet on the risk of developing eclampsia was unclear because the evidence was very low certainty.

Pre-eclampsia: among women with gestational hypertension, intrauterine growth restriction or both, antiplatelets probably reduce the risk of developing pre-eclampsia (moderate certainty evidence; seven studies, 1 813 women; 137/904 vs 185/909; RR 0.67, 95% CI 0.47 to 0.95).

Severe maternal morbidity: High certainty evidence suggests that antiplatelet agents probably make little or no difference to women developing **severe hypertension (per trialist definition)** when administered for secondary prevention (five studies, 1 834 women; 276/931 vs 293/903; RR 0.94, 95% CI 0.83 to 1.07; IPD only). Antiplatelet agents probably have little or no effect on women's risk of developing **severe pre-eclampsia** (moderate certainty evidence: three studies; 1 509 women; 62/755 vs 74/754; RR 0.78, 95% CI 0.48 to 1.26; IPD only) or **placental abruption** (low certainty evidence; five studies, 1 606 women; 14/802 vs 10/804; RR 1.39, 95% CI 0.63 to 3.05). It is unclear whether antiplatelet agents reduce **HELLP syndrome**, because the evidence was very low certainty. No included trials reported on **maternal intensive care unit admission** and other severe maternal morbidity outcomes.

Adverse effects of interventions:

Women who received antiplatelet agents for secondary prevention of pre-eclampsia did not have increased risks of bleeding**; antepartum haemorrhage**, five studies moderate certainty evidence, 1606 women, 49/802 vs 44/804; RR 1.11, 95%CI 0.75 to 1.64, individual patient data only) or **postpartum haemorrhage** (> 500 mL; moderate certainty evidence; 1 573 women, 110/785 vs 101/788; RR 1.09, 95% CI 0.85 to 1.4)

The Cochrane review did not report on **maternal well-being** or **maternal satisfaction**.

Neonatal outcomes:

Fetal or neonatal death: Among babies born to women with gestational hypertension at the time of trial entry, antiplatelet agents probably make little or no difference to the risk of **fetal death, neonatal death or death before hospital discharge** (moderate certainty evidence: nine studies, 2210 babies; 55/1120 vs 65/1090; RR 0.82, 95% CI 0.58 to 1.16).

Admission to neonatal intensive care unit (NICU) or special nursery: among women with gestational hypertension, intrauterine growth restriction or both, the use of antiplatelets make little or no difference to NICU admissions for their babies when compared with a placebo or no antiplatelet (high certainty evidence; six studies, 1910 babies; 305/971 vs 309/939; RR 0.97, 95% CI 0.86 to 1.10).

The Cochrane review did not report on **Apgar scores**. The review did not report on **neonatal intraventricular haemorrhage** or **other neonatal bleeds** among babies born to women given

antiplatelet agents for secondary prevention of pre-eclampsia.

Subgroup analyses

The review did not perform subgroup analyses for secondary prevention.

Judgements: Antiplatelet agents for prevention of pre-eclampsia (regardless of maternal risk, dosing, or timing of initiation)

Desirable effects

How substantial are the anticipated effects of antiplatelet agents versus placebo or no antiplatelet agents in the prevention of pre-eclampsia?

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

Undesirable effects

How substantial are the undesirable anticipated effects of antiplatelet agents versus placebo or no antiplatelet agents in the prevention of pre-eclampsia?

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

Certainty of the evidence

What is the overall certainty of the evidence on effects of antiplatelet agents versus placebo or no antiplatelet agents in the prevention of pre-eclampsia?

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

Additional considerations

The GDG discussed the results of a Swedish population register-based cohort study which found that the use of aspirin during pregnancy was associated with postpartum hemorrhage among those who had a vaginal birth. *(5)* Of note, the general practice in Sweden is to offer 75 mg aspirin for women at high risk of pre-eclampsia. There is also routine use of Pitocin in the third stage of labour.

The study included 313 624 women of which 4 088 women self-reported aspirin use in pregnancy. Analyses found an association with pregnancy-related bleeding. The incidence of bleeding during labor was 2.9% among aspirin users versus 1.5% in non-users, with an aOR of 1.63 [95% CI 1.30, 2.05]. The incidence of postpartum hemorrhage was 10.2% among aspirin users and 7.8% among non-users, an aOR of 1.23 (95% CI 1.08, 1.39). Additionally, women using aspirin were more likely to develop a postpartum hematoma; 0.4% among aspirin users vs 0.1% among non-users (aOR of 2.21 [95% CI 1.13, 4.34]) and neonatal intracranial hemorrhage (a 0.07% incidence among aspirin users *vs* 0.01% among non-users (aOR 9.66 [95% CI 1.88, 49.48]. Using this population data set, the authors suggest comparing the reduction of the absolute risk of preeclampsia by 0.4% but increase the absolute risk of a postpartum hemorrhage by 2%. In summary, they concluded that these risks argue against universal administration of aspirin to all pregnant women.

The GDG requested and was informed that evidence on the risk of haemorrhage in women who were prescribed 75 mg vs 150 mg of aspirin is not available.

Other outcomes of interest

The systematic review also reported on birth by gestational age and found a reduction of all preterm birth among women at risk for pre-eclampsia who used antiplatelet agents for primary prevention of pre-eclampsia. In combination, births occurring < 37 weeks' gestation were reduced by 10% (high certainty evidence: 47 studies, 35 212 women; 2827/17 706 vs 3082/17 506; RR 0.90, 95% CI 0.86 to 0.94).

Analyses by mutually exclusive weeks of gestation found that the effect appears to be most pronounced for reduction of preterm births between 32 and 33 week's gestation:

- < 28 weeks 291/16 177 vs 333/15 975, RR 0.87, 95% CI 0.74 to 1.01 (moderate certainty evidence; 30 studies; 32 155 women),
- 28-31 weeks 372/16 177 vs 370/15 978, RR 0.98, 95% CI 0.85 to 1.13 (high certainty evidence; 30 studies; 32 155 women),
- 32-33 weeks 356/16 177 vs 414/15 978, RR 0.84, 95% CI 0.73 to 0.97 (high certainty evidence; 30 studies; 32 155 women),
- 34-36 weeks 1241/16 177 vs 1308/15 978, RR 0.93, 95% CI 0.87 to 1.0 (high certainty evidence; 30 studies; 32 155 women),
- unknown 405/16 210 vs 370/16 007, RR 1.1, 95% CI 0.96 to 1.25 (high certainty evidence; 31 studies; 32 217 women).

These analyses did not further identify these preterm births as spontaneous or iatrogenic preterm deliveries.

Among women with gestational hypertension, intrauterine growth restriction or both (given aspirin for secondary prevention of pre-eclampsia), the use of antiplatelets compared to placebo or no antiplatelet agent make little or no difference to the risk of preterm birth < 37 weeks' gestation (high certainty evidence: 9 studies, 2070 women; 291/1049 vs 325/1021; RR 0.89, 95% CI 0.78 to 1.01).

Judgements: Antiplatelet agents for prevention of pre-eclampsia for women regardless of risk (low, moderate, or high)

Desirable effects

How substantially different are the anticipated effects of antiplatelet agents versus placebo or no antiplatelet agents in the prevention of pre-eclampsia, when comparing different levels of maternal risk?

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

Undesirable effects

How substantial different are the undesirable anticipated effects of antiplatelet agents versus placebo or no antiplatelet agents when comparing different levels of maternal risk?

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

Certainty of the evidence

What is the overall certainty of the evidence on effects of antiplatelet agents versus placebo or no antiplatelet agents, when comparing different levels of maternal risk?

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

Additional considerations

The GDG discussions noted that the desirable and undesirable effects of aspirin therapy for prevention of pre-eclampsia vary by the woman's baseline risk. The NNT for benefit (prevention of pre-eclampsia) is 151 in the low-risk group and 39 in the high-risk group. Due to this difference, the GDG considered each risk group separately in order to issue recommendations; summary of judgement tables, taking into account the effects of treatment and impact on values, equity, costs, etc are thus arranged by the women's baseline risk.

Judgements: dose of antiplatelet agents (aspirin) for prevention of pre-eclampsia

Desirable effects

How substantial are the anticipated effects of < 75 mg aspirin in the prevention of pre-eclampsia?

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

Undesirable effects

How substantial are the undesirable anticipated effects of < 75 mg aspirin in the prevention of pre-eclampsia?

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

Certainty of the evidence

What is the overall certainty of the evidence on effects of < 75 mg aspirin in the prevention of pre-eclampsia?

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

Additional considerations

None.

Judgements: Dose of antiplatelet agents (aspirin) for prevention of pre-eclampsia

Desirable effects

How substantial are the anticipated effects of > 75 mg aspirin in the prevention of pre-eclampsia?

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

Undesirable effects

How substantial are the undesirable anticipated effects of > 75 mg aspirin in the prevention of pre-eclampsia?

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

Certainty of the evidence

What is the overall certainty of the evidence on effects of > 75 mg aspirin in the prevention of pre-eclampsia?

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

Additional considerations

None.

Judgements: initiation of antiplatelet agents at < 20 weeks for prevention of pre-eclampsia

Desirable effects

How substantial are the anticipated effects of antiplatelet agents initiated at < 20 weeks in the prevention of pre-eclampsia?

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

Undesirable effects

How substantial are the undesirable anticipated effects of antiplatelet agents initiated at < 20 weeks' gestation in the prevention of pre-eclampsia?

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

Certainty of the evidence

How substantial are the anticipated effects of antiplatelet agents initiated at < 20 weeks' gestation versus in the prevention of pre-eclampsia?

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

Additional considerations

None.

Judgements: initiation of antiplatelet agents at < 20 weeks for prevention of pre-eclampsia

Desirable effects

How substantial are the anticipated effects of antiplatelet agents initiated at > 20 weeks in the prevention of pre-eclampsia?

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

Undesirable effects

How substantial are the undesirable anticipated effects of antiplatelet agents initiated at > 20 weeks' gestation in the prevention of pre-eclampsia?

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

Certainty of the evidence

How substantial are the anticipated effects of antiplatelet agents initiated at > 20 weeks' gestation versus in the prevention of pre-eclampsia?

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

Additional considerations

None.

2. VALUES

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with the use of antiplatelet agents for prevention of pre-eclampsia?

Research evidence

Evidence from a qualitative systematic review of what women want from antenatal care showed that healthy pregnant women from high-, medium- and low-resource settings valued having a positive pregnancy experience, the components of which included the provision of effective clinical practices (interventions, tests and medications), relevant and timely information and psychosocial and emotional support, by knowledgeable, supportive and respectful healthcare practitioners, to optimize maternal and newborn health (high confidence in the evidence). *(6)* No studies were identified on the values and preferences of pregnant women with regards to the use of antiplatelet agents specifically.

Additional considerations

Pre-eclampsia can increase the risk of adverse outcomes to mother (placental abruption, renal failure, liver failure, cerebrovascular accident, HELLP syndrome, and/or admission to the ICU) and baby (fetal or neonatal death, admission to the NICU), as well as increase the use of additional interventions and hospital admission. Considering these risks, the GDG considers it unlikely that there would be important variability in how women value this outcome.

☐ 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 aspirin or placebo/no treatment?

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

3. RESOURCES

How large are the resource requirements (costs) of the use of antiplatelet agents for the prevention of pre-eclampsia?

Research evidence

The Cochrane review did not pre-specify outcomes related to economic costs and a 2015 review of economic assessments for pre-eclampsia diagnosis and treatment did not identify any studies on the cost-effectiveness of antiplatelet agents. (*7*) A literature review conducted for the GDG found five applicable studies. Several cost-effectiveness models have considered different algorithms for the use of aspirin in the prevention of pre-eclampsia and found that aspirin use in pregnancy is a cost-effective intervention to prevent pre-eclampsia. *(8-12)*

A 2015 decision model analysis of a hypothetical cohort of 4 million women giving birth in the USA compared different treatment approaches using 81 mg aspirin and reported that risk-stratification treatment strategies were cost-effective. (*8)*

Another decision analysis comparing pre-eclampsia related costs and effects of four strategies for aspirin use by American women prior to 16 weeks' gestation was conducted in 2018. Compared with the use of a screen-and-treat approach, universal aspirin was associated with fewer cases of pre-eclampsia and overall costs. Taking into consideration the potential risks of gastrointestinal bleeding or aspirin-induced asthma, in 91% of modelled simulations, universal aspirin remained the preferred strategy. However, when compliance fell below 55.2% of pregnant women, screen-and-treat approach became the most cost-effective strategy (current United States Health Promotion Task Force recommendation). *(9)* The dose used in this model was not specified.

Using the same model and substituting the United Kingdom prevalence for pre-eclampsia and diagnostic accuracy, Cuckle found that decreased compliance with aspirin favoured a screen-and-treat approach rather than universal aspirin intervention. *(10)* Similarly, a 2019 decision-model analysis in a hypothetical population of 3 987 516 births in Canada indicated that a first trimester screening program coupled with early use of 162 mg aspirin in (screen-and-treat approach) among women at high risk was cost-effective. *(11)*

In contrast, an economic decision analysis compared the cost-effectiveness of a Fetal Medicine Foundation (FMF) screen-and-treat strategy to routine (universal) treatment with 75 mg aspirin for the prevention of pre-eclampsia in 100 000 low-risk Irish nulliparous women and assessed the cost-effectiveness of disaggregated components of the FMF algorithm. *(12)* Results indicated that routine use of 75mg aspirin gave the greatest health gains and larger cost savings. In a sub-analysis of the disaggregated FMF screening components (screen-and-treat) vs. routine aspirin for all low-risk women, routine aspirin remained the most cost-effective approach. These results remained even with an assumption of 50% adherence.

Using the MSH International drug price calculator, the median supplier unitary cost of 75 mg aspirin is 0.0148 USD/tablet. Thus, 1 x 75 mg tablet per day for 20 weeks is estimated to cost US$ 2.072

☐ Cost: x 20 wks (2015, supplier cost)

– 75 mg $2.072

– 100 mg $0.294

– 300 mg $0.448

– 500 mg $0.658

It has been suggested that economic analyses on the use of aspirin with a view on difference adherence rates and relative reduction rates for growth restriction, preterm birth, placental dysfunction etc may further elucidate the best approach for preeclampsia prophylaxis. *(9)*

https://www.msh.org/resources/international-medical-products-price-guide (accessed 20.11.2020

Main resource requirements

Resource	Description
Staff training	• Correct performance of blood pressure measurement • Recognition and treatment of pre-eclampsia
Staff time	• Regular visits for blood pressure monitoring and urine tests (10 minutes of ante-natal care provider's time per visit).
Supplies	• Adequate supplies of antiplatelet agents (e.g. 75 mg tablets daily for 20 weeks or more, depending on timing of initiation). Antiplatelet agents may be available in different formulations in different settings. • Regular testing for proteinuria (dipstick)
Equipment and infrastructure	• Sphygmomanometer • Treatment algorithm

Additional considerations

None.

Resources required

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

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

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

Cost–effectiveness

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

4. EQUITY

What would be the impact of the use of antiplatelet agents for prevention of pre-eclampsia health equity?

Research evidence

No direct evidence identified.

Additional considerations

Amongst women with risk factors for pre-eclampsia who participated in trials of any antiplatelet agent versus placebo or no treatment for those in the untreated (placebo or no treatment) arm:

- 9.4% of women experienced pre-eclampsia; and
- 3.4% of women experienced fetal death, neonatal death or death before hospital discharge.

It is likely that adverse consequences of pre-eclampsia in pregnancy are worse in women living in disadvantaged circumstances – the poorest, least educated, those residing in rural areas and those with poor access to quality antenatal care (13).

The availability of a health-care intervention enables the fulfilment of a person's human rights with regard to health when it is shown to decrease prevalence of a disease or death. In this case, aspirin may be an inexpensive and accessible drug but it is able to prevent pre-eclampsia (which is the first or second ranked among the top causes of maternal death in most countries).

The equity domain was discussed for these recommendations by the GDG in their formulation. It was agreed that an important aspect regarding equity is that in fact some women who may have the least access to tertiary care for management of pre-eclampsia or eclampsia may see the greatest improvement in outcomes, i.e. might benefit the most from preventative measures.

In summary, the GDG believe that this intervention responds to the Human Rights Council resolution 11/8, para. 2 which states that "understanding at the international and regional levels that reducing maternal mortality and morbidity is not solely an issue of development, but a matter of human rights… the Human Rights Council identifies a range of human rights directly implicated by maternal mortality and morbidity, namely, the 'rights to life, to be equal in dignity, to education, to be free to seek, receive and impart information, to enjoy the benefits of scientific progress, to freedom from discrimination, and to enjoy the highest attainable standard of physical and mental health, including sexual and reproductive health'…maternal mortality implicates a wider range of human rights and have recommended that States parties take effective measures to reduce maternal mortality".

Therefore, effective and equitable implementation of this intervention (and its potential complications) could reduce health inequities.

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

5. ACCEPTABILITY

Is the use of antiplatelet agents for prevention of pre-eclampsia acceptable to key stakeholders?

Research evidence

A literature review identified one multicentre open-label acceptability/feasibility randomized control trial (RCT). Conducted in two Dublin tertiary maternity hospitals, 546 low-risk nulliparous women were randomized to routine 75 mg aspirin from 11 to 36 weeks' gestation, no aspirin, or aspirin based upon FMF first trimester screening. *(14)* The primary objective of the study was to assess the acceptability and feasibility of women taking 75 mg aspirin vs screening-test indicated treatment. The average aspirin adherence was 90%, as assessed by self-reporting and measurement of urinary thromboxane B2 levels. Differences between the groups were noted in the risk of vaginal spotting (OR 2.1, CI 1.2, 3.6), but these were not associated with pregnancy loss. Higher rates of PPH greater than 1000mL were also noted, but there were few cases in each arm (7/192 aspirin, 5/354 non-aspirin; OR 2.8, CI, 0.9, 9.0). The researchers noted that compared to other RCTs requiring medication, almost twice the number of women had to be approached in order to ensure adequate sample size.

Approximately half of the women approached for the study were willing to be randomized. But for those who agreed to randomization, the authors concluded that low-risk nulliparous women are open to taking aspirin in pregnancy and have high levels of adherence.

Additional considerations

A qualitative evidence synthesis exploring provision and uptake of routine antenatal services (15) suggests that women tend to view antenatal care as a source of knowledge and information and generally appreciate advice or interventions that may lead to a healthy baby and a positive pregnancy experience (high confidence in the evidence). However, in some low-income settings, the indirect costs associated with procuring drugs, travelling to clinics for additional check-ups or both may restrict access (high confidence in the evidence) and a reliance on traditional beliefs or practices to treat common pregnancy-related conditions may limit engagement in these contexts (moderate confidence in the evidence).

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

6. FEASIBILITY

Is the use of antiplatelet agents for prevention of pre-eclampsia feasible to implement?

Research evidence

A qualitative evidence synthesis exploring provision and uptake of routine antenatal services suggests that a lack of basic medical equipment (including blood pressure monitoring devices) and inconsistent supplies of pharmaceuticals may be an issue in some LMICs (high confidence in the evidence). (15) A lack of suitably trained staff may also be a problem, particularly in rural areas of low- and middle-income countries (moderate confidence in the evidence). Where there are likely to be additional costs associated with the intervention (high confidence in the evidence) or where the recommended interventions are unavailable because of resource constraints (low confidence in the evidence) women may be less likely to engage with services.

Additional considerations

Acetylsalicylic acid (100 mg to 500 mg tablets) and clopidogrel (75 mg and 300 mg tablets) are listed on the WHO Model List of Essential Medicines (2019). *(16)* Aspirin is identified as an antiplatelet agent (also used for pain/palliative care and juvenile joint disease). Clopidogrel is identified as an antiplatelet agent.

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

C) SUMMARY OF JUDGEMENTS

SUMMARY OF JUDGEMENTS – Antiplatelet agents for prevention of pre-eclampsia (all women, all doses, any gestational age)

Desirable effects	— Don't know	— Varies		— Trivial	— Small	✔ **Moderate**	— Large
Undesirable effects	— Don't know	— Varies		— Large	— Moderate	✔ **Small**	— Trivial
Certainty of the evidence	— No included studies			— Very low	— Low	✔ **Moderate**	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✔ **Probably no important uncertainty or variability**	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours antiplatelet agent**	Favours antiplatelet agent
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 placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours antiplatelet agent**	— Favours antiplatelet agent
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

SUMMARY OF JUDGEMENTS – Antiplatelet agents for prevention of pre-eclampsia by maternal risk categories

For ***women at low risk*** (no identifiable risk factor or one of the following: primiparity, family history of pre-eclampsia, age greater than 40 years or multiple pregnancy).

Desirable effects	— Don't know	— Varies		— Trivial	✓ **Small** (7/1000 fewer cases of pre-eclampsia)	— Moderate	— Large
Undesirable effects	— Don't know	— Varies		— Large	— Moderate	✓ **Small**	— Trivial
Certainty of the evidence	— No included studies			— Very low	— Low	✓ **Moderate**	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✓ **Probably favours antiplatelet agent**	— Favours antiplatelet agent
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 placebo/no treatment	Probably favours placebo/no treatment	✓ **Does not favour either**	— Probably favours antiplatelet agent	— Favours antiplatelet agent
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 difference	— Probably no difference	✓ **Probably Yes**	— Yes

For women at moderate risk (two of the following risk factors: primiparity, family history of pre-eclampsia, age greater than 40 years or multiple pregnancy).

Desirable effects	— Don't know	— Varies		— Trivial	— **Small**	✔ **Moderate** (57 fewer cases of pre-eclampsia)	— Large
Undesirable effects	— Don't know	— Varies		— Large	— Moderate	✔ **Small**	Trivial
Certainty of the evidence	— No included studies			— Very low	✔ **Low**	— Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✔ **Probably no important uncertainty or variability**	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours antiplatelet agent**	— Favours antiplatelet agent
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 placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours antiplatelet agent**	— Favours antiplatelet agent
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 difference	— Probably no difference	✔ **Probably Yes**	— Yes

For women at high risk (woman with at least one of the following: diabetes, chronic hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal or neonatal death associated with pre-eclampsia).

Desirable effects	— Don't know	— Varies		— Trivial	— Small	✔ **Moderate** (27/1000 fewer cases of pre-eclampsia)	— Large
Undesirable effects	— Don't know	— Varies		— Large	— Moderate	✔ **Small**	— Trivial
Certainty of the evidence	— No included studies			— Very low	— Low	✔ **Moderate**	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✔ **Probably no important uncertainty or variability**	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours antiplatelet agent**	— Favours antiplatelet agent
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 placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours antiplatelet agent**	— Favours antiplatelet agent
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 difference	— Probably no difference	✔ **Probably Yes**	— Yes

Table 3. Summary of judgement comparison by maternal risk level

	Low risk	***Moderate risk***	***High risk***
Desirable effects	Small	Moderate	Moderate
Undesirable effects	Low	Low	Low
Certainty of the evidence	Moderate	Low	Moderate
Values	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favours antiplatelet agent	Probably favours antiplatelet agent	Probably favours antiplatelet agent
Resources required	Negligible costs or savings	Moderate savings	Moderate savings
Certainty of the evidence on required resources	Moderate	Moderate	Moderate
Cost–effectiveness	Does not favour either	Probably favours antiplatelet agent	Probably favours antiplatelet agent
Equity	Probably increased	Probably increased	Probably increased
Acceptability	Probably Yes	Probably Yes	Probably Yes
Feasibility	Probably Yes	Probably Yes	Probably Yes

SUMMARY OF JUDGEMENTS – Aspirin dosage when used for the prevention of pre-eclampsia

Use of < 75 mg aspirin

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
Resources required	— Don't know	— Varies	— Large costs	— Moderate costs	✔ **Negligible costs or savings**	— Moderate savings	— Large savings
Certainty of the evidence on required resources	— No included studies			— Very low	— Low	✔ **Moderate**	— High
Equity	— Don't know	— Varies	— Reduced	— Probably reduced	✔ **Probably no impact**	— Probably increased	— Increased
Acceptability	— Don't know	— Varies		— No change	✔ **Probably no difference**	— Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No change	✔ **Probably no difference**	— Probably Yes	— Yes

Use of ≥ 75 mg aspirin

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
Resources required	— Don't know	— Varies	— Large costs	— Moderate costs	✔ **Negligible costs or savings**	— Moderate savings	— Large savings
Certainty of the evidence on required resources	— No included studies			— Very low	— Low	✔ **Moderate**	— High
Equity	— Don't know	— Varies	— Reduced	— Probably reduced	✔ **Probably no impact**	— Probably increased	— Increased
Acceptability	— Don't know	— Varies		— No change	✔ **Probably no difference**	— Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No change	✔ **Probably no difference**	— Probably Yes	— Yes

Table 4. Summary of judgement comparison by aspirin dose

	< 75 mg	***≥ 75 mg***
Desirable effects	Small	Large
Undesirable effects	Small	Do not know (extent of increased risk for haemorrhage with increasing dose)
Certainty of the evidence	Moderate	Moderate
Values	Possibly important uncertainty or variability	Possibly important uncertainty or variability
Balance of effects	–	Probably Favours ≥ 75 mg
Resources required	–	No difference
Cost–effectiveness	–	Probably favours ≥ 75 mg
Equity	–	No difference
Acceptability	–	No difference
Feasibility	–	No difference

SUMMARY OF JUDGEMENTS – Antiplatelet agents for prevention of pre-eclampsia; timing of initiation, impact of beginning before 20 weeks' gestation

Desirable effects	— Don't know	— Varies		— Trivial	✔ **Small**	— Moderate	— Large
Undesirable effects	✔ **Don't know**	— Varies		— Large	— Moderate	— Small	— Trivial
Certainty of the evidence	— No included studies			— Very low	— Low	✔ **Moderate**	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✔ **Probably no important uncertainty or variability**	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours less than 20 weeks**	— Favours less than 20 weeks
Resources required	— Don't know	— Varies	— Large costs	— Moderate costs	✔ **Negligible costs or savings**	— Moderate savings	— Large savings
Certainty of the evidence on required resources	— No included studies			— Very low	— Low	✔ **Moderate**	— High
Cost–effectiveness	— Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	✔ **Probably favours less than 20 weeks**	— Favours less than 20 weeks
Equity	— Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	✔ **Probably increased**	— Increased
Acceptability	— Don't know	— Varies		— No change	✔ **Probably no difference**	— Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No change	✔ **Probably no difference**	— Probably Yes	— Yes

Table 5. Summary of judgement comparison by timing of aspirin initiation

	< 20 weeks	***≥ 20 weeks***
Desirable effects	Large	Large
Undesirable effects	Do not know	Do not know
Certainty of the evidence	Moderate	Moderate
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favours less than 20 weeks	–
Resources required	Negligible higher costs with longer duration of therapy	Possibly slightly less than starting earlier
Certainty of the evidence on required resources	Moderate	Moderate
Cost–effectiveness	Likely favours starting less than 20 weeks	–
Equity	Possibly increased	–
Acceptability	Probably no difference	–
Feasibility	Probably no difference	–

D) SUMMARY OF FINDINGS

Population: Pregnant women at risk for developing pre-eclampsia

Question: Antiplatelet agents compared to placebo/no antiplatelet agent for preventing pre-eclampsia and its complications (primary prevention)

Setting: Hospitals (Algeria, Argentina, Australia, Barbados, Belgium, Brazil, Canada, Chile, China, Egypt, Finland, France, Germany, Greece, India, Iran (Islamic Republic of), Israel, Italy, Jamaica, Japan, Republic of Korea, Netherlands, Romania, Russian Federation, South Africa, Spain, United Republic of Tanzania, United Kingdom, USA, Venezuela (Bolivarian Republic of), Zimbabwe)

Bibliography: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
18	randomized trials	serious [a]	not serious	not serious	very serious [b,c]	none	6/14 339 (0.0%)	3/14 336 (0.0%)	**RR 1.75** (0.51 to 5.96)	**0 fewer per 1 000** (from 0 fewer to 1 more)	⨁◯◯◯ VERY LOW	PRIORITY
Eclampsia												
17	randomized trials	serious [a]	not serious	not serious	serious [c]	none	38/12 496 (0.3%)	37/12 451 (0.3%)	**RR 1.03** (0.66 to 1.60)	**0 fewer per 1 000** (from 1 fewer to 2 more)	⨁⨁◯◯ LOW	PRIORITY
Pre-eclampsia												
60	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [d]	1 424/ 18 567 (7.7%)	1 713/18 304 (9.4%)	**RR 0.82** (0.77 to 0.88)	**17 fewer per 1 000** (from 22 fewer to 11 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Gestational hypertension												
25	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [d]	1 676/14 019 (12.0%)	1 739/13 815 (12.6%)	**RR 0.95** (0.90 to 1.01)	**6 fewer per 1 000** (from 13 fewer to 1 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Cerebrovascular accident (stroke)												
9	randomized trials	serious [a]	not serious	not serious	very serious [b,c]	none	1/5 408 (0.0%)	0/5 420 (0.0%)	**RR 2.99** (0.12 to 73.40)	**0 fewer per 1 000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Disseminated intravascular coagulation												
9	randomized trials	serious [a]	not serious	not serious	very serious [b,c]	none	0/5 408 (0.0%)	1/5 420 (0.0%)	**RR 0.32** (0.01 to 7.57)	**0 fewer per 1 000** (from 0 fewer to 1 more)	⨁◯◯◯ VERY LOW	PRIORITY
HELLP syndrome												
16	randomized trials	not serious	not serious	not serious	serious [c]	none	19/10 063 (0.2%)	25/10 067 (0.2%)	**RR 0.77** (0.44 to 1.36)	**1 fewer per 1 000** (from 1 fewer to 1 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Liver failure												
9	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	0/5 408 (0.0%)	0/5 420 (0.0%)	not pooled	see comment	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Placental abruption												
29	randomized trials	not serious	not serious	not serious	serious [f]	none	145/15 442 (0.9%)	114/15 333 (0.7%)	**RR 1.21** (0.95 to 1.54)	**2 more per 1 000** (from 0 fewer to 4 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Pulmonary oedema												
12	randomized trials	not serious	not serious	not serious	very serious [b,c]	none	10/8 407 (0.1%)	12/8 325 (0.1%)	**RR 0.84** (0.37 to 1.89)	**0 fewer per 1 000** (from 1 fewer to 1 more)	⨁⨁◯◯ LOW	PRIORITY
Renal failure												
11	randomized trials	serious [a]	not serious	not serious	very serious [b,c]	none	3/8 251 (0.0%)	2/8 251 (0.0%)	**RR 1.29** (0.35 to 4.79)	**0 fewer per 1 000** (from 0 fewer to 1 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal intensive care unit (ICU) admission - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Adverse effects of intervention - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Antepartum haemorrhage - IPD only												
25	randomized trials	not serious	not serious	not serious	not serious	none	534/15 308 (3.5%)	506/15 205 (3.3%)	**RR 1.04** (0.92 to 1.17)	**1 more per 1 000** (from 3 fewer to 6 more)	⨁⨁⨁⨁ HIGH	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Postpartum haemorrhage > 500 mL												
19	randomized trials	not serious	not serious	not serious	not serious	none	1 795/11 893 (15.1%)	1 691/11 876 (14.2%)	**RR 1.06** (1.00 to 1.12)	**9 more per 1 000** (from 0 fewer to 17 more)	⊕⊕⊕⊕ HIGH	PRIORITY
Maternal well-being - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Fetal death, neonatal death, or death before hospital discharge												
52	randomized trials	not serious	not serious	not serious	not serious	none	509/17 777 (2.9%)	594/17 614 (3.4%)	**RR 0.85** (0.76 to 0.95)	**5 fewer per 1 000** (from 8 fewer to 2 fewer)	⊕⊕⊕⊕ HIGH	PRIORITY
Fetal death												
41	randomized trials	not serious	not serious	not serious	not serious	none	360/16 749 (2.1%)	392/16 632 (2.4%)	**RR 0.92** (0.80 to 1.06)	**2 fewer per 1 000** (from 5 fewer to 1 more)	⊕⊕⊕⊕ HIGH	PRIORITY
Death in first week of life												
27	randomized trials	not serious	not serious	not serious	serious [g]	none	113/13 296 (0.8%)	128/13 252 (1.0%)	**RR 0.88** (0.68 to 1.13)	**1 fewer per 1 000** (from 3 fewer to 1 more)	⊕⊕⊕◯ MODERATE	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Admission to neonatal intensive care unit (NICU)/special nursery												
29	randomized trials	not serious	not serious	not serious	not serious	none	2 468/16 441 (15.0%)	2 562/16 367 (15.7%)	**RR 0.95** (0.91 to 1.00)	**8 fewer per 1 000** (from 14 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	PRIORITY
Apgar scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Intraventricular haemorrhage												
20	randomized trials	not serious	not serious	not serious	serious [c]	none	73/16 094 (0.5%)	74/16 130 (0.5%)	**RR 0.99** (0.72 to 1.36)	**0 fewer per 1 000** (from 1 fewer to 2 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Other neonatal bleed												
20	randomized trials	not serious	not serious	not serious	not serious	none	203/15 357 (1.3%)	227/15 358 (1.5%)	**RR 0.90** (0.75 to 1.08)	**1 fewer per 1 000** (from 4 fewer to 1 more)	⨁⨁⨁⨁ HIGH	PRIORITY

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

Explanations

a. Most of pooled effect provided by studies at moderate or high risk of bias, without a substantial proportion (< 50%) at high risk of bias.
b. Few events.
c. Wide confidence interval including appreciable benefit and appreciable harm.
d. Funnel plot asymmetry favours antiplatelet agents.
e. No events, not estimable.
f. Wide confidence interval including appreciable harm and crossing line of no effect.
g. Wide confidence interval including appreciable benefit and crossing line of no effect.

Population: Pregnant women at risk for developing pre-eclampsia

Question: Antiplatelet agents compared to placebo/no antiplatelet agent for preventing pre-eclampsia and its complications (primary prevention, subgrouped by maternal risk)

Setting: Hospital (Algeria, Argentina, Australia, Barbados, Belgium, Brazil, Canada, Chile, China, Egypt, Finland, France, Germany, Greece, India, Iran (Islamic Republic of), Israel, Italy, Jamaica, Japan, Republic of Korea, Netherlands, Romania, Russian Federation, South Africa, Spain, United Republic of Tanzania, United Kingdom, USA, Venezuela (Bolivarian Republic of), Zimbabwe)

Bibliography: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pre-eclampsia - Low-risk women												
31	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	419/10 623 (3.9%)	484/10 503 (4.6%)	**RR 0.85** (0.75 to 0.97)	**7 fewer per 1 000** (from 12 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Pre-eclampsia - Moderate-risk women												
20	randomized trials	serious [b]	not serious	not serious	not serious	publication bias strongly suspected [a]	70/734 (9.5%)	108/682 (15.8%)	**RR 0.64** (0.49 to 0.83)	**57 fewer per 1 000** (from 81 fewer to 27 fewer)	⨁⨁◯◯ LOW	PRIORITY
Pre-eclampsia - High-risk women												
39	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	927/7 084 (13.1%)	1 098/6 998 (15.7%)	**RR 0.83** (0.77 to 0.90)	**27 fewer per 1 000** (from 36 fewer to 16 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pre-eclampsia - Unclear-/unspecified-risk women												
2	randomized trials	serious [b]	not serious	not serious	serious [c]	publication bias strongly suspected [a]	1/46 (2.2%)	10/46 (21.7%)	**RR 0.14** (0.03 to 0.76)	**187 fewer per 1 000** (from 211 fewer to 52 fewer)	⨁◯◯◯ VERY LOW	PRIORITY
Fetal death, neonatal death, or death before hospital discharge - Low-risk women												
28	randomized trials	serious [b]	not serious	not serious	not serious	none	281/10 536 (2.7%)	310/10 425 (3.0%)	**RR 0.90** (0.77 to 1.05)	**3 fewer per 1 000** (from 7 fewer to 1 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Fetal death, neonatal death, or death before hospital discharge - Moderate-risk women												
16	randomized trials	serious [b]	not serious	not serious	serious [d]	none	29/437 (6.6%)	34/447 (7.6%)	**RR 0.94** (0.60 to 1.48)	**5 fewer per 1 000** (from 30 fewer to 37 more)	⨁⨁◯◯ LOW	PRIORITY
Fetal death, neonatal death, or death before hospital discharge - High-risk women												
37	randomized trials	not serious	not serious	not serious	not serious	none	188/6 731 (2.8%)	239/6 668 (3.6%)	**RR 0.77** (0.64 to 0.93)	**8 fewer per 1 000** (from 13 fewer to 3 fewer)	⨁⨁⨁⨁ HIGH	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fetal death, neonatal death, or death before hospital discharge - Unclear-/unspecified-risk women												
3	randomized trials	serious [b]	not serious	not serious	very serious [c,d]	none	11/73 (15.1%)	11/74 (14.9%)	**RR 1.00** (0.49 to 2.03)	**0 fewer per 1 000** (from 76 fewer to 153 more)	⨁◯◯◯ VERY LOW	PRIORITY

CI: Confidence interval; RR: Risk ratio

The Cochrane review further stratified results by IPD and AD. For the purposes of this guideline update, the results from IPD and AD trials were combined for all subgroup analyses.

Explanations

a. Publication bias strongly suspected in results for all subgroups for this outcome. There is funnel plot asymmetry in the pooled results (not subgrouped by risk), with multiple subgroups reported by many of the included trials.
b. Most of pooled effect provided by studies at moderate or high risk of bias, but without a substantial proportion (< 50%) from studies at high risk of bias.
c. Few events, small sample size.
d. Wide confidence interval including appreciable benefit and appreciable harm.

Population: Pregnant women at risk for developing pre-eclampsia

Question: Antiplatelet agents compared to placebo/no antiplatelet agent for preventing pre-eclampsia and its complications (primary prevention, subgrouped by gestation at trial entry)

Setting: Hospital (Algeria, Argentina, Australia, Barbados, Belgium, Brazil, Canada, Chile, China, Egypt, Finland, France, Germany, Greece, India, Iran (Islamic Republic of), Israel, Italy, Jamaica, Japan, Republic of Korea, Netherlands, Romania, Russian Federation, South Africa, Spain, United Republic of Tanzania, United Kingdom, USA, Venezuela (Bolivarian Republic of), Zimbabwe)

Bibliography: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pre-eclampsia - Entered < 20 weeks												
46	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	844/11 378 (7.4%)	1 035/11 132 (9.3%)	**RR 0.80** (0.73 to 0.87)	**19 fewer per 1 000** (from 25 fewer to 12 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Pre-eclampsia - Entered into the study ≥ 20 weeks												
33	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	547/6 862 (8.0%)	614/6 826 (9.0%)	**RR 0.88** (0.79 to 0.99)	**11 fewer per 1 000** (from 19 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Pre-eclampsia – Unclassified												
14	randomized trials	serious [b]	not serious	not serious	serious [c]	publication bias strongly suspected [a]	26/247 (10.5%)	47/271 (17.3%)	**RR 0.65** (0.41 to 1.02)	**61 fewer per 1 000** (from 102 fewer to 3 more)	⨁◯◯◯ VERY LOW	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fetal death, neonatal death, or death before hospital discharge - Entered into the study < 20 weeks												
38	randomized trials	not serious	not serious	not serious	not serious	none	343/10 890 (3.1%)	402/10 717 (3.8%)	**RR 0.83** (0.72 to 0.95)	**6 fewer per 1 000** (from 11 fewer to 2 fewer)	⨁⨁⨁⨁ HIGH	PRIORITY
Fetal death, neonatal death, or death before hospital discharge - Entered into the study ≥ 20 weeks												
32	randomized trials	not serious	not serious	not serious	not serious	none	164/6 776 (2.4%)	180/6 747 (2.7%)	**RR 0.92** (0.75 to 1.13)	**2 fewer per 1 000** (from 7 fewer to 3 more)	⨁⨁⨁⨁ HIGH	PRIORITY
Fetal death, neonatal death, or death before hospital discharge – Unclassified												
15	randomized trials	serious [b]	not serious	not serious	very serious [d,e]	none	2/111 (1.8%)	12/150 (8.0%)	**RR 0.42** (0.14 to 1.23)	**46 fewer per 1 000** (from 69 fewer to 18 more)	⨁◯◯◯ VERY LOW	PRIORITY

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

The Cochrane review further stratified results by IPD and AD. For the purposes of this guideline update, the results from IPD and AD trials were combined for all subgroup analyses.

Explanations

a. Publication bias strongly suspected in results for all subgroups for this outcome. There is funnel plot asymmetry in the pooled results (not subgrouped by gestation), with many of the included trials reporting women that fall into multiple subgroups.
b. Most of pooled effect provided by studies at moderate or high risk of bias, but without a substantial proportion (< 50%) from studies at high risk of bias.
c. Wide confidence interval including appreciable benefit and appreciable harm.
d. Few events, small sample size.
e. Wide confidence interval including appreciable benefit and crossing line of no effect.

Population: Pregnant women at risk for developing pre-eclampsia

Question: Antiplatet agents compared to placebo/no antiplatelet agent for preventing pre-eclampsia and its complications (primary prevention, subgrouped by dose of aspirin)

Setting: Hospital (Algeria, Argentina, Australia, Barbados, Belgium, Brazil, Canada, Chile, China, Egypt, Finland, France, Germany, Greece, India, Iran (Islamic Republic of), Israel, Italy, Jamaica, Japan, Republic of Korea, Netherlands, Romania, Russian Federation, South Africa, Spain, United Republic of Tanzania, United Kingdom, USA, Venezuela (Bolivarian Republic of), Zimbabwe)

Bibliography: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pre-eclampsia < 75 mg aspirin												
17	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	987/11 636 (8.5%)	1 092/11 568 (9.4%)	**RR 0.90** (0.83 to 0.98)	**9 fewer per 1 000** (from 16 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Pre-eclampsia ≥ 75 mg aspirin												
35	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	393/6 349 (6.2%)	560/6 263 (8.9%)	**RR 0.69** (0.61 to 0.78)	**28 fewer per 1 000** (from 35 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Pre-eclampsia ≥ 75 mg aspirin, plus dipyridamole												
6	randomized trials	serious [b]	not serious	not serious	not serious	none	11/235 (4.7%)	29/231 (12.6%)	**RR 0.38** (0.20 to 0.73)	**78 fewer per 1 000** (from 100 fewer to 34 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fetal death, neonatal death, or death before hospital discharge < 75 mg aspirin												
26	randomized trials	not serious	not serious	not serious	not serious	none	426/13 898 (3.1%)	480/13 847 (3.5%)	**RR 0.88** (0.78 to 1.00)	**4 fewer per 1 000** (from 8 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	PRIORITY
Fetal death, neonatal death, or death before hospital discharge ≥ 75 mg aspirin												
18	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	67/3 453 (1.9%)	99/3 445 (2.9%)	**RR 0.69** (0.51 to 0.93)	**9 fewer per 1 000** (from 14 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Fetal death, neonatal death, or death before hospital discharge ≥ 75 mg aspirin, plus dipyridamole												
7	randomized trials	not serious	not serious	not serious	serious [c]	none	8/241 (3.3%)	11/233 (4.7%)	**RR 0.71** (0.30 to 1.64)	**14 fewer per 1 000** (from 33 fewer to 30 more)	⨁⨁⨁◯ MODERATE	PRIORITY

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

The Cochrane review further stratified results by IPD and AD. For the purposes of this guideline update, the results from IPD and AD trials were combined for all subgroup analyses.

Explanations

a. Funnel plot asymmetry favours intervention.
b. Most of pooled effect provided by studies at moderate or high risk of bias, but without a substantial proportion (<50%) from studies at high risk of bias.
c. Few events.

Population: Pregnant women at risk for developing pre-eclampsia

Question: Antiplatelet agents compared to placebo/no antiplatelet for preventing pre-eclampsia and its complications (secondary prevention)

Setting: Hospital (Argentina, Australia, Belgium, Brazil, Canada, India, Israel, Italy)

Bibliography: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Eclampsia												
5	randomized trials	serious [a]	not serious	not serious	very serious [b,c]	none	2/868 (0.2%)	6/875 (0.7%)	**RR 0.47** (0.13 to 1.67)	**4 fewer per 1 000** (from 6 fewer to 5 more)	⨁◯◯◯ VERY LOW	PRIORITY
Pre-eclampsia												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	137/904 (15.2%)	185/909 (20.4%)	**RR 0.67** (0.47 to 0.95)	**67 fewer per 1 000** (from 108 fewer to 10 fewer)	⨁⨁⨁◯ MODERATE	PRIORITY
Severe pre-eclampsia												
3	randomized trials	not serious	not serious	not serious	serious [c]	none	62/755 (8.2%)	74/754 (9.8%)	**RR 0.78** (0.48 to 1.26)	**22 fewer per 1 000** (from 51 fewer to 26 more)	⨁⨁⨁◯ MODERATE	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe hypertension												
5	randomized trials	not serious	not serious	not serious	not serious	none	276/931 (29.6%)	293/903 (32.4%)	**RR 0.94** (0.83 to 1.07)	**19 fewer per 1 000** (from 55 fewer to 23 more)	⨁⨁⨁⨁ HIGH	PRIORITY
HELLP Syndrome												
2	randomized trials	serious [a]	not serious	not serious	very serious [d]	none	0/69 (0.0%)	0/71 (0.0%)	not pooled	see comment	⨁◯◯◯ VERY LOW	PRIORITY
Placental abruption												
5	randomized trials	not serious	not serious	not serious	very serious [b,c]	none	14/802 (1.7%)	10/804 (1.2%)	**RR 1.39** (0.63 to 3.05)	**5 more per 1 000** (from 5 fewer to 25 more)	⨁⨁◯◯ LOW	PRIORITY
Maternal adverse effects of intervention - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Antepartum haemorrhage - IPD only												
5	randomized trials	not serious	not serious	not serious	serious [e]	none	49/802 (6.1%)	44/804 (5.5%)	**RR 1.11** (0.75 to 1.64)	**6 more per 1 000** (from 14 fewer to 35 more)	⨁⨁⨁◯ MODERATE	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Postpartum haemorrhage > 500 mL - IPD only												
5	randomized trials	not serious	not serious	not serious	serious [e]	none	110/785 (14.0%)	101/788 (12.8%)	**RR 1.09** (0.85 to 1.40)	**12 more per 1 000** (from 19 fewer to 51 more)	⨁⨁⨁◯ MODERATE	
Maternal well-being - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Fetal death, neonatal death, or death before hospital discharge - AD only												
2	randomized trials	serious [a]	not serious	not serious	serious [f]	none	6/129 (4.7%)	18/131 (13.7%)	**RR 0.36** (0.15 to 0.84)	**88 fewer per 1 000** (from 117 fewer to 22 fewer)	⨁⨁◯◯ LOW	PRIORITY
Fetal and neonatal deaths - IPD only												
7	randomized trials	not serious	not serious	not serious	serious [c]	none	49/991 (4.9%)	47/959 (4.9%)	**RR 1.00** (0.68 to 1.47)	**0 fewer per 1 000** (from 16 fewer to 23 more)	⨁⨁⨁◯ MODERATE	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiplatelet agents**	**Placebo/no antiplatelet agents**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fetal deaths, neonatal deaths or deaths before hospital discharge (Manual IPD and AD combined)												
9	randomized trials	not serious	not serious	not serious	serious [g]	none	55/1 120 (4.9%)	65/1 090 (6.0%)	**RR 0.82** (0.58 to 1.16)	**11 fewer per 1 000** (from 25 fewer to 10 more)	⨁⨁⨁◯ MODERATE	PRIORITY
Admission to neonatal intensive care unit (NICU) / special care baby unit												
6	randomized trials	not serious	not serious	not serious	not serious	none	305/971 (31.4%)	309/939 (32.9%)	**RR 0.97** (0.86 to 1.10)	**10 fewer per 1 000** (from 46 fewer to 33 more)	⨁⨁⨁⨁ HIGH	PRIORITY
Apgar scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY

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

Explanations

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

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