



WHO recommendations on **Antenatal corticosteroids** for improving preterm birth outcomes



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Acronyms and abbreviations

BMGF	Bill & Melinda Gates Foundation
CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
CPAP	Continuous positive airway pressure
DOI	Declaration of Interest
EtD	Evidence-to-Decision
FIGO	International Federation of Gynecology and Obstetrics
GA	Gestational age
GDG	Guideline Development Group
GSG	Guideline Steering Group
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
ICM	International Confederation of Midwives
IPA	International Pediatric Association
IM	Intramuscular
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health
mg	Milligram
MMAT	Mixed Methods Appraisal Tool
PICO	population (P), intervention (I), comparison (C), outcome (O)
RoB 2	[Cochrane] Risk of Bias 2
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
SRH	[WHO Department of] Sexual and Reproductive Health and Research
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

Complications of preterm birth are the single largest cause of newborn deaths and deaths among children under the age of five years. Preterm babies who survive are more prone to serious illnesses during childhood. Global efforts to reduce newborn and child morbidity and mortality demand urgent action to address preterm birth.

In 2021, the World Health Organization (WHO) convened the Executive Guideline Steering Group (GSG) for maternal and perinatal health recommendations, which prioritized updating WHO recommendations on the use of antenatal corticosteroid therapy to improve preterm birth outcomes. This decision was based on the availability of new evidence on the efficacy of antenatal corticosteroid therapy. The recommendations in this document thus supersede the antenatal corticosteroid recommendations in the *WHO recommendations on interventions to improve preterm birth outcomes* published in 2015.

Target audience

The primary audiences for this document are health care professionals responsible for developing national and local health care protocols and policies, as well as managers of maternal and child health programmes, and policy-makers in all settings. The recommendations in this document will also be useful to those directly providing care to pregnant women and preterm infants, such as obstetricians, paediatricians, midwives, nurses and general practitioners. The information in this document will be useful for developing job aids and tools for pre- and in-service training of health workers to enhance their delivery of maternal and neonatal care relating to preterm birth.

Recommendation development methods

The update of these recommendations was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were 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.

Updated systematic reviews were used to prepare evidence profiles for the prioritized questions. The quality of the scientific evidence underpinning the

recommendations was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approaches, for quantitative and qualitative evidence, respectively. The GRADE evidence-to-decision (EtD) framework (an evidence-to-decision tool that includes intervention effects, values, resource use, equity, acceptability and feasibility criteria) was used to guide the formulation of recommendations by the Guideline Development Group (GDG). The GDG was composed of an international group of experts and a representative of the affected population and convened to update these recommendations in January 2022.

Recommendations

The GDG issued one overarching recommendation and nine sub-recommendations on antenatal corticosteroid therapy for improving preterm birth outcomes. Based on assessments of the GRADE EtD criteria, which informed the direction and, in some instances, the specific context of the recommendation, the GDG classified their recommendations using the categories defined below.

Recommended: This category indicates that the intervention or option should be implemented.

Not recommended: This category indicates that the intervention or option should not be implemented.

Recommended only in specific contexts (“context-specific recommendation”): This category indicates that the intervention or option 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 or option. In such instances, implementation can still be undertaken on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

To ensure that each recommendation is correctly understood and applied in practice, the GDG provided additional remarks as needed. As the GDG recommended the use of antenatal corticosteroid therapy only in specific contexts, further detail was included about the particular context and which key

issues needed to be examined. Users of this document should refer to these remarks, which are presented directly beneath each recommendation (section 3.1). The recommendations on the use of antenatal corticosteroid therapy to improve preterm birth outcomes are summarized in Table 1.

Derivative products from these recommendations will include policy briefs for programme managers to enable their application at different levels of care. The GDG identified important implementation considerations for these recommendations as outlined in Section 4.2.

In accordance with the process for updating WHO maternal and perinatal health recommendations, a systematic and continuous process of identifying and bridging evidence gaps of these recommendations will be employed. In the event that new evidence (that could potentially impact the current evidence base for any of the recommendations) is identified, the recommendations will be updated. WHO welcomes suggestions regarding additional questions for inclusion in future updates of these recommendations. Please email your suggestions to srhmph@who.int.

Table 1: WHO recommendations on antenatal corticosteroid therapy for improving preterm birth outcomes

Recommendation	Category of recommendation
<p>1.0 Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth¹ from 24 weeks to 34 weeks of gestation when the following conditions are met:</p> <ul style="list-style-type: none"> ■ Gestational age assessment can be accurately undertaken ■ There is a high likelihood of preterm birth within 7 days of starting therapy ■ There is no clinical evidence of maternal infection ■ Adequate childbirth care is available (including capacity to recognize and safely manage preterm labour and birth) ■ The preterm newborn can receive adequate care (including resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support including continuous positive airway pressure [CPAP] as needed) 	Context-specific recommendation
1.1 Antenatal corticosteroid therapy should be administered to women with a high likelihood of giving birth preterm in the next 7 days, even if it is anticipated that the full course of corticosteroids may not be completed.	Context-specific recommendation
1.2 Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth, irrespective of whether single or multiple birth is anticipated.	Context-specific recommendation
1.3 Antenatal corticosteroid therapy is recommended for women with preterm prelabour rupture of membranes and no clinical signs of infection.	Context-specific recommendation
1.4 Antenatal corticosteroid therapy <i>is not</i> recommended for women with chorioamnionitis who are likely to give birth preterm.	Not recommended
1.5 Antenatal corticosteroid therapy <i>is not</i> recommended for women undergoing planned caesarean section at 34 weeks 0 days to 36 weeks 6 days.	Not recommended
1.6 Antenatal corticosteroid therapy is recommended for women with hypertensive disorders in pregnancy who have a high likelihood of preterm birth.	Context-specific recommendation
1.7 Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth of a growth-restricted fetus.	Context-specific recommendation
1.8 Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes when there is a high likelihood of preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.	Context-specific recommendation
1.9 Either intramuscular (IM) dexamethasone or IM betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice.	Recommended
1.10 A single repeat course of antenatal corticosteroids is recommended for women who have received a single course of antenatal corticosteroids at least 7 days prior and, on clinical assessment, have a high likelihood of giving birth preterm in the next 7 days.	Recommended

¹ Risk of preterm birth within seven days includes women with: preterm membrane rupture without preterm labour, spontaneous preterm labour with intact membranes, or planned preterm birth by induction or caesarean section.

1. Introduction

1.1 Background

The World Health Organization (WHO) envisions a world where “every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and postnatal period” (1). High-quality maternal health care for all women and babies is a necessary step towards the achievement of the health targets agreed in the Sustainable Development Goals (SDGs) (2) and the targets and indicators of the WHO’s Thirteenth General Programme of Work (3), particularly those for achieving universal health coverage.

Ensuring accessibility and acceptability of interventions to improve maternal and newborn health outcomes is consistent with international human rights laws, which include fundamental commitments of states to enable women and adolescent girls to survive pregnancy and childbirth; to assure their sexual and reproductive health rights; and to live a life of dignity. High-quality health care could reduce the profound inequities in maternal and newborn health globally and is essential for the prevention of morbidity and mortality in pregnancy and childbirth.

Preterm birth is defined as a baby born prior to 37 completed weeks of gestation (4). Worldwide, an estimated 14.8 million babies are born preterm each year, with most of these babies (81%) being born in Asian and sub-Saharan African countries (5). Preterm birth is the leading cause of death in children under five years, and an estimated 35% of neonatal deaths in the first 28 days of life are caused by preterm birth complications (6). Preterm newborns are at increased risk of short-term morbidities, including respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis and sepsis, as well as longer-term morbidities, such as chronic lung disease and neurological disabilities (7–16).

Death and disability following preterm birth can be reduced through interventions provided to the mother before or during pregnancy, and to the preterm newborn after birth. Interventions can be directed at all women to reduce the risk of preterm birth (i.e. primary prevention), or directed at pregnant women with known risk factors (i.e. secondary prevention). Tertiary prevention interventions are provided to the woman shortly before or during the birth process with the aim of overcoming immediate and future health challenges of the preterm newborn, such as lung immaturity, susceptibility to infection, and neurological complications. Essential and additional care of the preterm newborn to prevent or treat potential complications is also critical to newborn survival without disability. This may include

resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support including CPAP.

Animal and human studies have shown that when glucocorticoids (such as dexamethasone or betamethasone) are administered to women with a high likelihood of preterm birth, they cross the placenta and enhance the structural maturity of developing fetal lungs, including inducing differentiation of mesenchymal tissue, accelerating production and secretion of surfactant and decreasing vascular permeability, leading to increased compliance and maximal lung volume (17). These changes can prevent respiratory-related morbidity and mortality affecting preterm newborns.

In recent years, the benefits and possible harms of antenatal corticosteroid therapy were called into question, with the findings of an implementation trial conducted in six low-resource countries which found that a multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels of health care did not confer benefit, and led to additional harms for women and newborn (18). The uncertainty regarding the safe and effective use of antenatal corticosteroids in low-resource countries was recently addressed by a placebo-controlled trial in five low-resource countries (19, 20). New evidence has also become available on the use of antenatal corticosteroids in other clinical situations, such as in the late preterm period (21, 22).

1.2 Rationale and objectives

Since 2017, the Department of Sexual and Reproductive Health and Research (SRH) at WHO has implemented a “living guidelines” approach to updating maternal and perinatal health recommendations, whereby an Executive Guideline Steering Group (GSG) oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating (23). Recommendations are prioritized for update based on changes or important new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation.

The Executive GSG prioritized the updating of WHO’s recommendations on antenatal corticosteroid therapy to improve preterm birth outcomes in response to new, potentially important evidence on this intervention. The primary goal of this update is to improve the

quality of care and outcomes for pregnant women and newborns in relation to preterm birth-related care.

These updated recommendations were developed in accordance with the standards and procedures in the *WHO handbook for guideline development* (24), including the synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)² methodology, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders. The recommendations in this document thus supersede the recommendations on antenatal corticosteroids that were published as part of the *WHO recommendations on interventions for improving preterm birth outcomes* in 2015 (25).

1.3 Aim

The primary aim of these recommendations is to improve the quality of care and outcomes for women with a high likelihood of experiencing preterm birth and babies born preterm. Antenatal corticosteroids have the potential to have a positive impact on newborn morbidities. These recommendations thus provide a foundation for sustainable implementation of antenatal corticosteroid therapy as one of the interventions for improving preterm birth outcomes.

1.4 Target audience

These recommendations are primarily for health care professionals who are responsible for developing national and local health guidelines and protocols (particularly those related to management of preterm birth) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes and relevant staff in ministries of health and training institutions, in all settings.

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

1.5 Identification of priority questions and outcomes

The priority questions for updating these recommendations were identified by the WHO Executive Guideline Steering Group through a systematic prioritization process in the first quarter of 2021. The recommendations on antenatal corticosteroids were prioritized for updating primarily on the basis of new, potentially important evidence affecting the main recommendation.

The priority outcomes were aligned with the prioritized outcomes from the 2015 *WHO recommendations on interventions to improve preterm birth outcomes* (25). These outcomes were initially identified through consultation with international stakeholders (including midwives, obstetricians, neonatologists, researchers, experts in health programmes and representatives of user groups) and a prioritization of outcomes by the 2015 guideline panel. Two additional outcomes were included (maternal well-being and maternal satisfaction) for this update to ensure that evidence synthesis and recommendation decision-making by the GDG are driven by outcomes that are important to women, and that the final recommendations are women-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendations. The list of priority outcomes is provided in *Annex 2*.

1.6 Scope of the recommendations

These recommendations focus on the use of antenatal corticosteroid therapy among women with a high likelihood of imminent preterm birth. The overarching PICO question considers the benefits and possible harms of this intervention, while the sub-questions consider which sub-populations of women can safely receive antenatal corticosteroid therapy, as well as which corticosteroids and regimens are safe and effective.

The priority question that guided evidence synthesis and decision-making for these recommendations are presented below using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format. The sub-questions are also listed below.

² Further information is available at: <http://www.gradeworkinggroup.org/>.

PRIORITY QUESTION AND SUB-QUESTIONS

Among pregnant women with a high likelihood of preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy or placebo (C), effective in reducing adverse newborn outcomes (O)?

- Which population of pregnant women should be offered antenatal corticosteroids, considering gestational age at presentation?
- Which population of pregnant women should be offered antenatal corticosteroids, considering interval between therapy and birth?
- Which population of pregnant women should be offered antenatal corticosteroids, considering single and multiple birth?
- Which population of pregnant women should be offered antenatal corticosteroids, considering preterm premature rupture of the membranes?
- Which population of pregnant women should be offered antenatal corticosteroids considering presence of chorioamnionitis?
- Which population of pregnant women should be offered antenatal corticosteroids, considering women undergoing elective caesarean section in the late preterm period (34 weeks 0 days to 36 weeks 6 days)?
- Which population of pregnant women should be offered antenatal corticosteroids, considering hypertensive disorders in pregnancy?
- Which population of pregnant women should be offered antenatal corticosteroids, considering fetal growth restriction?
- Which population of pregnant women should be offered antenatal corticosteroids, considering pregestational and gestational diabetes?
- Which corticosteroids (and regimens) should be used for eligible women?
- Should repeat course(s) of corticosteroids be offered to a woman who has completed a course of corticosteroid but remains at risk of preterm birth 7 days or more after the initial treatment?

2. Methods

The recommendations were developed using the standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development* (24). In summary, the process included: (i) identification of the priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

In 2021, updating the WHO recommendations on antenatal corticosteroid therapy was identified by the Executive GSG as a high priority in response to new evidence on the benefits and possible harms of this intervention. Six main groups participated in this process. Their specific roles are described below.

2.1 Executive Guideline Steering Group

The Executive Guideline Steering Group (GSG) is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region. Members of the Executive GSG serve for a period of three years and advise WHO on the prioritization of new and existing questions in maternal and perinatal health for development or updating of recommendations (23).

2.2 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, managed the updating process. The WHO Steering Group drafted the key recommendation questions in PICO format. They also identified the systematic review teams and guideline methodologists, as well as members of the Guideline Development Group and the External Review Group. In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the Guideline Development Group meetings, finalized the recommendation document, and managed dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in [Annex 1](#).

2.3 Guideline Development Group (GDG)

For the development of these recommendations, 18 external experts and relevant stakeholders were invited to participate as members of the Guideline

Development Group (GDG). These individuals were drawn from a pool of approximately 50 experts and relevant stakeholders that constitute the WHO Maternal and Perinatal Health Guideline Development Group. Those selected were a diverse group with expertise in research, guideline development methods, and clinical policy and programmes relating to improving preterm birth outcomes, as well as a representative of the affected population.

The GDG members were selected in a way that ensured geographic representation and gender balance and that there were no important conflicts of interest. Based on the documents prepared by the Steering Group, the GDG appraised and interpreted the evidence, and formulated the final recommendations at meetings convened on 27–28 January 2022 and 31 January–1 February 2022. The group also reviewed and approved the final recommendation document. The members of this group are listed in [Annex 1](#).

2.4 Evidence Synthesis Group

WHO convened an Evidence Synthesis Group (ESG) composed of guideline methodologists and systematic review teams for the conduct or updating of systematic reviews, appraisal of evidence, and development of the evidence-to-decision frameworks (EtD).

Technical experts from the Burnet Institute, Australia, and the Cochrane Pregnancy and Childbirth (CPC), United Kingdom, served as the guideline methodologists. In relation to quantitative evidence on the effects of the interventions, the Cochrane CPC provided input on the scoping of the priority questions and supervised the updating of relevant systematic reviews following the standard processes of the Cochrane Collaboration. The WHO Steering Group coordinated with the review authors on the updating of the reviews. The guideline methodologists appraised the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (26).

New systematic reviews of qualitative and cost-effectiveness studies were commissioned to generate evidence for other domains of the GRADE EtD. This included:

- a systematic review of qualitative, quantitative and mixed-methods studies related to women's and health care professionals' views and experiences on the use of antenatal corticosteroid therapy
- a systematic review of studies on the cost-effectiveness of antenatal corticosteroid therapy.

The Steering Group worked closely with the Evidence Synthesis Group to review the evidence and prepare the GRADE EtD frameworks. Members of the Evidence Synthesis Group attended the GDG meetings to provide an overview of the synthesized evidence, and to respond to technical queries from the GDG. The members of the Evidence Synthesis Group are listed in [Annex 1](#).

2.5 External partners and observers

Representatives of the United States Agency for International Development (USAID), the Bill & Melinda Gates Foundation (BMGF), the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) and the International Pediatric Association (IPA) participated in the GDG meetings as observers. These organizations with their long history of collaboration with the relevant WHO Departments in guideline dissemination and implementation, were identified as significant implementers of the recommendations. The list of observers who participated in the GDG meetings is included in [Annex 1](#).

2.6 External Review Group

An external review group was established to review the recommendations, composed of five technical experts with interest and expertise in the provision of evidence-based care to improve outcomes after preterm birth. The group was gender balanced and members were from four different WHO regions (African Region, Region of the Americas, South-East Asia Region, and Western Pacific Region). The members had no important 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 External Review Group are listed in [Annex 1](#).

2.7 Evidence identification and retrieval

Evidence to support the update of the recommendations was derived from several sources by the systematic review teams working in collaboration with the WHO Steering Group.

2.7.1 Evidence on effectiveness

The WHO Steering Group, in collaboration with the external team of systematic reviewers and guideline methodologists, retrieved evidence on the effectiveness

of interventions from systematic reviews of randomized controlled trials (RCTs) and non-randomized studies as needed. The Steering Group provided the methodologists with standard operating procedures and a briefing on the desired output of the systematic reviews, and together the members of these groups agreed on the format and timelines for reporting.

Using the assembled list of priority questions and outcomes, the WHO Steering Group, along with the external teams of systematic reviewers and guideline methodologists, identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. A systematic review was considered to be out of date if the last search date was two years or more prior to the date of assessment. The authors of reviews that were found to be out of date were requested to update them within a specified time period. In instances where the authors were unable to do so, the updates were undertaken by the external team of systematic reviewers, in consultation with the WHO Steering Group.

Cochrane systematic reviews were the primary source of effectiveness evidence for the recommendations included in this guideline. The Cochrane reviews were based on studies identified from searches of the Cochrane Pregnancy and Childbirth Group's Trials Register. This Register is maintained by the Trials Search Coordinator and contains trials identified from: monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of Medline; weekly searches of Embase; hand searches of 30 journals and the proceedings of major conferences; weekly "current awareness" alerts for a further 44 journals; and monthly BioMed Central email alerts.

The WHO Steering Group and methodologists worked together to determine the appropriateness and suitability of each systematic review in providing the evidence base for the main PICO question and sub-questions, by assessing the review's relevance, timeliness and quality. Relevance was ascertained by examining whether the population, intervention, comparison and outcomes considered in the full text of the review were compatible with those in the priority question. The quality of each review was determined by assessing: the clarity of its primary question with respect to the PICO; the comprehensiveness of the search strategies and databases; the potential for bias in the study selection and data extraction processes; the methods of assessing the risk of bias; and the methods of data syntheses and reporting.

In situations where there were no suitable systematic reviews (Cochrane or non-Cochrane) or where the reviews lacked data that were relevant to the specific priority question, new systematic reviews

were commissioned to various groups to inform the development of the recommendations. In such cases, the external groups of systematic reviewers were asked to prepare a standard protocol with a clear PICO question and criteria for identification of studies, including search strategies for different bibliographic databases, methods for assessing risk of bias and a data analysis plan. The WHO Steering Group and selected members of the evidence synthesis group then reviewed and endorsed the protocol before the group of reviewers embarked on the review. The search strategies employed to identify the studies and the specific criteria for inclusion and exclusion of studies are described in the individual systematic reviews. Studies from low-, middle- and high-resource countries were considered and there were no language restrictions. The entire systematic review development process was iterative, with the systematic reviewers and methodologists constantly communicating with the WHO Steering Group to discuss challenges and agree on solutions, while adhering to the review protocol.

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

Values, equity, acceptability and feasibility

A systematic review was conducted on factors influencing appropriate use of interventions for management of women experiencing preterm birth (27). This review was the primary source of evidence on acceptability, feasibility and equity. This review included primary qualitative, quantitative, and mixed-methods studies that discussed use of antenatal corticosteroid therapy in the management of preterm birth. An iterative narrative synthesis approach to analysis was taken.

Resource use and cost-effectiveness

Evidence on resource use and cost-effectiveness was based on a systematic review of the literature (28). The review aimed to synthesize all available evidence on the cost-effectiveness of antenatal corticosteroid therapy for improving preterm birth outcomes. Eligible studies were identified from specialist health economic databases (NHS Economic Evaluation Database and EconLit) and medical databases (PubMed, Embase, CINAHL and PsycInfo). Eligible studies were full economic evaluations that assessed cost-benefit, cost-effectiveness and/or cost-utility for women who received antenatal corticosteroid therapy. Two reviewers independently screened citations, extracted data and assessed study quality.

2.8 Quality assessment and grading of the evidence

2.8.1 Quality assessment of primary studies included in the reviews

The assessment of the quality of individual studies included in a Cochrane review follows a specific and explicit method of risk-of-bias assessment using six standard criteria outlined in the Cochrane handbook for systematic reviews of interventions (29). Each included study is assessed and rated by reviewers to be at low, high or unclear risk of bias for sequence generation, allocation concealment, blinding of study personnel and participants, attrition, selective reporting and other sources of bias, such as publication bias. The assessment along these domains provides an overall risk of bias for each included study that indicates the likely magnitude and direction of the bias and how it is likely to impact the review findings.

Other systematic reviews that included randomized trials also used the process outlined above. For non-randomized quantitative studies, assessment of study quality was in accordance with Cochrane handbook guidance, using the Cochrane Risk of Bias 2 (RoB 2) tool for trials and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (30).

Studies identified in the mixed-methods systematic review were assessed using an adapted Mixed Methods Appraisal Tool (MMAT) (27). MMAT is a critical appraisal tool designed specifically for mixed methods reviews and includes assessment of different criteria for different study designs (quantitative, qualitative and mixed-methods).

The quality of included studies on cost-effectiveness was assessed using the International Society of Pharmacoeconomics and Outcomes Research Taskforce Consolidated Health Economic Evaluation Reporting Standards statement (31).

2.8.2 Assessment of certainty of the effectiveness evidence

The certainty of evidence for a given outcome was rated using the standard GRADE approach based on consideration of study design limitations (risk of selection, performance, detection, attrition and reporting bias), inconsistency (heterogeneity or variability in results), indirectness (differences in study populations), imprecision (small study populations and few events) and publication bias (29).

Summary of findings tables were prepared that included the relative and absolute risk and an overall certainty rating for each outcome.

GRADE certainty of evidence

The certainty of evidence for each outcome was rated as ‘high’, ‘moderate’, ‘low’ or ‘very low’ as defined by the GRADE methodology:

- **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; and
- **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.

2.8.3 Assessment of the certainty (confidence) of the qualitative evidence

The findings of qualitative studies included in the mixed-methods systematic review were appraised using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool (27). The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence 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.

2.9 Formulation of recommendations

The WHO Steering Group supervised the preparation and finalization of summary of findings tables and narrative evidence summaries in collaboration with the Evidence Synthesis Group using the GRADE EtD framework (32). The EtD framework includes explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For each priority question, judgements were made on the impact of the intervention on each domain, to inform and guide the decision-making process. Using the EtD framework template, the Steering Group and Evidence Synthesis Group created summary documents for each priority question covering evidence on each domain.

The WHO Steering Group provided the EtD frameworks, including evidence summaries and summary of findings tables, to GDG members two weeks prior to the first GDG meeting. The GDG members were asked to review and electronically provide comments on the documents before the GDG meetings. During online meetings of the GDG (27–28 January and 31 January–1 February 2022), under the leadership of the GDG chairperson, the GDG members collectively reviewed the frameworks and any comments received.

The purpose of the meetings was to formulate recommendations, reach consensus on each recommendation and, where required, provide the specific context for the recommendation, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members.

In formulating the recommendations, the GDG used the recommended GRADE evidence-to-decision frameworks and considered separately synthesized evidence on effectiveness of the intervention, values (outcome importance) of the stakeholders, resource use and cost-effectiveness of the intervention, acceptability and feasibility of the intervention and the impact of the intervention on equity. For each of these domains, an appraisal of the certainty of evidence was performed using appropriate methods including GRADE or GRADE CerQual depending on the type of synthesis. It was the view of the GDG that, as certainty of evidence was evaluated across several domains to arrive at the recommendation, and not just for evidence on effectiveness of the intervention, this cannot be captured within a single ‘certainty’ rating. Providing the certainty of evidence for effectiveness alone within the recommendation texts does not adequately demonstrate the consideration of all the types of evidence, and could potentially confuse the target audience.

The GDG classified each recommendation into one of the following categories defined below.

- **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. In such instances, implementation can still be undertaken on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

This classification approach has been used for the development of all consolidated WHO maternal and perinatal health guidelines and updates of recommendations since 2016, spanning more than 90 individual recommendations. The approach was adopted in response to the feedback received from end users of maternal and perinatal health guidelines about the challenges of interpreting recommendations coupled with specific evidence ratings. The GRADE Public Health Group has also acknowledged that a key challenge for GRADE in public health is to identify how to reconcile the tension between the methodologically correct presentation of recommendations and the implications of strong versus conditional recommendations from the perspective of decision-makers (33).

2.10 Management of declaration 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 (24). 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. A short biography of the GDG members was also published on WHO's SRH website for more than four weeks for public review and comments prior to the first GDG meeting.

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 ensure that the work of WHO and the contribution of its experts is, actually and ostensibly, objective and independent. Where conflicts of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, experts were only required to openly declare such conflicts of interest at the beginning of the GDG meetings 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.

2.11 Decision-making during the GDG meetings

The GDG meetings were designed to allow participants to discuss the supporting evidence and to reach a consensus on the final wording of each recommendation. Consensus was defined as the agreement by three quarters or more of the GDG, provided that those who disagreed did not feel strongly about their position. Where required, the GDG determined the context of the recommendations by the same process of consensus, based on discussions about the balance of evidence on effects (benefits and harms) of the intervention across different contexts.

2.12 Document preparation and peer review

The WHO Steering Group made draft versions of the EtD frameworks available to the participants two weeks before the meetings for their comments. During the meetings, these documents were modified in line with the participants' deliberations and remarks. Following the meetings, the WHO Steering Group worked with the guideline methodologists to prepare a full recommendation document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members for their final review and approval. The final document was also sent for peer review to five external independent experts who were not involved in the recommendation development. The WHO Steering Group evaluated the inputs of the peer-reviewers for inclusion in this document. After the meetings and external peer reviews, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and edits to address any lack of clarity.

3. Recommendations and supporting evidence

The GDG issued one overarching recommendation and nine sub-recommendations on antenatal corticosteroid therapy. This section outlines the recommendations corresponding to the prioritized questions in section 1.3. To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional ‘remarks’ reflecting the summary of the discussions by the GDG are included under each recommendation. The recommendations should be applied in conjunction with the implementation considerations.

The summary of findings tables and EtD frameworks – presenting the balance between the desirable and undesirable effects, values of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in formulating each recommendation – are presented separately in the [Web Annex \(https://apps.who.int/iris/bitstream/handle/10665/363132/9789240057319-eng.pdf\)](https://apps.who.int/iris/bitstream/handle/10665/363132/9789240057319-eng.pdf) to this document. The EtD frameworks are numbered according to the specific recommendations to which they refer.

3.1 Recommendations

RECOMMENDATION 1.0:

Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met:

- Gestational age assessment can be accurately undertaken
- There is a high likelihood of preterm birth within 7 days of starting therapy
- There is no clinical evidence of maternal infection
- Adequate childbirth care is available (including capacity to recognize and safely manage preterm labour and birth)
- The preterm newborn can receive adequate care (including resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support including continuous positive airway pressure as needed)

REMARKS

- This recommendation applies to all other recommendations relating to the use of antenatal corticosteroid therapy in this guideline (i.e. Recommendations 1.1 to 1.10).

- High likelihood of preterm birth within 7 days may be assessed using the following criteria: preterm membrane rupture without preterm labour, spontaneous preterm labour with intact membranes (where preterm labour is defined as at least six regular uterine contractions/hour and at least one of the following: cervix ≥ 3 cm dilated or $\geq 75\%$ effaced), or planned preterm birth by induction or caesarean section.
- The recommendation is largely based on evidence derived from settings where the certainty of gestational age estimation is reasonably high. Therefore, accurate and standardized gestational age assessment (ideally from first trimester ultrasound, or an ultrasound performed at the time of presentation in situations where an early ultrasound of reasonable quality is not available) is essential to ensure that all eligible women receive corticosteroid therapy while avoiding unnecessary treatment of ineligible women. Antenatal corticosteroids should not be routinely administered in situations where ultrasound for gestational age assessment cannot be performed.
- In defining the upper limit of gestational age for antenatal corticosteroid therapy, the GDG placed its emphasis on study populations where there is convincing evidence that the benefits of antenatal corticosteroid therapy outweigh the potential harms. The GDG acknowledged the overlap in the populations of the subgroups considered (≤ 35 weeks and ≥ 34 weeks) and that the overall benefits of antenatal corticosteroid therapy probably extend up to 35 weeks. Nonetheless, the GDG specified 34 weeks 0 days as the upper limit because of the uncertainties in the balance between benefits and harms that clearly exist in the ≥ 34 weeks subgroup (respiratory morbidity benefits versus increased risk of neonatal hypoglycaemia), that is largely based on evidence derived from studies conducted in high-income settings. Additionally, the GDG considered 34 weeks (rather than 35 weeks) as a reasonable safeguard to prevent the use of corticosteroids in women at risk of preterm birth later in gestation, given the limitations in accuracy of gestational age assessment during the final weeks of the third trimester.

REMARKS *(continued)*

- The GDG agreed that while the lower limit of gestational age for antenatal corticosteroid therapy was based on available trial evidence, corticosteroids may be associated with substantial clinical benefits among infants born at <24 weeks who were exposed to corticosteroids antenatally, based on evidence from observational studies. The GDG noted that the probability of survival without long-term residual morbidity (“intact survival”) at <24 weeks is low, even in high-resource settings, and therefore shared decision-making among women and health care professionals on the immediate and long-term risks of extreme prematurity even in the context of antenatal corticosteroid therapy is warranted.
- The GDG acknowledged that the recommendation conditions listed above may not be operationalized in a standard and consistent manner across settings. However, the GDG placed its emphasis on the new evidence of mortality and morbidity reduction from antenatal corticosteroid therapy in low-resource countries where these conditions were reasonably and consistently met (20), against the background of previous evidence suggestive of harms in low-resource countries where these conditions were not prioritized (18). The GDG agreed that the possibility of harms from antenatal corticosteroid therapy cannot be excluded in settings where these conditions cannot be met such as lower-level health facilities and at the community level. To successfully operationalize these conditions, further details are provided under the implementation considerations section.
- The GDG acknowledged evidence of possible benefit to neonates born at 34 weeks to <37 weeks as well as potential increased risks of harm (neonatal hypoglycaemia) and noted that further trials are required to improve understanding of the balance of harms and benefits, particularly in low-resource settings.

RECOMMENDATION 1.1:

Antenatal corticosteroid therapy should be administered to women with a high likelihood of giving birth preterm in the next 7 days, even if it is anticipated that the full course of corticosteroids may not be completed.

REMARKS

- Antenatal corticosteroid therapy should be started even when the completion of a full course before preterm birth is uncertain.
- The GDG acknowledges the limitations and potential biases of evidence on interval between antenatal corticosteroid administration and preterm birth as derived from subgroup analyses of trials and observational studies, but agreed that available evidence confirms there is an association between the interval from administration to birth and preterm newborn outcomes. The GDG agreed that there is sufficient evidence to support benefit when the interval between antenatal corticosteroid administration and birth is 1–7 days. However, the GDG acknowledged that there is also evidence to indicate that there may be benefits of antenatal corticosteroids within the first 24 hours, and benefit which continues beyond 7 days after the first dose. The GDG considered this broader window of administration-to-birth interval as reassuring in the context of the challenges of accurately predicting spontaneous preterm birth.
- Antenatal corticosteroids should not be administered (“just in case”) to women who do not have a high likelihood of preterm birth, due to the potential newborn harms associated with prolonged administration-to-birth intervals (for example, 3 or more weeks) or administration to women who are likely to give birth at term.
- The GDG highlighted the importance of counselling and shared decision-making regarding antenatal corticosteroid use in the context of the uncertainties surrounding the prediction of spontaneous preterm birth, and the need for health care professionals to provide the necessary information and support to women during the course of their treatment.
- Where considered safe, tocolytic therapy should be considered as an intervention to gain time to complete a single course of antenatal corticosteroids. There are separate WHO recommendations relating to use of tocolytic therapy for women with a high likelihood of preterm birth prior to 34 weeks’ gestation (34).
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.2:

Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth, irrespective of whether single or multiple birth is anticipated.

REMARKS

- This recommendation precludes the routine (or prophylactic) administration of antenatal corticosteroids to any woman with a multiple pregnancy on the basis of increased risk of preterm birth.
- The GDG acknowledged the lack of clarity on the benefits of antenatal corticosteroid therapy in the subgroup of women with a multiple pregnancy but based its judgement on the overall improvement in critical outcomes among singleton infants, in addition to the fact that the point estimates were all in favour of reduced risks of adverse critical outcomes reported in multiple pregnancy. The group considered the potential impact of any clinical benefit in this group of women (who are inherently more likely to deliver preterm) on the overall preterm newborn survival and morbidity rates, and therefore recommended the intervention.
- Given that there remains some level of uncertainty about the effectiveness of antenatal corticosteroid therapy in multiple pregnancy, the GDG highlighted the importance of including multiple birth in future studies, as well as reporting of outcomes for single and multiple births separately.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.3:

Antenatal corticosteroid therapy is recommended for women with preterm prelabour rupture of membranes and no clinical signs of infection.

REMARKS

- The use of prophylactic antibiotics should be included as part of standard care for the woman once preterm prelabour rupture of the membranes is confirmed.
- The GDG noted the paucity of evidence on benefits with regards to the duration of membranes rupture, due to the lack of such information from trials included in the review. However, the group placed its emphasis on the overall balance favouring benefits over harms of using antenatal corticosteroid therapy in terms of reducing severe adverse neonatal outcomes without evidence of increased risk of infection to the mother or the baby, and with the consideration that a substantial proportion of women at risk of preterm birth would present with ruptured membranes.
- The GDG cautioned against the use of antenatal corticosteroid therapy for women with prolonged rupture of the membranes and with confirmed or suspected bacterial infection.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.4:

Antenatal corticosteroid therapy is not recommended for women with chorioamnionitis who are likely to give birth preterm.

REMARKS

- Timely birth of the baby to avoid further intrauterine insult should be the priority when the diagnosis of clinical chorioamnionitis is made. Antenatal corticosteroid therapy should not be initiated at the expense of timely birth when indicated by maternal or fetal condition.
- Antenatal corticosteroids should be avoided in women with evidence of ongoing systemic infection, e.g. septicaemia or tuberculosis.
- In the light of evidence from the Antenatal Corticosteroids Trial, (18) the GDG acknowledged the concern about the risk of exacerbating maternal infection, particularly in low- and middle-income settings where baseline risk of maternal infectious morbidity is higher than in the settings where previous trials have been conducted. The GDG felt that this potential risk may outweigh the known benefits of antenatal corticosteroids in the majority of populations where steroid use is essential for improving newborn survival.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.5:

Antenatal corticosteroid therapy is not recommended for women undergoing planned caesarean section at 34 weeks 0 days to 36 weeks 6 days.

REMARKS

- The GDG noted the paucity of evidence on the balance of benefits versus harms when antenatal corticosteroids are administered to women undergoing planned caesarean section (CS) at 34 weeks 0 days to 36 weeks 6 days gestation. The GDG acknowledged that, while there might be some benefits, there might also be harms. Reference was made to the overall evidence on antenatal corticosteroids, which included women undergoing provider-initiated (planned) preterm birth, and also suggested potential harms in late preterm infants.
- The GDG considered this to be a research priority but chose to recommend against the practice until further evidence becomes available.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.6:

Antenatal corticosteroid therapy is recommended for women with hypertensive disorders in pregnancy who have a high likelihood of preterm birth.

REMARKS

- An appropriate standard of care for the management of women with hypertensive disorders in pregnancy should be provided to the mother in addition to corticosteroid therapy in a hospital setting.
- The GDG placed its emphasis on the benefits to the preterm infants in terms of reducing early morbidity and mortality outcomes, the low cost and wide availability of corticosteroids globally, the feasibility of implementing the intervention, and the potential impact on health care resource use across settings.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.7:

Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth of a growth-restricted fetus.

REMARKS

- The GDG noted the limited evidence on the benefits of antenatal corticosteroids in this subgroup of women. However, the GDG placed its emphasis on the overall benefits of antenatal corticosteroids, the potential benefits in terms of reduced neurodevelopmental disability among surviving intrauterine growth-restricted infants, and evidence of reduced odds of adverse newborn mortality and morbidity outcomes.
- The GDG acknowledged that there are concerns about the effect of antenatal corticosteroids on fetal growth, but agreed that there is no evidence to suggest that corticosteroids will perform differently in this subgroup compared to the overall preterm population.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.8:

Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes when there is a high likelihood of preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.

REMARKS

- The GDG acknowledged the paucity of evidence on the benefits of antenatal corticosteroid therapy in this subgroup of women. However, the group placed its emphasis on the overall benefits of antenatal corticosteroids in preterm infants, the potential benefits in terms of reducing the higher risk of newborn respiratory morbidity posed by maternal diabetes, and the potential impact on overall newborn survival.
- The GDG considered the concern about the maternal hyperglycemic effect of antenatal corticosteroids, but agreed that it was insufficient to counterbalance the potential benefits for the baby if appropriate measures are taken to ensure glycemic control.
- Clinicians should ensure strict control of maternal blood glucose prior to and/or during pregnancy to reduce the risk of newborn respiratory distress syndrome, and ensure neonatal glucose monitoring.
- Delay in fetal lung maturity is generally more frequent in pregnant women with diabetes compared with the general obstetric population. Therefore, in pregnant women with poorly controlled diabetes, the use of corticosteroids could also be considered at >34 weeks of gestation.
- The GDG reaffirms that all pre-conditions outlined for antenatal corticosteroid therapy in Recommendation 1.0 apply.

RECOMMENDATION 1.9:

Either intramuscular (IM) dexamethasone or IM betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice.

REMARKS

- The GDG noted that there is no evidence on the comparative efficacy of dexamethasone and betamethasone that would support a recommendation of one over the other. The GDG acknowledged that dexamethasone has an advantage over betamethasone in terms of lower cost and wider availability, and it is currently listed for use in pregnant women on the *WHO Essential Medicine List*.
- The GDG acknowledged that the doses and regimens for both dexamethasone and betamethasone varied slightly across trials comparing the two, but noted that in the majority a total steroid dose of 24 mg was administered in divided doses 12 hours or 24 hours apart. Four doses of IM dexamethasone 6 mg 12 hours apart or 2 doses of IM betamethasone 12 mg 24 hours apart were the preferred choice in most of the studies.
- When deciding on the dosing frequency, consideration should be given to the likely timing of preterm birth to ensure that the woman completes the total course of antenatal corticosteroids or receives a substantial amount of the total dose before birth. Although there were no data on women's satisfaction, women are likely to prefer fewer injections.
- The GDG reviewed the important differences in the type and preparation of antenatal corticosteroids across settings and emphasized that local protocols on the type and dosing regimen should be informed by the preparations that are readily available in their setting. This will not only encourage uptake and ease their use by health care professionals but also avoid incorrect dosing and wastage of resources.
- The GDG acknowledged that there are ongoing antenatal corticosteroid studies using different doses, regimens, and routes of administration and welcome these as research priorities.

RECOMMENDATION 1.10:

A single repeat course of antenatal corticosteroids is recommended for women who have received a single course of antenatal corticosteroids at least 7 days prior and, on clinical assessment, have a high likelihood of giving birth preterm in the next 7 days.

REMARKS

- The GDG noted that only betamethasone was tested in this context but concluded that there were no reasons not to extend the recommendation to dexamethasone.
- The GDG considered evidence that a repeat course of antenatal corticosteroids is associated with a reduction in the composite outcomes (comprising one or more of perinatal death, respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, periventricular leukomalacia and neonatal sepsis), as well as respiratory morbidity and less oxygen supplementation and surfactant use (which could save costs). While there was a small reduction in mean neonatal birth weight and increased risk of small-for-gestational-age neonates, the GDG considered these effects to be clinically less significant in the context of the overall benefits for the preterm newborn.
- The GDG considered the evidence that newborn benefit of antenatal corticosteroids may be conferred beyond 7 days and may peak around 14 days after the initiation of the first treatment dose, and therefore recommends that the repeat course of antenatal corticosteroids should be administered between 7 and 14 days after first treatment dose.
- Clinical assessment occurring between 7 and 14 days after initiation of first course of antenatal corticosteroids should consider the gestational age of the pregnancy, and ensuring the woman has a high likelihood of preterm birth in the next 7 days. Antenatal corticosteroid administration to women with a pregnancy >34 weeks' gestation should be avoided.
- This recommendation applies to women who received an *incomplete* single course of antenatal corticosteroids at least 7 days prior, and on clinical assessment have a high likelihood of giving birth preterm in the next 7 days.
- This recommendation should only be applied to women between 24 and 34 weeks of gestation at time of the repeat course.
- A single course of antenatal corticosteroids in this context refers to a regimen 24 mg in divided doses, as for recommendation 1.9 in this guideline.

4. Dissemination and implementation of the recommendations

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

4.1 Dissemination and evaluation

An executive summary containing the recommendations, remarks, implementation considerations and research priorities will be prepared for public dissemination.

The WHO steering group will also develop tools to aid understanding and adaptation of these recommendations to local contexts, including an evidence brief on use of antenatal corticosteroid therapy, and a clinical algorithm. The recommendations and derivative tools will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. The recommendations will be published on the WHO's SRH website, and highlighted as part of the monthly HRP News. This newsletter currently reaches over 8000 subscribers including clinicians, programme managers, policy-makers and health service users from around the world. Updated recommendations are also routinely disseminated during meetings and scientific conferences attended by WHO maternal and perinatal health staff.

The executive summary and recommendations from this publication will be translated into the six UN languages for dissemination through the WHO regional and country offices and during meetings organized by, or attended by, staff of the WHO SRH and MCA Departments. Technical assistance will be provided to any WHO regional office willing to translate the full recommendations into any of these languages.

In addition, the publication of journal articles presenting the recommendations and key implementation considerations will be considered in compliance with WHO's open access and copyright policies. Relevant WHO clusters, departments and

partnerships, such as the Partnership for Maternal, Newborn and Child Health (PMNCH), will also be part of this dissemination process.

In order to ensure these recommendations have impact on maternal and perinatal health at country level, co-ordinated action between international agencies, national departments of health and key maternal and perinatal health stakeholders is required. National and sub-national working groups should assess current national guidelines and protocols, and determine whether development of new guidelines or updating is required in line with these new WHO recommendations. WHO staff at Headquarters, Regional and Country level, as well as international agency partners and international professional societies (such as FIGO and ICM, as well as national professional associations) can support national stakeholders in developing or revising existing national guidelines or protocols, and optimizing their implementation.

In the context of humanitarian emergencies, the adaptation of the current recommendations should consider the 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 recommendation in humanitarian emergencies by stakeholders.

4.2 Implementation considerations

The successful introduction of evidence-based policies related to the use of antenatal corticosteroid therapy to improve preterm birth outcomes into national programmes and health services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include developing or revising existing national guidelines and/or clinical protocols based on this document. The recommendations in this document should be adapted into local appropriate documents that are able to meet the specific needs of each country and health services. Modifications to the recommendations, if necessary, should be limited to conditional recommendations, and justifications for any change should be made in an explicit and transparent manner. The Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and

Adolescent Health at WHO will support national and subnational subgroups to adapt and implement the recommendations based on existing strategies.

Implementation of antenatal corticosteroid therapy needs to be made appropriate to local needs, intended users and recipients, and the overall health system.

As part of the recommendation development process, overarching implementation considerations were developed, which may help to assist policy-makers and clinicians to better prepare for implementation.

Considerations for implementation of antenatal corticosteroid therapy are outlined in Table 2.

Table 2: Overarching implementation considerations for antenatal corticosteroids

Implementation consideration	Description
Accurate assessment of gestational age	This includes a need to ensure that health care professionals are aware of the importance of ultrasound dating in the management of preterm birth, ensuring that early pregnancy ultrasound is routinely practiced, optimising the coverage, training and supervision of sonographers or other health care professionals skilled in ultrasound dating, and ensuring that ultrasound equipment is available at the health facility or in antenatal care. Standards, guidelines and training curricula in relation to gestational age estimation would also be required (35).
Shared decision-making, counselling, and family engagement	This includes that resources are in place to support shared decision-making between the woman, her family, and health care professionals about the potential short- and long-term consequences, decision about resuscitation, limit of viability, and benefits and harms of repeat courses of antenatal corticosteroids. During early pregnancy, this also includes that women, partners, and families receive education and educational materials on signs of preterm birth and preterm birth management, along with sufficient time and opportunity to discuss preterm birth management plans with health care professionals.
Appropriate settings for administration	<p>The WHO ACTION-I Trial was conducted in 29 secondary or tertiary hospitals in low-resource countries that reasonably met these criteria (20). In practice this included the following.</p> <p>Minimum package of care for pregnant women with high likelihood of preterm birth: ultrasound examinations for gestational age (GA) assessment and ensuring comprehensive emergency obstetric care was available.³ One ultrasound machine was provided to each hospital, and clinical staff underwent GA dating ultrasound training. Hospitals were encouraged to follow WHO recommendations on the use of tocolytics, magnesium sulfate for fetal neuroprotection and use of antibiotics.</p> <p>Minimum package of care for preterm newborns: all hospitals were supported to ensure that preterm newborns could receive a minimum package of care, including:</p> <ul style="list-style-type: none"> - <i>Care at birth and newborn resuscitation in the birthing room:</i> Hospitals had a newborn care corner in the labour room with a radiant warmer. All personnel were trained in essential newborn care (36) including neonatal resuscitation using bag and mask. Functioning equipment for bag and mask ventilation were available, including sizes appropriate for preterm babies - <i>Identification and management of respiratory distress, safe use of oxygen and respiratory support including optimal use of CPAP:</i> Neonatal care units in all hospitals were supported with CPAP machines to provide non-invasive respiratory support and pulse-oximeters to monitor oxygen saturation. The CPAP machines could concentrate oxygen from air thereby providing oxygen concentrations from 21% (room air) to 100%. These were also used in centres where there was no source of compressed air. Staff were trained to monitor respiratory rate and identify signs of respiratory distress including chest indrawing and grunting. - <i>Thermal care:</i> Facilities had radiant warmers or incubators to ensure preterm babies were protected from the risk of hypothermia. Staff were trained to monitor temperature at set intervals, and to detect and correct hypothermia by placing the baby under a radiant warmer. - <i>Breastfeeding and assisted feeding:</i> Staff encouraged mothers whose preterm babies were in the neonatal care unit, to express breast milk (fed to the newborn by gavage/cup) or to breastfeed the newborn. Early feeding and escalation of feeds was encouraged to limit the need for intravenous fluids. - <i>Monitoring of hypoglycaemia:</i> Staff were trained to monitor blood sugar for timely detection and correction of hypoglycemic episodes.

³ Nine signal functions include: parenteral antibiotics for treating peripartum infections, parenteral anticonvulsants for treatment of pre-eclampsia and eclampsia, parenteral oxytocic drugs for postpartum haemorrhage prevention and treatment, manual removal of retained products, blood transfusion, caesarean birth and hysterectomy.

Implementation consideration	Description
	<ul style="list-style-type: none"> - <i>Prevention and management of infection:</i> There was an emphasis on infection prevention and control including handwashing on entering the neonatal intensive care unit, sanitizing hands between contact with babies, encouraging the use of disposable goods wherever possible. Staff were trained to recognize signs of infection and possible sepsis. Antibiotics stewardship in the neonatal unit was encouraged. - Additionally, kangaroo mother care was encouraged for all preterm and low birthweight babies. Special rooms adjacent to the neonatal care unit were available to provide this care, in some hospitals. - Neither surfactant nor mechanical ventilation were available for the management of preterm infants in most hospitals, and neither was part of the respiratory support provided in the trial.
Procurement and administration	This includes that there is sufficient funding and budget allocation to ensure continuous procurement and distribution of antenatal corticosteroids, that antenatal corticosteroids are readily available in the antenatal, labour and emergency obstetric wards, that the safe administration of antenatal corticosteroids can be simplified for health care professionals, and that there is standardized communication about administration and dosing during handover and referral.
Guideline and clinical protocol adaptation	This includes ensuring that there has been a multi-stakeholder, consensus-driven process for local guideline adaptation and implementation, that guidelines and clinical protocols are consistent between WHO, national, sub-national and facility-levels, and that national guidelines have clear criteria on appropriate use and acceptable regimens of antenatal corticosteroids.
Strategies to improve use	<p>Prior to implementation, understanding that there are potential barriers to use of antenatal corticosteroids is important, including that health care professionals are aware of the benefits of antenatal corticosteroids (including for women with certain comorbidities e.g. diabetes, fetal growth restriction), and whether health care professionals have any scepticism or concerns about adverse effects of antenatal corticosteroids that can be addressed.</p> <p>Specific strategies that may improve appropriate use include:</p> <ul style="list-style-type: none"> - Training for health care professionals on safe and appropriate use of antenatal corticosteroids - Training for health care professionals on ultrasound for gestational age dating - Training for health care professionals on preterm newborn care (newborn resuscitation, oxygen, CPAP, thermal care, breastfeeding, blood glucose monitoring, prevention and management of infection, kangaroo mother care) - Reminder systems, educational materials, and decision aids available and accessible for health care professionals - Key performance indicators and audit and feedback available and accessible for antenatal corticosteroids - Appointing change champions or opinion leaders to promote appropriate use of antenatal corticosteroids.

4.3 Anticipated impact on the organization of care and resources

Effective implementation of the recommendations in this guideline may require re-organization of care and redistribution of health care resources, particularly in low- and middle-income countries. The potential barriers to implementation include:

- Non-availability or irregular supply of essential medicines (e.g. corticosteroids, or other medicines used in preterm labour management such as antibiotics, magnesium sulfate, tocolytic drugs) and lack of equipment and supplies for preterm babies (e.g. oxygen, resuscitator, masks, nasal prongs, CPAP, pulse oximeter, incubators, and radiant warmers);
- Lack of human resources with the necessary expertise and skills to implement the recommended

practices and monitor the clinical response of the newborn (e.g. application of continuous positive airway pressure, intubation, oxygen therapy);

- Low certainty of gestational age estimation, particularly for women living in settings where antenatal ultrasound is not routinely available;
- Lack of effective referral mechanisms and care pathways that ensure management of women with preterm labour and preterm newborns within a continuum.

In order to overcome these barriers, the GDG noted that the following issues should be considered before these recommendations are applied:

- Local protocols should be developed that integrate the management of women with a high likelihood

of preterm birth and preterm newborns within a continuum, with due consideration for contextual factors that influence preterm newborn survival.

- Careful attention should be paid to dating of pregnancy with the best method available during early antenatal care visits.
- Health care staff should be trained on how to determine the best estimate of gestational age and clinical features of women in spontaneous preterm labour.
- Local arrangements should be made to ensure ample and consistent supplies of antenatal corticosteroids (dexamethasone or betamethasone) with appropriate dose vials.
- Consideration should be given to all other aspects of maternal and newborn care quality at the health care facility level, including the provision of radiant warmers and kangaroo mother care for preterm newborns.
- Clear referral pathways for women with a high likelihood of preterm birth should be established within the health care facility.

4.4 Monitoring and evaluating guideline implementation

The implementation and impact of these recommendations will be monitored at the health-service, regional and country levels, based on clearly defined criteria and indicators that are associated with locally agreed targets. In the 2015 *WHO recommendations on interventions to improve preterm birth outcomes (25)*, the GDG suggested a set of outcomes, measures and indicators that can be adapted at regional and country levels to assess the impact of guideline implementation and adherence to the guideline recommendations. In collaboration with the monitoring and evaluation teams of the WHO Department of Maternal, Newborn, Child and Adolescent Health and the Department of Sexual and Reproductive Health and Research, data on country- and regional-level implementation of the recommendations will be collected and evaluated in the short to medium term to evaluate its impact on the national policies of individual WHO Member States.

Interrupted time series, clinical audits or criterion-based clinical audits could be used to obtain relevant data related to antenatal corticosteroid therapy. Clearly defined review criteria and indicators are needed and these could be associated with locally agreed targets. In this context, the following indicators could be considered.

INDICATOR	NUMERATOR	DENOMINATOR
1. Coverage: Measures initiation of antenatal corticosteroid use	All women who gave birth between 24 and 34 weeks' gestational age and received at least one dose of antenatal corticosteroids	All women who gave birth between 24 and 34 weeks' gestational age
2. Effective coverage (quality): Measures initiation of antenatal corticosteroid use in conjunction with a measurement of quality	All women who gave birth between 24 and 34 weeks' gestational age and received a single course of antenatal corticosteroids	All women who gave birth between 24 and 34 weeks' gestational age
3. Effectiveness (pair): Measures impact of antenatal corticosteroid use on neonatal outcomes	Perinatal deaths in babies born between 24 and 34 weeks whose mother received antenatal corticosteroids	Babies born between 24 and 34 weeks in women who received antenatal corticosteroids
	Perinatal deaths in babies born between 24 and 34 weeks whose mothers did not receive antenatal corticosteroids	Babies born between 24 and 34 weeks in women who did not receive antenatal corticosteroids
4. Safety: Measures if antenatal corticosteroid therapy is used safely and according to WHO recommendations	All women who received antenatal corticosteroids > 34 weeks' gestational age	All women who gave birth > 34 weeks' gestational age

5. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on these recommendations. The following questions were identified as high priorities and are listed in order of ranking by GDG members.

- What factors (barriers/facilitators) affect the typical use and potential scale-up of antenatal corticosteroids in low- and middle-income countries, and how can these factors be addressed through implementation research?
- What are the benefits and risks of antenatal corticosteroids when used for women with a high likelihood of preterm birth from 34 weeks' to 36 weeks 6 days' gestation, particularly in low- and middle-income countries?
- What are the effects of antenatal corticosteroids in women undergoing prelabour or elective caesarean section at 34 weeks to 36 weeks 6 days?
- What strategies can effectively and safely increase the use of antenatal corticosteroids in low- and middle-income country settings to improve preterm infant outcomes?
- What is the most effective regimen for antenatal corticosteroid therapy, including for repeat course?
- What is the optimal antenatal corticosteroid administration-to-birth interval in order to maximize benefits for preterm newborns (considering individual patient data meta-analysis or other advanced research methods and analysis techniques)?
- How can antenatal corticosteroid therapy implementation and scale up be optimized to ensure equitable distribution of benefits, including for groups experiencing disadvantage (such as racial, ethnic, or minority populations)?
- What are the long-term outcomes of infants exposed to antenatal corticosteroids, including those born at term?
- What is the minimum effective dose of antenatal corticosteroid therapy?
- What strategies can support women (and their families) in the shared decision-making process for antenatal corticosteroid use?
- What are the benefits and risks of antenatal corticosteroids among women with multiple pregnancies who are at risk of preterm birth between 34 weeks and 36 weeks 6 days gestation?

6. Updating the recommendations

The Executive GSG convenes regularly 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. These recommendations will be included in those reviews. In the event that new evidence that could potentially impact the current evidence base is identified, these recommendations may be updated. If no new reports or information is identified, the recommendations may be revalidated.

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

WHO welcomes suggestions regarding additional questions for inclusion in future recommendation reviews. Please email your suggestions to srhmph@who.int.

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Annex 2. Priority outcomes used in decision-making

Priority outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness)
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever)
- Adverse effects of treatment
- Maternal well-being
- Maternal satisfaction

Critical newborn outcomes considered were:

- Perinatal death (fetal or early neonatal death)
- Neonatal death

- Fetal death or stillbirth
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome (RDS), intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity)
- Birth weight (mean; low or very low)
- Infant or childhood death
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment)

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

Name	Expertise contributed to guideline development	Declared Interest	Management of declared interest
GUIDELINE DEVELOPMENT GROUP			
Shabina ARIFF	Content expert and end-user (Neonatology)	Principal Investigator (Pakistan) for WHO Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns (ACTION)-I trial, conducted between December 2017 and November 2019	This was declared to the group; the published findings of the trial are included as part of the evidence synthesis. In the event that the trial's findings alone would impact the formulation of a recommendation; the GDG member agreed not to participate in that aspect of the meeting
Elena ATEVA	Human rights expert	Project Lead for a White Ribbon Alliance-led health policy project (in collaboration with WHO and ICM), that is funded by USAID	The interest was declared to the group, and not considered a serious conflict that would warrant exclusion from GDG deliberations
Maria Laura COSTA	Content expert and end-user (Obstetrics)	None	Not applicable
Gary DARMSTADT	Content expert and end-user (Neonatology)	None	Not applicable
Bissallah EKELE	Content expert and end-user (Neonatology)	None	Not applicable
David HAAS	Content expert and end-user (Obstetrics)	Received grant support for pharmacogenetics of betamethasone; grant ending February 2022	The focus of the grant was not considered a conflict for the questions related to the use of ACS or tocolysis. In the event that dosing of ACS was to be discussed, the GDG member would be able to participate in discussions but not formulate recommendations.
Caroline HOMER	Content expert and end-user (Midwifery)	None	Not applicable
Sankar JEEVA	Content expert and end-user (Neonatology)	None	Not applicable
Joy LAWN	Content expert and end-user (Neonatology)	None	Not applicable
Pisake LUMBIGANON	Content expert and end-user (Obstetrics)	None	Not applicable
Silke MADER	Representative of the affected population	None	Not applicable
Elizabeth MOLYNEUX	Content expert and end-user (Neonatology)	None	Not applicable
Ashraf NABHAN	Content expert and end-user (Obstetrics)	None	Not applicable
Hiromi OBARA	Content expert and implementer	None	Not applicable

Name	Expertise contributed to guideline development	Declared Interest	Management of declared interest
Sarah STOCK	Content expert and end-user (Obstetrics)	Author on UK Royal College of Obstetricians and Gynaecologists guideline on Antenatal corticosteroids (2020-2022) and NVOG (Netherlands) European Guidance on Antenatal Corticosteroids (2020-2022) and FIGO statement on antenatal corticosteroids (2021) Research grants on use of antenatal steroids from Wellcome Trust, National Institute of Healthcare Research, Medical Research Council, Chief Scientist Office, Health Data Research UK	The knowledge and expertise of the GDG member was declared to the group. In areas for which recommendations may have been impacted by the findings of active grants; the GDG member would be able to participate in discussions but not in the formulation of any recommendation related to the topic of grants.
Zahida QURESHI	Content expert and end-user (Obstetrics)	Principle investigator at a site included in the WHO ACTION-I trial, concluded in 2019	This was declared to the group; the published findings of the trial are included as part of the evidence synthesis. In the event that the trial's findings alone would impact the formulation of a recommendation; the GDG member agreed not to participate in that aspect of the meeting
Khalid YUNIS	Content expert and end-user (Neonatology)	None	Not applicable
Hoang Thi TRAN	Content expert and end-user (Neonatology)	None	Not applicable
EVIDENCE SYNTHESIS GROUP			
Meghan BOHREN	Evidence synthesis	None declared	Not applicable
Jenny CAO	Evidence synthesis	None declared	Not applicable
Leanne JONES	Content expert, evidence synthesis	None declared	Not applicable
Frances KELLIE	Content expert, evidence synthesis	None declared	Not applicable
Jen RAMSON	Content expert, evidence synthesis, guideline methodology	None declared	Not applicable
Joshua VOGEL	Content expert, evidence synthesis, guideline methodology	WHO ACTION-I trial, concluded in 2019	This was declared to the group; the published findings of the trial are included as part of the evidence synthesis. In the event that the trial's findings alone would impact the formulation of a recommendation; the individual agreed not to participate in that aspect of the meeting
Myfanwy WILLIAMS	Content expert, evidence synthesis, guideline methodology	None declared	Not applicable

Web Annex. Evidence-to-Decision Frameworks and Summary of Findings Tables

The web annex accompanying this guideline is available here: <https://apps.who.int/iris/bitstream/handle/10665/363132/9789240057319-eng.pdf>.

WEB ANNEX	COMPARISON	CONTENTS
1.0	Antenatal corticosteroids compared to placebo or no treatment: all women and babies	Evidence-to-decision framework GRADE Tables
1.1	Antenatal corticosteroids compared to placebo or no treatment: interval between corticosteroid therapy and birth	Evidence-to-decision framework GRADE Tables
1.2	Antenatal corticosteroids compared to placebo or no treatment: single or multiple birth	Evidence-to-decision framework GRADE Tables
1.3	Antenatal corticosteroids compared to placebo or no treatment: preterm premature rupture of the membranes	Evidence-to-decision framework GRADE Tables
1.4	Antenatal corticosteroids compared to placebo or no treatment: presence of chorioamnionitis	Evidence-to-decision framework GRADE Tables
1.5	Antenatal corticosteroids compared to placebo or no treatment: planned caesarean section at 34 weeks to 36 weeks 6 days	Evidence-to-decision framework GRADE Tables
1.6	Antenatal corticosteroids compared to placebo or no treatment: hypertensive disorders in pregnancy	Evidence-to-decision framework GRADE Tables
1.7	Antenatal corticosteroids compared to placebo or no treatment: fetal growth restriction	Evidence-to-decision framework GRADE Tables
1.8	Antenatal corticosteroids compared to placebo or no treatment: pre-gestational or gestational diabetes	Evidence-to-decision framework GRADE Tables
1.9	Type and regimen of antenatal corticosteroids	Evidence-to-decision framework GRADE Tables
1.10	Repeat course compared to a single course of antenatal corticosteroids	Evidence-to-decision framework GRADE Tables



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