WHO recommendations on interventions to improve preterm birth outcomes

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Acronyms and abbreviations

BPD	bronchopulmonary dysplasia
CI	confidence interval
CDP	continuous distending pressure
CPAP	continuous positive airway pressure
EB	evidence base
EDD	estimated date of delivery
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (a WHO project and international partnership)
HIC	high-income country
IM	intramuscular
IUGR	intrauterine growth restriction
IV	intravenous
IVH	intraventricular haemorrhage
KMC	Kangaroo mother care
LMIC	low- and middle-income country
LMP	last menstrual period
MD	mean difference
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
OR	odds ratio
PICO	population, intervention, comparison, outcome
PPROM	preterm prelabour rupture of membranes
PPV	positive pressure ventilation
RCT	randomized controlled trial
RDS	respiratory distress syndrome
RR	relative risk
SGA	small for gestational age
SRT	surfactant replacement therapy
USA	United States of America
WHO	World Health Organization

Executive summary

Introduction

Preterm babies are prone to serious illness or death during the neonatal period. Without appropriate treatment, those who survive are at increased risk of lifelong disability and poor quality of life. Complications of prematurity are the single largest cause of neonatal death and the second leading cause of deaths among children under the age of 5 years. Global efforts to further reduce child mortality demand urgent action to address preterm birth.

Infant death and morbidity following preterm birth can be reduced through interventions provided to the mother before or during pregnancy, and to the preterm infant after birth. Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programmes) or used to minimize the risk in pregnant women with known risk factors (e.g. progestational agents, cervical cerclage). However, the most beneficial set of maternal interventions are those that could improve survival chances and health outcomes of preterm infants when preterm birth is inevitable. These interventions are provided to the mother shortly before or during the birth process with the aim of overcoming immediate and future health challenges of the preterm infant, 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.

WHO's *Managing complications of pregnancy and childbirth: a guide for midwives and doctors* (published in 2000) and *Pocket book of hospital care for children* (published in 2013) have, respectively, provided guidance on maternal and newborn interventions that could improve the outcomes of preterm birth. In keeping with the WHO procedures for guideline development, these documents needed to be updated to include the current evidence-based practices and to respond to Member States' requests for guidance on controversial areas of practice. The present guideline is focused on interventions that could be provided during pregnancy, labour and during the newborn period with the aim of improving outcomes for preterm infants. Recommendations on interventions to prevent and reduce the risk of preterm birth or modify risk in at-risk pregnant women are outside the scope of this guideline.

Target audience

The primary audience for this guideline includes health-care professionals who are 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 guideline 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 guideline 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.

Guideline development methods

The guideline was developed using standard operating procedures in accordance with the process described in the *WHO handbook for guideline development*. Briefly, these included (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline. The scientific evidence underpinning the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Up-to-date systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a Technical Consultation in May 2014 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the evidence profiles. In November 2014, an online consultation of the GDG was conducted to review and revise the recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in low-resource countries.

Recommendations

The WHO Technical Consultation led to the adoption of 10 main recommendations (and 17 additional sub-recommendations) covering antenatal corticosteroids, tocolysis, magnesium sulfate, antibiotic prophylaxis, mode of preterm birth (for the mother) and Kangaroo mother care, plastic wraps, continuous positive airway pressure therapy, surfactant and oxygen therapy (for the newborn). For each recommendation, the quality of evidence was graded as "very low", "low", "moderate" or

"high". The GDG qualified the direction and strength of each recommendation by considering the quality of evidence and other factors, including balance between benefits and harms, values and preferences of stakeholders, and the resource implications of the intervention. To ensure that each recommendation is correctly understood and applied in practice, the contributing experts provided additional remarks where needed. Guideline users should refer to these remarks, as well as the evidence summaries in the full version of the guideline, if there is any doubt as to the basis for any of the recommendations.

The recommendations on maternal and newborn interventions to improve health outcomes for the preterm infants are summarized in the table below. In accordance with WHO guideline development procedures, these recommendations will be constantly reviewed and updated following identification of new evidence, with major reviews and updates at least every five years. WHO welcomes suggestions regarding additional questions for inclusion in future updates of the guideline.

Summary list of WHO recommendations on interventions to improve preterm birth outcomes

Maternal interventions	Recommendations	Strength of recommendation and quality of the evidence[a]
Antenatal corticosteroids to improve newborn outcomes	**1.0.** Antenatal corticosteroid therapy is recommended for women at risk of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met: ■ gestational age assessment can be accurately undertaken; ■ preterm birth is considered imminent; ■ there is no clinical evidence of maternal infection; ■ adequate childbirth care is available (including the capacity to recognize and safely manage preterm labour and birth); ■ the preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment and safe oxygen use).	**Strong recommendation** based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes
	1.1. For eligible women, antenatal corticosteroid should be administered when preterm birth is considered imminent within 7 days of starting treatment, including within the first 24 hours.	**Strong recommendation** based on low-quality evidence
	1.2. Antenatal corticosteroid therapy is recommended for women at risk of preterm birth irrespective of whether a single or multiple birth is anticipated.	**Strong recommendation** based on low-quality evidence
	1.3. Antenatal corticosteroid therapy is recommended in women with preterm prelabour rupture of membranes and no clinical signs of infection.	**Strong recommendation** based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes
	1.4. Antenatal corticosteroid therapy *is not* recommended in women with chorioamnionitis who are likely to deliver preterm.	**Conditional recommendation** based on very low-quality evidence
	1.5. Antenatal corticosteroid therapy *is not* recommended in women undergoing planned caesarean section at late preterm gestations (34–36^{+6} weeks).	**Conditional recommendation** based on very low-quality evidence
	1.6. Antenatal corticosteroid therapy is recommended in women with hypertensive disorders in pregnancy who are at risk of imminent preterm birth.	**Strong recommendation** based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes

[a] For recommendations related to maternal interventions, the rating of the quality of evidence applies to both the maternal and newborn outcomes where the quality of the evidence for the two is not separately presented.

Maternal interventions	Recommendations	Strength of recommendation and quality of the evidence[a]
Antenatal corticosteroids to improve newborn outcomes (*continued*)	1.7. Antenatal corticosteroid therapy is recommended for women at risk of imminent preterm birth of a growth-restricted fetus.	**Strong recommendation** based on very low-quality evidence
	1.8. Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes who are at risk of imminent preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.	**Strong recommendation** based on very low-quality evidence
	1.9. Either intramuscular (IM) dexamethasone or IM betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice when preterm birth is imminent.	**Strong recommendation** based on low-quality evidence
	1.10. A single repeat course of antenatal corticosteroid is recommended if preterm birth does not occur within 7 days after the initial dose, and a subsequent clinical assessment demonstrates that there is a high risk of preterm birth in the next 7 days.	**Conditional recommendation** based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes
Tocolytics for inhibiting preterm labour	**2.0.** Tocolytic treatments (acute and maintenance treatments) *are not* recommended for women at risk of imminent preterm birth for the purpose of improving newborn outcomes.	**Conditional recommendation** based on very low-quality evidence
Magnesium sulfate for fetal protection against neurological complications	**3.0.** The use of magnesium sulfate is recommended for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy in the infant and child.	**Strong recommendation** based on moderate-quality evidence
Antibiotics for preterm labour	**4.0.** Routine antibiotic administration *is not* recommended for women in preterm labour with intact amniotic membranes and no clinical signs of infection.	**Strong recommendation** based on moderate-quality evidence
	5.0. Antibiotic administration is recommended for women with preterm prelabour rupture of membranes.	**Strong recommendation** based on moderate-quality evidence
	5.1. Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes.	**Conditional recommendation** based on moderate-quality evidence
	5.2. The use of a combination of amoxicillin and clavulanic acid ("co-amoxiclav") *is not* recommended for women with preterm prelabour rupture of membranes.	**Strong recommendation** based on moderate-quality evidence
Optimal mode of delivery	**6.0.** Routine delivery by caesarean section for the purpose of improving preterm newborn outcomes *is not* recommended, regardless of cephalic or breech presentation.	**Conditional recommendation** based on very low-quality evidence
Thermal care for preterm newborns	**7.0.** Kangaroo mother care is recommended for the routine care of newborns weighing 2000 g or less at birth, and should be initiated in health-care facilities as soon as the newborns are clinically stable.	**Strong recommendation** based on moderate-quality evidence
	7.1. Newborns weighing 2000 g or less at birth should be provided as close to continuous Kangaroo mother care as possible.	**Strong recommendation** based on moderate-quality evidence
	7.2. Intermittent Kangaroo mother care, rather than conventional care, is recommended for newborns weighing 2000 g or less at birth, if continuous Kangaroo mother care is not possible.	**Strong recommendation** based on moderate-quality evidence

Maternal interventions	Recommendations	Strength of recommendation and quality of the evidence[a]
Thermal care for preterm newborns (*continued*)	7.3. Unstable newborns weighing 2000 g or less at birth, or stable newborns weighing less than 2000 g who cannot be given Kangaroo mother care, should be cared for in a thermo-neutral environment either under radiant warmers or in incubators.	**Strong recommendation** based on very low-quality evidence
	7.4. There is insufficient evidence on the effectiveness of plastic bags/wraps in providing thermal care for preterm newborns immediately after birth. However, during stabilization and transfer of preterm newborns to specialized neonatal care wards, wrapping in plastic bags/wraps may be considered as an alternative to prevent hypothermia.	**Conditional recommendation** based on low-quality evidence
Continuous positive airway pressure for newborns with respiratory distress syndrome	**8.0.** Continuous positive airway pressure therapy is recommended for the treatment of preterm newborns with respiratory distress syndrome.	**Strong recommendation** based on low-quality evidence
	8.1. Continuous positive airway pressure therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made.	**Strong recommendation** based on very low-quality evidence
Surfactant administration for newborns with respiratory distress syndrome	**9.0.** Surfactant replacement therapy is recommended for intubated and ventilated newborns with respiratory distress syndrome.	**Conditional recommendation** (*only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available*) based on moderate-quality evidence
	9.1. Either animal-derived or protein-containing synthetic surfactants can be used for surfactant replacement therapy in ventilated preterm newborns with respiratory distress syndrome.	**Conditional recommendation** (*only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available*) based on moderate-quality evidence
	9.2. Administration of surfactant before the onset of respiratory distress syndrome (prophylactic administration) in preterm newborns *is not* recommended.	**Strong recommendation** based on low-quality evidence
	9.3. In intubated preterm newborns with respiratory distress syndrome, surfactant should be administered early (within the first 2 hours after birth) rather than waiting for the symptoms to worsen before giving rescue therapy.	**Conditional recommendation** (*only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available*) based on low-quality evidence
Oxygen therapy and concentration for preterm newborns	**10.0.** During ventilation of preterm babies born at or before 32 weeks of gestation, it is recommended to start oxygen therapy with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen.	**Strong recommendation** based on very low-quality evidence
	10.1. The use of progressively higher concentrations of oxygen should only be considered for newborns undergoing oxygen therapy if their heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation with 30% oxygen or air.	**Strong recommendation** based on very low-quality evidence

1. Background

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life *(1)*. Globally, it is the leading cause of perinatal and neonatal mortality and morbidity *(2)*. Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection *(3–5)*. With the increasing contribution of neonatal deaths to overall child mortality, it is critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in child mortality *(6–8)*.

Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the mother before or during pregnancy, and to the preterm infant after birth *(9)*. Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programme) or aimed at minimizing the risk in women with known risk factors (e.g. progestational agents, cervical cerclage) *(10)*. However, the most beneficial set of maternal interventions are those that are aimed at improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids, magnesium sulfate and antibiotic prophylaxis) *(9)*. Special care of the preterm newborn to prevent and treat complications of prematurity is also critical to newborn survival. In high-income countries, reductions in mortality rates in infants that were born preterm have been driven largely by improved care and, more importantly, by appropriate policy changes.

Existing World Health Organization (WHO) guidance on maternal interventions for preterm labour is available in the reference manual *Managing complications of pregnancy and childbirth (11)*. This manual was published in 2000, and reprinted in 2013. In view of the changes to the WHO guideline development process since 2007, it is imperative that the recommendations are reviewed and updated accordingly. Similarly, the latest WHO guidance on neonatal interventions for management of preterm infants can be found in the *Pocket book of hospital care for children (12)*. The second edition of this manual was published in 2013, but only a limited number of controversial areas were revised in accordance with the current WHO guideline development procedures. Moreover, a substantial amount of new evidence has emerged in recent years on preterm newborn interventions, including the use of Kangaroo mother care (KMC) *(13–16)*, plastic wraps (17, 18), continuous positive airway pressure *(19)* and surfactant therapy (20, 21). It is therefore necessary to review and update the recommendations using the current WHO guideline development procedures.

The global agenda, as captured in the global action report on preterm birth, to substantially reduce preterm-related death, demands careful integration of the care of pregnant women and preterm newborns *(22)*. However, this integration requires evidence-based guidance as an essential component to be effective in delaying preterm birth; providing appropriate intrapartum interventions to reduce complications in the preterm newborn; and providing effective care to the preterm newborn to reduce risk of death and long-term disability.

The purpose of this guideline is to provide evidence-based recommendations for interventions during pregnancy, labour and during the newborn period that are aimed at improving outcomes for preterm infants. Recommendations on interventions for the prevention of preterm birth are not within the scope of this guideline.

1.1 Target audience

The target audience for this guideline includes 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 public health policy-makers in all settings. The guideline will also be useful to those directly providing care to pregnant women and preterm infants, such as obstetricians, paediatricians, midwives, nurses and general practitioners. This guideline is evidence-informed and covers topics related to interventions for improving outcomes of preterm birth that were selected and prioritized by an international, multidisciplinary group of health-care professionals, consumer representatives and other stakeholders. It provides specific recommendations for the management of imminent preterm birth and preterm infants, and is intended to inform the development of health-care protocols and policies related to interventions to improve preterm birth outcomes. It is not intended to provide a comprehensive practical guide for the management of preterm labour and preterm infants.

1.2 Scope of the guideline

Populations of interest

This guideline focuses on improving maternal and neonatal outcomes associated with preterm birth,

and specifically includes both the care of pregnant women at imminent risk of preterm birth (birth < 37 weeks of gestation) and the care of preterm babies immediately after birth in all settings. Women at imminent risk of preterm birth were defined as pregnant women who are very likely to deliver a preterm baby either as a result of onset of spontaneous preterm labour, preterm prelabour rupture of membranes or elective (or indicated) preterm birth. The guideline scope does not include preventive care for non-pregnant or pregnant women with previous history of preterm birth or other known risk factors of preterm birth.

Critical outcomes

Critical maternal outcomes considered were:

- birth prior to 28, 32, 34 or 37 weeks of gestation;
- pregnancy prolongation (interval between randomization into the study and birth, birth within 48 hours or birth within 7 days);
- severe maternal morbidity or death;
- maternal sepsis (chorioamnionitis, puerperal sepsis);
- severe adverse effects of treatment.

Critical newborn outcomes considered were:

- neonatal death;
- fetal death or stillbirth;
- perinatal death (fetal or early neonatal death);
- 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);
- birth weight (mean; low or very low);
- infant or child death;
- long-term morbidity.

Priority questions

The priority questions guiding the evidence review and synthesis for this guideline are listed below in PICO format – population (P), intervention (I), comparison (C) and outcome (O).

1. Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy (C), effective in reducing adverse newborn outcomes (O)? If so:

- Which population of pregnant women should be offered antenatal corticosteroids? (*considering the gestational age at presentation or birth; interval between presentation and anticipated birth; single and multiple birth; status of amniotic membranes; and women undergoing elective caesarean section in late preterm*)
- Which population of pregnant women should not be offered antenatal corticosteroids? (*considering conditions where there are concerns that associated risks may outweigh benefits: women with diabetes mellitus, hypertensive disorders, chorioamnionitis and growth-restricted babies*)
- 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. Among pregnant women at risk of imminent preterm birth (P), is the use of tocolytic agent(s) (I), compared with no tocolytic agent, effective in delaying preterm birth and reducing adverse newborn outcomes? If so:

- Which population of pregnant women should be offered tocolytics? (*considering gestational age at presentation or birth; interval between presentation and anticipated birth*)
- Which population of pregnant women should not be offered tocolytics? (*considering potential contraindications: women with preterm prelabour rupture of membranes, multiple pregnancy, antepartum haemorrhage, fetal growth restriction and medical conditions*)
- Which tocolytic agents (and regimens) should be used for eligible women?
- Should a tocolytic maintenance regimen be offered following successful first-line tocolysis of a preterm labour? If so, which maintenance regimen should be recommended?

3. Among pregnant women at risk of imminent preterm birth (P), is magnesium sulfate therapy (I), compared with no magnesium sulfate therapy (C), effective in protecting the fetus from neurological complications (i.e. fetal neuroprotection) (O)? If so:

- Which population of pregnant women should be offered antenatal magnesium sulfate for fetal neuroprotection? (*considering gestational age at presentation; interval between presentation and anticipated birth; single and multiple birth*)
- Which regimen of antenatal magnesium sulfate should be used for fetal neuroprotection in eligible women?

4. Among pregnant women at risk of imminent preterm birth (P), is routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), effective in improving maternal and newborn outcomes (O)? If so:

- Which population of women should be offered antenatal prophylactic antibiotics? (*considering women with preterm rupture of membranes*)
- Which population of pregnant women should not be offered antenatal prophylactic antibiotics? (*considering women with intact amniotic membranes*)
- Which antibiotics (and regimens) should be used in eligible women?

5. Among women with refractory preterm labour (P), is a policy of routine caesarean delivery of preterm infants (I), compared with planned vaginal birth (C), effective in reducing adverse newborn outcomes (O)? If so:

- What is the optimal mode of birth by fetal presentation?
- What is the optimal mode of birth by gestational age?

6. Among preterm babies who require thermal care (P), is practicing Kangaroo mother care (I) compared with conventional care (C), effective in reducing adverse newborn outcomes (O)? If so:

- How effective is continuous Kangaroo mother care (KMC) in the thermal care of preterm babies?
- Is KMC equally effective when administered intermittently rather than continuously, with or without alternative conventional methods of care during the intervention periods?
- In which subgroup of preterm newborns is KMC effective? (*considering babies weighing <2000 g; sick and unstable babies, with respiratory distress, feed intolerance, etc.*)

7. In unstable preterm newborns who cannot be (exclusively) cared for by Kangaroo mother care (P), are there other superior methods for providing thermal care to maintain optimal body temperatures (I), compared with incubators (C), that are effective in improving newborn outcomes (O)? If so:

- Are radiant warmers superior to incubators in the provision of thermal care for these preterm babies?

8. In newly born extremely preterm or very preterm infants (P), is the use of plastic wraps/caps (I), compared with conventional care including Kangaroo mother care (C), effective in improving newborn outcomes? If so:

- Should these plastic wraps/caps be used instead of KMC immediately after birth in a subgroup of preterm infants?

9. In newly born preterm babies with or at risk of respiratory distress syndrome (P), is continuous positive airway pressure (I), compared with routine care (C), effective in preventing adverse newborn outcomes? If so:

- Under what conditions and when should continuous positive airway pressure be provided?
- What are the indications for additional interventions?

10. In newly born preterm babies who have or are at risk of respiratory distress syndrome (P), is surfactant therapy (I), compared with routine care without surfactants (C), effective in reducing adverse newborn outcomes (O)? If so:

- How early should the surfactant therapy be started?
- Should surfactants be given for prophylaxis in newborns where respiratory distress syndrome has not yet set in, or selectively when existing respiratory distress is worsening?
- Which types of surfactant are effective – animal-derived or synthetic; protein-containing or protein-free?

11. In newly born preterm babies born before 32 weeks of gestation (P), is optimal oxygen therapy (O), compared to no guided administration (C), effective in improving newborn outcomes (O)? if so:

- What concentration of oxygen should be administered?
- What should guide the administration of the oxygen to these babies?

2. Methods

This document represents WHO's support for using evidence-informed norms, policies and practices in all countries. The guideline was developed using standard operating procedures in accordance with the process described in the *WHO handbook for guideline development (23)*. In summary, the process included: (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The guideline development process involved the formation of three main groups to guide the process; their specific roles are described in the following sections.

2.1 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Maternal, Newborn, Child and Adolescent Health and the Department of Reproductive Health and Research, guided and managed the entire guideline development process. The group drafted the initial scope of the guideline and priority questions in PICO format (population, intervention, comparison, outcome) and identified systematic review teams, guideline methodologists and members of the Guideline Development Group (GDG). Additionally, the WHO Steering Group supervised the evidence retrieval and syntheses, organized the GDG meetings, prepared draft recommendations for the GDG and the final guideline document, and managed the guideline publication and dissemination. The members of the WHO Steering Group are presented in Annex 1.

2.2 Guideline Development Group

The WHO Steering Group identified 27 external experts and stakeholders from the six WHO regions to constitute the GDG. This was a diverse and gender-balanced group of individuals with expertise in research, clinical policy and programmes relating to maternal and newborn interventions to improve outcomes of preterm birth. The group included clinical researchers, obstetricians, neonatologists, paediatricians, midwives, representatives of user groups and guideline methodology experts. Members of this group provided input into the drafting of the guideline scope and the PICO questions, and participated in prioritization of outcomes that guided the evidence reviews. In addition, the GDG appraised the evidence that was used to inform the recommendations, advised on the interpretation of the evidence, formulated the final recommendations based on the draft prepared by the WHO Steering Group, and reviewed and approved the final guideline document. The members of the GDG are presented in Annex 1.

2.3 External Review Group

This group included six technical experts and other stakeholders with an interest in the provision of evidence-based maternal and newborn care. The group was geographically balanced, gender-representative and no member declared a conflict of interest. The group reviewed the final guideline document to identify any factual errors and commented on the clarity of the language, contextual issues and implications for implementation. The group ensured that the guideline decision-making processes had incorporated contextual values and preferences of potential users of the recommendations, health-care professionals and policy-makers. It was not within the group's remit to change the recommendations formulated by the GDG. The members of the External Review Group are presented in Annex 1.

2.4 Identification of priority questions and critical outcomes

The WHO Steering Group first drafted a list of priority questions and potential critical and important outcomes related to interventions to improve outcomes of preterm birth. WHO then consulted a larger group of international stakeholders (including midwives, obstetricians, neonatologists, researchers, experts in health programmes and representatives of user groups) to review the draft questions and prioritize the outcomes at a Technical Consultation in Geneva in April 2013. The international stakeholders ranked the relative importance of the outcomes on a scale from 1 to 9. In this context, an outcome was ranked as "critical" if it was given an average score of 7 or more. Questions and outcomes with a score of between 4 and 6 were considered "important but not critical", while those with a score lower than 4 were not considered to be important for the purposes of the guideline. The prioritized outcomes rated as critical were included in the scope of this document for evidence searching, retrieval, grading and formulation of recommendations.

2.5 Evidence identification and retrieval

The WHO Steering Group, in collaboration with an 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 critical outcomes from the scoping exercise, 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 evidence for the recommendations included in this guideline.[1] The Cochrane reviews relating to maternal interventions 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 details of the search strategies for key databases such as CENTRAL, Medline and Embase, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the "Specialized Register" section within the editorial information about the Cochrane Pregnancy and Childbirth Group.[2] Trials identified through the search activities described above are each assigned to a review topic (or topics). Cochrane's Trials Search Coordinator searches the register for each review using the topic list rather than keywords.

Similar to the maternal health interventions, the evidence review and summary for the development of the guidelines on interventions for the newborn were primarily based on Cochrane reviews. The newborn interventions, derived from the scoping questions, were based on studies identified from the Cochrane Neonatal Review Group. This Cochrane group prepares and disseminates evidence-based systematic reviews of RCTs of treatment for neonatal diseases or conditions. These reviews are prepared following standard methods, including comprehensive searches for eligible trials using search engines such as Ovid and PubMed from key databases, as described for the maternal interventions. Cochrane reviews are regularly updated as new trials are published.

The assessment of quality of individual intervention studies included in Cochrane reviews follows a specific and explicit method for assessing the risk of bias. Briefly, using the criteria outlined in the *Cochrane handbook for systematic reviews of interventions*, two review authors independently assess the risk of bias along six domains: sequence generation, allocation concealment, blinding of study personnel and participants, attrition, selective reporting, and other sources of bias such as publication bias *(24)*. Each included study is assessed and rated to be at "low", "high" or "unclear" risk of bias for each of these six domains, and these assessments together provide an overall risk of bias that indicates the likely magnitude and direction of the bias and how it is likely to impact the review findings. Each Cochrane review is preceded by a publication of a peer-reviewed protocol describing the proposed methods and search strategy for that review.

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 key PICO 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

[1] As part of the Cochrane pre-publication editorial process, reviews are commented on by three peers (one editor and two referees external to the editorial team) and the Group's Statistical Adviser (see http://www.cochrane.org/cochrane-reviews). *The Cochrane handbook for systematic reviews of interventions* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

[2] Available at: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/PREG/frame.html

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 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 content experts among the GDG members then reviewed and endorsed the protocol before the group of reviewers embarked on the review. To identify relevant studies, systematic searches of various electronic databases were conducted, including Medline, Embase, CENTRAL, CINAHL, Popline, NLM Gateway and WHO regional databases. The search strategies employed to identify the studies and the specific criteria for inclusion and exclusion of studies were described in the individual systematic reviews. Studies from low-, middle- and high-income 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.

2.6 Quality assessment and grading of the evidence

Quality assessment of the body of evidence for each outcome was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(25)*. Using this approach, the quality of evidence for each outcome was rated as "high", "moderate", "low", or "very low" based on a set of criteria. The rating of the quality of evidence was dependent on consideration of the factors briefly described below.

Limitations in the study design and execution: The risk of bias was first examined at the level of the individual study and then across studies contributing to the outcome. For RCTs, quality was first rated "high" and then downgraded by one level ("moderate") or two ("low"), depending on the minimum quality criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions and confidence limits showed minimal overlap.

Indirectness: Rating of the quality of evidence were downgraded where there were serious or very serious concerns regarding the directness of the evidence, i.e. where there were important differences between the research reported and the context for which the recommendations are being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes.

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

Publication bias: Quality rating could also be affected by perceived or statistical evidence of bias that may have led to underestimation or overestimation of the effect of an intervention as a result of selective publication based on study results. Where publication bias was strongly suspected, evidence was downgraded by one level.

GRADE profiler software was used to construct "Summary of Findings" tables for each priority question; these tables include the assessments and judgements relating to the elements described above and the illustrative comparative risks for each outcome. Relevant information and data were extracted in a consistent manner from the systematic reviews relating to each priority question by applying the following procedures. First, up-to-date review documents and/or data (e.g. RevMan file) were obtained from the review authors or the Cochrane Library. Secondly, analyses relevant to the critical outcomes were identified and selected. The data were then imported from the RevMan file (for Cochrane reviews) or manually entered into the GRADE profilers (for non-Cochrane reviews). For each outcome, GRADE assessment criteria (as described above) were applied to evaluate the quality of the evidence. In the final step of the assessment process, GRADE evidence profiles were generated for each priority question.

2.7 Formulation of recommendations

The GRADE framework was applied to formulate each recommendation based on the synthesized evidence *(26)*. For each priority question, the WHO Steering Group used the corresponding summaries of evidence for the critical outcomes, and the assessments of the overall quality of the evidence, balance between benefits and risks, values and preferences, and resource implications to draft the recommendations. The draft recommendations, evidence summaries, the corresponding GRADE tables, and other related documents were provided in advance to members of the GDG who were then asked to comment on the document. The GDG members and other participants were then invited to attend the Technical Consultation organized at WHO headquarters in Geneva, Switzerland, in May 2014 (see Annex 1 for a full list of participants). At the Technical Consultation, the GDG members systematically reviewed and discussed these documents to finalize the recommendations and determine their directions and strengths.

2.8 Declaration of interests by external contributors

According to WHO regulations, all experts must declare their relevant interests prior to participation in WHO guideline development processes and meetings. All GDG members and external contributors were therefore required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and participating in related meetings. The WHO Steering Group reviewed all the DOI forms before finalizing experts' invitations to participate in the guideline development. Where any conflict of interest was declared, the Steering Group determined whether such conflicts were serious enough to affect objective judgement of the expert on the guideline development process and recommendations. To ensure consistency, the Steering Group applied the criteria for assessing the severity of a conflict of interest in the *WHO handbook for guideline development for all experts (23)*. All statements on the received DOI forms were managed in accordance with the WHO DOI guidelines on a case-by-case basis and the decisions were communicated to the experts.

The procedures for the management of declared conflicts of interests were undertaken in accordance with the *WHO guidelines for declaration of interests (WHO experts)*. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare such conflict at the beginning of the Technical Consultation and no further action was taken. Conflict of interest that warranted action by WHO staff arose where experts had obtained funding from a body or an institution to perform primary research or a systematic review directly related to any of the guideline recommendations. At the Technical Consultation, the concerned experts were restricted from participating in discussions and/or formulation of recommendations pertaining to their conflicts of interest. A summary of the DOI statements and how conflicts of interest were managed is included in Annex 3.

2.9 Decision-making during the Technical Consultation

The Technical Consultation process was guided by a clear protocol, as described here. The meeting was designed to allow participants to discuss each of the recommendations drafted by the WHO Steering Group. Where necessary, each of these recommendations was revised through group discussion. The final adoption of each recommendation was confirmed by consensus – defined as the agreement of at least three quarters of the participants – provided that those who disagreed did not feel strongly about their position. Strong disagreements would have been recorded as such in the guideline. If the participants were unable to reach a consensus, the disputed recommendation, or any other decision, was put to a vote. Voting was by a show of hand by members of the GDG. A recommendation or decision stood if a simple majority (more than half of the participants) voted in support of it, unless the disagreement was related to a safety concern, in which case the WHO Secretariat would choose not to issue a recommendation at all. WHO staff at the meeting, external technical experts involved in the collection and grading of the evidence, and the observers (see list in Annex 1) were not eligible to vote. If the issue to be voted upon involved primary research or systematic reviews conducted by any of the participants who had declared an academic conflict of interest, the participants in question would be allowed to participate in the discussion, but would not be allowed to vote on that issue.

The Technical Consultation also determined the strength of each recommendation. By default, the strength of each recommendation under discussion was initially aligned with the quality of the evidence (i.e. at the start of the discussion, "strong recommendations" were based on evidence of "moderate" and "high" quality, while "conditional recommendations" were based on evidence of "low"

and "very low" quality). In addition to the quality of the evidence, the following factors were considered when determining the strength and direction of the final recommendation: values and preferences, the balance of benefits versus harms, relevant applicability issues and resource/cost implications. The consideration of values and preferences was based on the experience and opinions of members of the GDG. Cost evaluation relied on reported estimates obtained during the evidence retrieval process as well as experience and opinions of the GDG members. "Evidence to Decision" tables were used to note and synthesize these considerations and record the reasons for changes made to the default strength of the recommendations.

In November 2014, a special Web-based consultation of the GDG was held to review the implications of new evidence on the effects of strategies to scale up antenatal corticosteroid therapy on neonatal mortality in low- and middle-income countries. Relevant recommendations were reviewed and further revisions were made taking the new evidence into consideration, as agreed by the GDG.

2.10 Document preparation and peer review

Prior to the Technical Consultation in May 2014, the WHO Steering Group prepared a draft version of evidence summaries and corresponding recommendations. The draft document was made available to the participants of the Technical Consultation one week before the meeting for their comments. During the meeting, the draft recommendations were modified in line with participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group prepared a draft of the full guideline document with revisions to accurately reflect the deliberations and decisions of the participants. The draft guideline document was then sent electronically to GDG members for further comments before it was sent to the External Review Group for peer review. The WHO Steering Group carefully evaluated the input of the peer reviewers for inclusion in the guideline document. After the Technical Consultation and peer review, the modifications made by the WHO Steering Group to the guideline were limited to correction of factual errors and improvement in language to address any lack of clarity. The revised final version was returned electronically to the participants of the Technical Consultation for their final approval.

3. Evidence and recommendations

In total, 48 systematic reviews summarized in 53 GRADE tables provided the evidence base for the recommendations included in this guideline. Sections 3.1 and 3.2 outline the recommendations and the corresponding narrative summaries of evidence for the priority questions. The corresponding GRADE tables for the recommendations are referred to in this section as evidence base (EB) Tables 1 to 9. These tables are presented separately in the electronic supplement to this document (see *WHO recommendations on interventions to improve preterm birth outcomes: evidence base* www.who.int/reproductivehealth/publications/maternal_perinatal_health/preterm-birth-guideline). "Evidence to Decision" tables summarizing the quality of evidence, values and preferences, balance between benefits and harms, and resource use that were considered in determining the strength and direction of the recommendations are presented in Annex 2.

The participants at the WHO Technical Consultation on this guideline in May 2014 adopted 10 main recommendations and 17 sub-recommendations, covering interventions provided to the mother before the birth of the preterm baby and to the preterm infant after birth. For the mother, the recommendations relate to the use of antenatal corticosteroids, tocolysis, magnesium sulfate, antibiotics, and optimal mode of delivery of preterm newborns (see sections 3.1.1–3.1.5). For the preterm infant, they relate to the use of Kangaroo mother care (KMC), plastic wraps, continuous positive airway pressure (CPAP) therapy, surfactant replacement therapy and oxygen therapy (see sections 3.2.1–3.2.3). The quality of the supporting evidence rated as "very low", "low", "moderate" or "high" and the strength of each recommendation assessed as "strong" or "conditional" are indicated. To ensure that each recommendation is correctly understood and appropriately implemented in practice, additional remarks reflecting the summary of the discussion by the Guideline Development Group (GDG) are included under the recommendation where necessary.

3.1 MATERNAL INTERVENTIONS

3.1.1 Antenatal corticosteroids for improving newborn outcomes

RECOMMENDATION 1.0

Antenatal corticosteroid therapy is recommended for women at risk of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met:

- gestational age assessment can be accurately undertaken;
- preterm birth is considered imminent;
- there is no clinical evidence of maternal infection;
- adequate childbirth care is available (including the capacity to recognize and safely manage preterm labour and birth);
- the preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment and safe oxygen use).

(Strong recommendation based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes)

REMARKS

- This recommendation applies to all other recommendations relating to the use of antenatal corticosteroids in this guideline (i.e. Recommendations 1.1 to 1.10).
- The recommendation is largely based on evidence derived from settings where the certainty of gestational age estimation is high. Therefore, accurate and standardized gestational age assessment (ideally from first trimester ultrasound) is essential to ensure that all eligible mothers receive corticosteroids while avoiding unnecessary treatment of ineligible mothers. Antenatal corticosteroid should not be routinely administered in situations where the gestational age cannot be confirmed, particularly when gestational age is suspected to be more than 34 weeks, as the risk of harm may outweigh the benefits if mature fetuses are exposed to corticosteroid in-utero.
- Due consideration should be given to local limits of fetal viability when determining the lowest limit of gestational age when antenatal steroids should be administered, including reference to local data on newborn survival and morbidity. The GDG noted that the probability of survival without residual morbidity ("intact survival") at < 24 weeks is low, even in high-resource settings.
- The GDG acknowledged that the conditions listed above may not be operationalized in a standard and consistent manner across settings. Identifying the most critical and essential preconditions to achieve clinical benefits from antenatal corticosteroid is uncertain and would benefit from further research. In setting these preconditions, the panel's emphasis was on minimizing harm to the mother and the baby.
- An appropriate standard of childbirth care should be available to the mother in a facility that has a team of health-care providers competent in recognizing and safely managing preterm labour and imminent preterm birth. Safe care during labour and childbirth requires close monitoring of the mother and fetus to identify and appropriately manage complications, such as maternal infection and fetal hypoxia.
- Essential and special care for the management of preterm newborns should be available to prevent or address any newborn complications related to prematurity or otherwise.
- The GDG made a strong recommendation, having 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 corticosteroid globally; the feasibility of implementing the intervention; and the potential impact on health-care resource use across settings.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (all women and babies) (EB Table 1a)

Evidence on the use of antenatal corticosteroids for reducing adverse neonatal outcomes associated with prematurity was extracted from a Cochrane systematic review of 26 trials (4469 women and 4853 babies) *(27)*. This review included trials that compared corticosteroid treatment with placebo or no treatment in women expected to deliver between 24 and 37 weeks of gestation as a result of either spontaneous preterm labour, preterm prelabour rupture of membranes (PPROM) or elective preterm birth. Exclusion criteria were variable but commonly included medical contraindications to steroid use, evidence of maternal infection, diabetes, lethal fetal anomalies, advanced first stage of labour, and any maternal or fetal indications requiring urgent delivery.

Most of the trials were conducted in hospital settings in high-income countries: Brazil (2 trials), Finland (2 trials), the United States of America (USA) (12 trials), and one trial each in Canada, Colombia, Jordan, the Netherlands, New Zealand, South Africa, Spain, Turkey, Tunisia and the United Kingdom.

Eighteen trials used betamethasone (3028 women and 3289 babies) as the corticosteroid in the treatment arm while six trials used dexamethasone (1391 women and 1514 babies). One study did not specify the corticosteroid used (18 women and babies), and another study used either betamethasone or dexamethasone (32 women and babies).

Evidence on the specific population of women whose preterm babies are most likely to benefit from antenatal corticosteroids and those in whom there are concerns that associated risks may outweigh benefits was extracted from the subgroup analyses of the same Cochrane review. Where a specific population of interest was not included in the Cochrane review, evidence was extracted from other systematic reviews that were specifically performed for this purpose.

Evidence regarding the overarching context of care specified for the main recommendation was based on the findings of a large cluster-randomized trial evaluating the effects of a population-based multifaceted strategy to increase antenatal corticosteroid coverage on neonatal mortality *(29)*.

Maternal outcomes

Severe maternal morbidity or death: Compared with placebo, corticosteroid therapy was not associated with increased risk of maternal mortality (RR 0.98, 95% CI 0.06–15.50; 3 studies, 365 women, 1 death in each arm of the pooled results). Two studies reported maternal admission to intensive care; there was no significant difference between the groups (RR 0.74, 95% CI 0.26–2.05; 319 women).

Maternal infectious morbidity: Corticosteroid therapy was not associated with increased risk of maternal infection; the rates of chorioamnionitis were similar in both groups (RR 0.90, 95% CI 0.69–1.17; 13 studies, 2525 women), as were the rates of puerperal sepsis (RR 1.35, 95% CI 0.93–1.95; 8 studies, 1003 women), and postnatal fever (RR 0.92, 95% CI 0.64–1.33; 5 studies, 1323 women).

Maternal side-effects: No cases of maternal side-effects were reported (4 studies, 533 women).

Infant outcomes

Fetal and neonatal death: Compared with placebo, corticosteroid therapy was associated with significantly fewer fetal and neonatal deaths (RR 0.77, 95% CI 0.67–0.89; 13 studies, 3627 infants). This was largely due to a 32% reduction in neonatal deaths (RR 0.68, 98% CI 0.58–0.80; 21 studies, 4408 infants, corresponding to 9.5% in the treatment group versus 14% for controls), whereas fetal deaths were comparable in both groups (RR 0.98, 95% CI 0.73–1.30; 13 studies, 3627 infants).

Childhood death: There were no significant differences in terms of childhood deaths (RR 0.68, 95% CI 0.36–1.27; 4 studies, 1010 children) or deaths occurring during adulthood (RR 1.00, 95% CI 0.56–1.81; 1 study, 988 adults).

Severe neonatal morbidity: The rate of respiratory distress syndrome (RDS) was reduced by 35% in the corticosteroids group (RR 0.65, 95% CI 0.58–0.73; 25 studies, 4590 infants). Moderate and severe RDS was also reduced (RR 0.55, 95% CI 0.43–0.71; 6 studies, 1686 infants). The mean duration of mechanical ventilation was reduced in the corticosteroids group (MD -1.42 days, 95% CI -2.28 to -0.56; 3 studies, 518 infants). Mean duration of oxygen supplementation was reported in one trial and results favoured the corticosteroids group (MD -2.86 days, 95% CI -5.51 to -0.21; 73 infants). There was no significant difference in chronic lung disease (RR 0.86, 95% CI 0.61–1.22; 6 studies, 818 infants). Corticosteroid therapy was associated with a reduction in the occurrence of cerebroventricular haemorrhage (RR 0.54, 95% CI 0.43–0.69; 13 studies, 2872 infants), infant systemic infection in the first 48 hours of life (RR 0.57, 95% CI 0.38–0.86; 6 studies, 1359 infants) and necrotizing enterocolitis (RR 0.46, 95% CI 0.29–0.74; 8 studies, 1675 infants) when compared with placebo.

No significant difference between the groups was observed for small-for-gestational-age (SGA) infants (RR 1.05, 95% CI 0.78–1.42; 4 studies, 698 infants), mean infant birth weight (MD -6.93 g, 95% CI -39.41 to 25.55; 13 studies, 2961 infants), admission to a neonatal intensive care unit (NICU) (RR 0.88, 95% CI 0.73–1.06; 4 studies, 629 infants) or mean duration of NICU stay (MD 0.00, 95% CI -1.08 to 1.09; 4 studies, 641 infants).

Long-term morbidity: Corticosteroid therapy was associated with a trend towards a reduction in the number of children treated for cerebral palsy in childhood (RR 0.60, 95% CI 0.34–1.03; 5 studies, 904 children), as well as a reduction in developmental delay (RR 0.49, 95% CI 0.24–1.00; 2 studies, 518 children). Differences between groups for visual and hearing impairment, neurodevelopmental delay, intellectual impairment and behavioural or learning difficulties were not

statistically significant in children or adults, although the relative risks were all in favour of a reduction.

Antenatal corticosteroids versus placebo or no treatment (analyses by gestational age at therapy) (EB Table 1b)

In the same review *(27)*, subgroup analyses were performed for six gestational age categories according to when corticosteroid therapy was initiated: < 26, 26 to < 30, 30 to < 33, 33 to < 35, 35 to < 37, and > 36 weeks. However, each of these analyses was based on one to three trials, and the number of participants per subgroup was generally small. Across the six subgroups, the number of participants was lowest in the < 26 and > 36 weeks gestational age categories for the critical outcomes reported (with < 50 women in each category).

Maternal outcomes

Maternal infectious morbidity: Chorioamnionitis was significantly reduced in the women given corticosteroids between 30 and < 33 weeks of gestation (RR 0.19, 95% CI 0.04–0.86; 1 study, 294 women), but not in other gestational age categories.

Infant outcomes

Fetal and neonatal death: Compared to controls, a reduction in neonatal deaths for those infants whose mothers had been treated with corticosteroids between 26 and < 30 weeks of gestation was observed (RR 0.67, 95% CI 0.45–0.99; 1 study, 227 infants), while there were no significant differences in all other gestational age categories. No statistically significant differences were observed between groups for combined fetal and neonatal deaths or fetal deaths alone in the subgroups of gestational age at which corticosteroid was administered.

Severe neonatal morbidity: The frequency of RDS among infants of women receiving treatment between 26 and 34^{+6} weeks of gestation was reduced by approximately 50% (26 to < 30 weeks: 2 studies, 242 women, RR 0.49, 95% CI 0.34–0.72; 30 to < 33 weeks: 2 studies, 361 women, RR 0.56, 95% CI 0.36–0.87; 33 to < 35 weeks: 2 studies, 434 women, RR 0.53, 95% CI 0.31–0.91). There were no observed significant differences across other gestational age groups. Only those infants whose mothers were treated with corticosteroids between 26 and 29^{+6} weeks of gestation showed a significant reduction in the incidence of cerebroventricular haemorrhage (RR 0.45, 95% CI 0.21–0.95; 229 infants), while there were no significant differences across all other gestational age subgroups.

Birth weight: Birth weight was significantly reduced for those infants whose mothers received treatment from 30 to < 33 weeks of gestation (MD -190.64 g, 95% CI -359.98 to -21.3). No differences in birth weight were observed in other gestational age subgroups.

Antenatal corticosteroids versus placebo or no treatment (analyses by gestational age at birth) (EB Table 1c)

Subgroup analyses were also performed according to five categories of gestational age at birth of the preterm infant exposed to antenatal corticosteroid: < 28, < 30, < 32, < 34 and < 36 weeks.

Maternal outcomes

Maternal infectious morbidity: No difference was observed in the rate of chorioamnionitis between those treated with corticosteroid and those given placebo or no treatment across any of the gestational age categories.

Infant outcomes

Fetal and neonatal death: There was a significant reduction in combined fetal and neonatal deaths among corticosteroid-exposed infants that were born before 32 weeks of gestation (RR 0.71, 95% CI 0.57–0.88; 3 studies, 453 infants), before 34 weeks (RR 0.73, 95% CI 0.58–0.91; 1 study, 598 infants) and before 36 weeks (RR 0.75, 95% CI 0.61–0.94; 2 studies, 969 infants). Neonatal deaths alone were significantly reduced in the corticosteroid-exposed infants that were born before 32 weeks (RR 0.59, 95% CI 0.43–0.80; 3 studies, 378 infants), before 34 weeks (RR 0.69, 95% CI 0.52–0.92; 2 studies, 715 infants) and before 36 weeks (RR 0.68, 95% CI 0.50–0.92; 2 studies, 869 infants). However, the significant reduction in both fetal and neonatal deaths, and in neonatal deaths alone was not observed for babies exposed to antenatal corticosteroids who were born before 28 weeks (fetal and neonatal death: RR 0.81, 95% CI 0.65–1.01, 2 studies, 129 infants; neonatal death: RR 0.79, 95% CI 0.56–1.12, 2 studies, 89 infants) nor those born before 30 weeks (fetal and neonatal death: RR 0.86, 95% CI 0.70–1.05, 1 study, 201 infants; neonatal death: RR 0.82, 95% CI 0.60–1.11, 1 study, 150 infants). Likewise, mortality was not reduced for infants born after 34 weeks of gestation (fetal and neonatal death: RR 1.13, 95% CI 0.66–1.96, 1 study, 770 infants; neonatal death: RR 1.58, 95% CI 0.71–3.50, 2 studies, 808 infants).

For infants born at 36 weeks of gestation or over, there was a non-significant trend towards an increase in combined fetal and neonatal deaths (RR 3.25, 95%

CI 0.99–10.66; 2 studies, 498 infants) associated with corticosteroid treatment, as well as in neonatal deaths alone (RR 2.62, 95% CI 0.77–8.96; 3 studies, 514 infants).

Severe neonatal morbidity: RDS was significantly reduced in infants of mothers treated with corticosteroids that were born before 30 weeks of gestation (RR 0.67, 95% CI 0.52–0.87; 4 studies, 218 infants), before 32 weeks (RR 0.56, 95% CI 0.45–0.71; 6 studies, 583 infants), before 34 weeks (RR 0.58, 95% CI 0.47–0.72; 5 studies, 1177 infants) and before 36 weeks (RR 0.52, 95% CI 0.40–0.69; 4 studies, 1022 infants). Antenatal corticosteroids were not shown to reduce RDS when analysed for all infants born after 34 weeks of gestation (RR 0.66, 95% CI 0.38–1.16; 5 studies, 1261 infants), after 36 weeks (RR 0.30, 95% CI 0.03–2.67; 5 studies, 557 infants) or before 28 weeks (RR 0.79, 95% CI 0.53–1.18; 4 studies, 102 infants).

Cerebroventricular haemorrhage was significantly reduced in corticosteroid-exposed infants born before 28 weeks of gestation (RR 0.34, 95% CI 0.14–0.86; 1 study, 62 infants), before 32 weeks (RR 0.52, 95% CI 0.28–0.99; 1 study, 277 infants) and before 34 weeks (RR 0.53, 95% CI 0.29–0.95; 1 study, 515 infants). However, this benefit was not observed in infants born before 30 weeks (RR 0.56, 95% CI 0.29–1.10; 1 study, 150 infants), before 36 weeks (RR 0.56, 95% CI 0.31–1.02; 1 study, 767 infants), at a gestation of at least 34 weeks (RR 1.13, 95% CI 0.07–17.92; 1 study, 746 infants) or at a gestation of at least 36 weeks (no events reported in 459 infants).

No statistically significant differences between the groups treated with antenatal corticosteroids and controls were seen for birth weight in the different subgroups of gestational age at birth that were examined.

Antenatal corticosteroids versus placebo or no treatment (gestational age at birth from 22 to 25 weeks)

A separate review was conducted for infants with gestational age at birth of 22–25 weeks. This review found a prospective multicentre cohort study of 10 541 infants born at 22–25 weeks in the USA, which investigated the effect of exposure to antenatal corticosteroid on death or childhood neurodevelopmental impairment *(28)*.

Infant outcomes

Fetal and neonatal death: Hospital deaths were significantly lower in corticosteroid-exposed infants who were born at 23 weeks of gestation (adjusted OR 0.49, 95% CI 0.39–0.61), 24 weeks (adjusted OR 0.64, 95% CI 0.54–0.76) and 25 weeks (adjusted OR 95% CI 0.57 0.48–0.69), but not those born at 22 weeks (adjusted OR 0.61, 95% CI 0.34–1.07), which may be due to the smaller sample size included in this group.

Long-term morbidity: After 18–22 months follow-up, intact survival in the entire cohort was 36%. However, intact survival was higher in infants whose mothers received corticosteroids compared to controls (35.8% versus 18.5%, adjusted OR 1.66, 95% CI 1.46–1.90). Death or neurodevelopmental impairment was also significantly less frequent in preterm babies born at 23–25 weeks of gestation, but not in those born at 22 weeks.

Antenatal corticosteroids scale-up versus usual care (context of care)

Evidence relating to the preconditions for administration of antenatal corticosteroid was informed by the findings of a large multicountry population-based cluster-randomized trial – the Antenatal Corticosteroids Trial (ACT). This trial assessed the feasibility, effectiveness and safety of a multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels of care (primary health centres and non-hospital facilities, community health clinics, dispensaries and hospitals) *(29)*. The study was conducted in 102 distinct geographical rural and semi-urban clusters in low-resource countries (Argentina, Guatemala, India, Kenya, Pakistan and Zambia) with birth records of close to 100 000 women.

The intervention involved health-care provider training to assess gestational age and to identify women at high risk of preterm birth (presenting between 24 and 36 weeks of gestation with signs of labour, PPROM, pre-eclampsia or eclampsia, or antenatal haemorrhage). Health-care providers in this context included all birth attendants working in the intervention clusters, including physicians, nurses, community health workers and traditional birth attendants (TBAs) providing delivery care at hospitals, clinics, in the community or in home birth settings, respectively. Gestational age was determined by the use of an algorithm that included last menstrual period (LMP) and estimated date of delivery (EDD), or uterine height if neither LMP nor EDD were known. Where LMP or EDD was known, gestational age was assessed using a specially designed obstetric disk. When reliable information on gestational age was not available, uterine fundal height was used as a proxy for gestational age and was measured using a validated colour-coded tape

with a red zone indicating estimated gestational age less than 36^{+0} weeks. For every woman identified to be at high risk of preterm birth, health-care providers received training to administer a single course of four doses of 6 mg of dexamethasone at intervals of 12 hours. The control sites received no intervention apart from training in essential newborn care as in the intervention clusters.

Identification of women at risk of preterm birth and use of corticosteroids: A total of 6214 (13%) of 48 219 women in the intervention cluster were identified as being at high risk of preterm birth. Of these women, 87% were identified at the community and primary health care levels, 77% were identified based on signs of preterm labour, 50% were identified at 33–36 weeks of gestation, and 98% received antenatal corticosteroids (out of which 83% received the first dose at the community and primary health care levels). Only 16% of all women who received antenatal corticosteroids in the intervention clusters gave birth to a < 5th-percentile-birth-weight infant (a proxy for preterm infant). The intervention strategy increased coverage of antenatal corticosteroids in the intervention compared with the control clusters. Compared with 10% in control clusters, 45% of < 5th-percentile-birth-weight infants in the intervention clusters were exposed to at least one dose of corticosteroid. In the intervention clusters, delivery care for < 5th-percentile-birth-weight infants was provided by physicians, nurses, TBAs and family members in 44%, 32%, 20% and 5% of cases, respectively; and the location of birth was in the hospital, clinic, and home or other birth setting in 51%, 26% and 23% of cases, respectively.

Maternal outcomes

Maternal infectious morbidity: "Suspected maternal infection" (a composite variable defined as antibiotic use plus hospital admission or referral, and use of intravenous fluids, surgery or other treatment related to infection, and evidence of antepartum or postpartum infection among mothers of infants with birth weight < 2500 g) was used to assess maternal safety in relation to corticosteroid use. Among women who delivered < 5th-percentile-birth-weight infants, there was a significantly increased risk of suspected maternal infection in intervention clusters as compared with control clusters (10% versus 6%; OR 1.67, 95% CI 1.33–2.09). Likewise, suspected maternal infection was significantly higher among all women in the intervention clusters compared with control clusters (3% versus 2%; OR 1.45, 95% 1.33–1.58; 99 737 women).

Infant outcomes

Neonatal death: Neonatal mortality among < 5th-percentile-birth-weight infants was not significantly different between intervention and control clusters (RR 0.96, 95% CI 0.87–1.06; 4778 infants), and neither were stillbirths (RR 0.99, 95% CI 0.90–1.09; 6262 infants) or perinatal deaths (RR 0.97, 95% CI 0.91–1.04; 6265 infants). However, there was a 12% increase in neonatal mortality among all liveborn infants (regardless of birth weight) in the intervention clusters as compared with the control clusters (RR 1.12, 95% CI 1.02–1.22; 98 137 infants). Likewise, there was an 11% increase in the rate of stillbirth (RR 1.11, 95% CI 1.02–1.22; 100 705 infants) and perinatal death (RR 1.11, 95% CI 1.04–1.19; 100 705 infants) in the intervention clusters compared with control clusters.

RECOMMENDATION 1.1

For eligible women, antenatal corticosteroid should be administered when preterm birth is considered imminent within 7 days of starting treatment, including within the first 24 hours. *(Strong recommendation based on low-quality evidence)*

REMARKS

- Antenatal corticosteroid therapy should be started even when the completion of a full course before preterm birth is uncertain.
- Tocolysis may be considered as an intervention to gain time to complete a single course of antenatal corticosteroids (see also Recommendation 2.0 on tocolytic treatments).
- The GDG acknowledged the limitations and potential bias of evidence derived from the subgroup analyses according to interval between steroid administration and preterm birth, which led to rating of the quality of evidence as "low". Nevertheless, the group made a strong recommendation on the basis of the balance being in favour of the benefits of antenatal corticosteroids (in terms of reducing respiratory morbidity and mortality for babies born within 24 hours and up to 7 days of starting treatment), the low resource requirements, and the feasibility of implementing the intervention.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (interval between corticosteroid therapy and birth: < 24 hours, < 48 hours, 1–7 days and > 7 days) (EB Table 1d)

In the Cochrane review that showed overall benefits of antenatal corticosteroids compared with placebo *(27)*, subgroup analyses were performed according to the interval between corticosteroid treatment and birth of the preterm infant. Only one to four trials could be included for most of the critical outcomes reported with the exception of RDS, which had eight to nine trials providing evidence for the < 24 hours, 1–7 days and > 7 days categories.

Maternal outcomes

Maternal infectious morbidity: No significant differences were observed in the occurrence of chorioamnionitis across all the subgroups.

Infant outcomes

Fetal and neonatal death: There was a significant reduction in combined fetal and neonatal deaths for infants born within 24 hours (RR 0.60, 95% CI 0.39–0.94; 3 studies, 293 infants) and within 48 hours (RR 0.59, 95% CI 0.41–0.86; 1 study, 373 infants) of corticosteroid therapy, but not those born between 1 and 7 days (RR 0.81, 95% CI 0.60–1.09; 3 studies, 606 infants) or those born after 7 days (RR 1.42, 95% CI 0.91–2.23; 3 studies, 598 infants). This pattern was consistent across the subgroup for neonatal deaths alone but no differences were observed for fetal deaths.

Severe neonatal morbidity: There were significantly fewer cases of RDS among babies born before 48 hours (RR 0.67, 95% CI 0.49–0.93; 3 studies, 374 infants) and between 1 and 7 days (RR 0.46, 95% CI 0.35–0.60; 9 studies, 1110 infants), but not among those born before 24 hours (RR 0.87, 95% CI 0.66–1.15; 9 studies, 517 infants) or those born more than 7 days after the first dose (RR 0.82, 95% CI 0.53–1.28; 8 studies, 988 infants). Significant reductions were also observed in cases of cerebroventricular haemorrhage among infants born within 48 hours of the first dose of steroids (RR 0.26, 95% CI 0.09–0.75; 1 study, 339 infants) but not in any of the other subgroups.

While there were no significant differences demonstrated in the birth weights of babies born before 24 hours, 48 hours, and between 1 and 7 days, there was a trend towards a reduction in birth weight among infants exposed to corticosteroid treatment who were born more than 7 days after the first dose (MD -147.01 g, 95% CI -291.97 to -2.05; 1 study, 486 infants).

RECOMMENDATION 1.2

Antenatal corticosteroid therapy is recommended for women at risk of preterm birth irrespective of whether a single or multiple birth is anticipated. *(Strong recommendation based on low-quality evidence)*

REMARKS

- This recommendation precludes the routine (or prophylactic) administration of antenatal corticosteroid 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 corticosteroids in the subgroup of women carrying multiple fetuses, 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), albeit modest, on the overall preterm newborn survival and morbidity rates, and therefore made a strong recommendation.
- Although there remains some level of uncertainty about the effectiveness of antenatal corticosteroids in multiple pregnancy, the GDG does not consider this to be a research priority.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (singleton versus multiple pregnancy) (EB Table 1e)

Results for the effects of corticosteroids compared with placebo according to whether the pregnancy was singleton or multiple were available from 12 trials included in the same Cochrane review *(27)*. Of these, only one to two trials provided data for comparisons related to multiple pregnancies.

Maternal outcomes

Maternal infectious morbidity: The review showed no statistically significant differences between comparison groups for chorioamnionitis, in women with singleton pregnancies or in women with multiple pregnancies.

Infant outcomes

Fetal and neonatal death: The reduction in fetal and neonatal deaths observed in singleton pregnancies (RR 0.79, 95% CI 0.65–0.96; 3 studies, 1425 babies) was not demonstrated in the analysis for multiple pregnancies (RR 0.71, 0.41–1.22; 2 studies, 252 babies), although there was a trend towards benefit. The same pattern was observed for neonatal deaths alone.

Severe neonatal morbidity: The reduction in RDS for singleton pregnancies treated with corticosteroids (RR 0.60, 95% CI 0.51–0.70; 12 studies, 2907 infants) did not reach statistical significance for multiple pregnancies (RR 0.85, 95% CI 0.60–1.20; 4 studies, 320 infants). Similarly, no significant reduction was demonstrated in the rate of cerebroventricular haemorrhage or mean infant birth weight in women with multiple pregnancies treated with corticosteroids compared with placebo/no treatment.

RECOMMENDATION 1.3

Antenatal corticosteroid therapy is recommended in women with preterm prelabour rupture of membranes and no clinical signs of infection. *(Strong recommendation based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes)*

REMARKS

- The use of prophylactic antibiotics should be included as part of standard care for the mother once preterm prelabour rupture of the membranes is confirmed (see Recommendation 5.0).
- The GDG noted the paucity of evidence on benefits with regard 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 corticosteroids 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 imminent preterm birth would present with ruptured membranes, and therefore made a strong recommendation.
- The GDG cautioned against the use of antenatal corticosteroids for women with prolonged rupture of the membranes and with features of sepsis.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (preterm prelabour rupture of membranes) (EB Table 1f)

In the same Cochrane review *(27)*, the effects of antenatal corticosteroids were examined in a subgroup of women with PPROM.

Maternal outcomes

Severe morbidity or death: No significant differences were observed between groups for maternal death, chorioamnionitis or puerperal sepsis in mothers when the first dose of corticosteroids was given to women with PPROM or prolonged rupture of membranes (> 24 hours).

Infant outcomes

Fetal and neonatal death: Combined fetal and neonatal deaths were significantly reduced among infants exposed to antenatal corticosteroid and born following PPROM at the time of first dose (RR 0.62, 95% CI 0.46–0.82; 4 studies, 733 infants), but not following prolonged rupture of membranes > 24 hours (RR 0.77, 95% CI 0.51–1.17; 2 studies, 508 infants) or > 48 hours (RR 0.93, 95% CI 0.57–1.51; 1 study, 255 women). As with previous outcomes, this reduction was due to the contribution of reduced neonatal mortality among corticosteroid-exposed infants (RR 0.61, 95% CI 0.46–0.83; 8 studies, 1024 infants), while no reduction in fetal deaths was observed for any of these subgroups.

Severe neonatal morbidity: RDS was significantly reduced in infants whose mothers received corticosteroids at the time of PPROM (RR 0.68, 95% CI 0.57–0.83; 12 studies, 1129 infants), as was cerebroventricular haemorrhage (RR 0.47, 95% CI 0.28–0.79; 5 studies, 895 infants), necrotizing enterocolitis (NEC) (RR 0.39, 95% CI 0.18–0.86; 4 studies, 583 infants), and duration of mechanical ventilation (MD -3.50 days, 95% CI -5.12 to -1.88 days; 1 study, 165 infants). No significant differences were observed for neonatal infection, systemic infection in the first 48 hours, or need for mechanical ventilation or continuous positive airway pressure (CPAP).

RECOMMENDATION 1.4

Antenatal corticosteroid therapy is not recommended in women with chorioamnionitis who are likely to deliver preterm. *(Conditional recommendation based on very low-quality evidence)*

REMARKS

- Timely delivery 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 delivery 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 *(29)*, the GDG reviewed 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 that of the settings where the evidence on women with chorioamnionitis was generated. The group 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. They acknowledged that the balance of benefits and harms may be context-specific and chose to make a conditional recommendation against the intervention in this situation.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (women with chorioamnionitis) (EB Table 1g)

Evidence on the effects of antenatal corticosteroid therapy for reducing adverse newborn outcomes in women with chorioamnionitis who are at risk of preterm birth was extracted from a systematic review that included eight cohort studies involving a total of 1424 mothers expected to deliver at or before 35 weeks of gestation *(30)*. All studies were conducted in high-resource settings: two in the USA, two in France, and one each in Australia, Canada, Korea and the Netherlands. Infections among participants in these studies were diagnosed either clinically or histologically. Four studies reported the effects of corticosteroid therapy in infants of women with histological chorioamnionitis only, two on infants of women with clinical chorioamnionitis only, and two further studies on infants in both groups of women separately.

All studies in the review evaluated the use of a corticosteroid compared with no treatment (or incomplete/suboptimal treatment). In four studies, betamethasone was used (996 mothers and infants), in two studies, dexamethasone was used (161 mothers and infants) and in the remaining two studies, either betamethasone or dexamethasone was used (267 mothers and infants).

This evidence was reviewed and interpreted in the context of the findings of a large cluster-randomized trial evaluating the effects on increasing antenatal corticosteroid coverage on neonatal mortality in low-income settings *(29)*.

Maternal outcomes

None of the studies in the systematic review reported on maternal outcomes.

Infant outcomes

Histological chorioamnionitis

Fetal and neonatal death: Antenatal corticosteroid use in women with histological chorioamnionitis was associated with a significant reduction in neonatal deaths (pooled OR 0.49, 95% CI 0.34–0.73; 6 studies, 1156 infants).

Severe neonatal morbidity: Antenatal corticosteroid use in women with histological chorioamnionitis was associated with significant reductions in RDS (pooled OR 0.58, 95% CI 0.44–0.76; 5 studies, 1084 babies), intraventricular haemorrhage (IVH) (pooled OR 0.41, 95% CI 0.24–0.69; 5 studies, 621 babies) and severe IVH (grade 3–4) (pooled OR 0.40, 95% CI 0.20–0.79; 4 studies, 491 babies). One study found a significant reduction in the incidence of babies with Apgar score < 7 associated with corticosteroid therapy (OR 0.45, 95% CI 0.28–0.70; 527 babies). In another study, no significant differences between exposed and control groups were observed in the need for mechanical ventilation (OR 0.30, 95% CI 0.08–1.07; 121 babies) nor in the duration of mechanical ventilation (MD -2.00, 95% CI -4.23–0.23; 88 babies). No significant differences were observed in periventricular leukomalacia (pooled OR 0.74, 95% CI 0.26–2.09; 3 studies, 419 babies), neonatal sepsis (pooled OR 1.03, 95% CI 0.72–1.48; 5 studies, 1084 babies), NEC (pooled OR 1.33, 95% CI 0.78–2.26; 5 studies, 1084 babies), surfactant use (pooled OR 0.93, 95% CI 0.67–1.30; 3 studies, 720 babies) or chronic lung disease/bronchopulmonary dysplasia (BPD) (pooled OR 0.66, 95% CI 0.38–1.14; 3 studies, 427 babies).

Long-term morbidity: One small study that followed participants through childhood was unable to show any difference in incidence of cerebral palsy (OR 0.35, 95% CI 0.07–1.67; 72 children) or neurodevelopmental outcome (general development quotient) at the ages of 1 year (MD 6.00, 95% -9.94 to 20.94; 72 children) and 3 years (MD 13.00, 95% CI -3.75 to 29.75; 72 children).

Clinical chorioamnionitis

Fetal and neonatal death: Antenatal corticosteroid therapy in women with clinical chorioamnionitis was not associated with a significant difference in neonatal mortality (pooled OR 0.77, 95% 0.36–1.65; 3 studies, 247 babies).

Severe neonatal morbidity: Corticosteroid therapy in women with clinical chorioamnionitis was not associated with significant differences in RDS (pooled OR 0.73, 95% CI 0.73–1.12; 4 studies, 417 babies), neonatal sepsis (pooled OR 0.94, 95% CI 0.40–2.18; 2 studies, 150 babies) or NEC (pooled OR 2.63, 95% CI 0.72–9.68; 2 studies, 150 babies). Significant reductions in IVH (pooled OR 0.36, 95% CI 0.16–0.82; 3 studies, 318 babies), severe IVH (pooled OR 0.29, 95% CI 0.10–0.89; 3 studies, 318 babies) and periventricular leukomalacia (pooled OR 0.35, 95% CI 0.14–0.85; 3 studies, 318 babies) were observed among babies of mothers who were treated with antenatal corticosteroids. In one study, corticosteroid therapy significantly decreased the need for mechanical ventilation (OR 0.05; 95% CI 0.00–0.94; 93 babies), but had no significant effect on the duration of mechanical ventilation (MD -2.00, 95% CI -4.23 to 0.23; 88 babies). No significant differences were observed in the frequencies of chronic lung disease/BPD (pooled OR 0.91, 95% CI 0.44–1.86; 3 studies, 232 babies).

Clinical and/or histological chorioamnionitis

Fetal and neonatal death: Corticosteroid treatment in mothers with clinical and/or histological chorioamnionitis was associated with significant reductions in neonatal mortality (pooled OR 0.54, 95% CI 0.38–0.76; 7 studies, 1403 babies).

Severe neonatal morbidity: Corticosteroid therapy was associated with significant reductions in RDS (pooled OR 0.62, 95% CI 0.49–0.78; 7 studies, 1501 babies), IVH (pooled OR 0.39, 95% CI 0.25–0.61; 6 studies, 939 babies), severe IVH (grade 3–4) (pooled OR 0.36, 95% CI 0.20–0.65; 5 studies, 854 babies) and periventricular leukomalacia (pooled OR 0.47, 95% CI 0.24–0.90; 4 studies, 737 babies). One study found a significantly decreased need for mechanical ventilation (OR 0.18, 95% CI 0.06–0.57; 214 babies) in babies of treated women, but corticosteroid therapy had no significant effect on the duration of mechanical ventilation (MD -2.00, 95% CI -4.23 to 0.23; 88 babies). No significant difference was observed in neonatal sepsis (pooled OR 1.02, 95% CI 0.73–1.42; 5 studies, 1234 babies), NEC (pooled OR 1.49, 95% CI 0.91–2.53; 5 studies, 1234 babies) or chronic lung disease/BPD (pooled OR 0.74, 95% CI 0.48–1.15; 4 studies, 659 babies).

RECOMMENDATION 1.5

Antenatal corticosteroid therapy is not recommended in women undergoing planned caesarean section at late preterm gestations (34–36^{+6} weeks). *(Conditional recommendation based on very low-quality evidence for newborn and maternal outcomes)*

REMARKS

- The GDG noted the paucity of evidence on the balance of benefits versus harms when antenatal corticosteroid is administered to mothers undergoing elective caesarean section (CS) in late preterm. The group acknowledged that while there might be some benefits, there might also be harms. Reference was made to the overall evidence on antenatal corticosteroid, which suggests potential harms in late preterm infants, and the fact that the population providing the evidence also included provider-initiated (elective) preterm birth.
- Elective CS should not normally be performed at any gestational age < 39 weeks.
- The GDG considered this to be a research priority but chose to recommend against the practice until further evidence becomes available.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (elective caesarean section in late preterm birth) (EB Table 1h)

A systematic review of randomized and non-randomized studies evaluating the effectiveness of antenatal corticosteroid therapy for reducing adverse newborn outcomes in women undergoing elective caesarean section (CS) in the late preterm period (i.e. > 34 weeks to 36^{+6} weeks of gestation) identified no eligible studies *(30)*. Indirect evidence was extracted from a Cochrane systematic review that assessed the effects of corticosteroid therapy

compared with usual treatment on the prevention of neonatal respiratory morbidity after term elective CS *(31)*. This review included one unblinded randomized trial in the United Kingdom (involving 942 mother and their babies), which compared betamethasone with usual treatment without corticosteroids in women undergoing elective CS *(32)*.

Maternal outcomes

Maternal infectious morbidity: No events were reported for maternal infections, including wound infection.

Infant outcomes

Fetal and neonatal death: No events were reported for perinatal death or neonatal sepsis in either group.

Severe neonatal morbidity: No statistically significant reduction was found in the incidence of RDS (0.2% and 1.1% in corticosteroid-exposed and unexposed infants, respectively; RR 0.32, 95% CI 0.07–1.58), transient tachypnea of the newborn (RR 0.52, 95% CI 0.25–1.11), need for mechanical ventilation (RR 4.07, 95% CI 0.46–36.27), or duration of stay in the NICU (MD -2.14 days, 95% CI -5.58 to 1.30). Antenatal betamethasone was associated with significant reduction in the risk of admission to neonatal special care units (all levels) (RR 0.45, 95% CI 0.22–0.90), and particularly for respiratory complications (RR 0.15, 95% CI 0.03–0.64). The corresponding risk differences were -0.03 (i.e. 3% reduction, 95% CI -5% to -1%) and -0.03 (i.e. 3% reduction, 95% CI -5% to -0%), respectively, underscoring the low rates of the two outcomes. Antenatal betamethasone did not significantly reduce the overall rate of admission to neonatal special care (all levels) for any respiratory or non-respiratory indication (RR 0.81, 95% CI 0.49–1.33).

Long-term morbidity: Academic ability during childhood was reported for 407 infants followed through childhood; there were no clear differences between the comparison groups.

RECOMMENDATION 1.6

Antenatal corticosteroid therapy is recommended in women with hypertensive disorders in pregnancy who are at risk of imminent preterm birth. *(Strong recommendation based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes)*

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 corticosteroid globally, the feasibility of implementing the intervention, and the potential impact on health-care resource use across settings, and therefore made a strong recommendation.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (hypertensive disorders in pregnancy) (EB Table 1i)

In the Cochrane review evaluating the effectiveness of antenatal corticosteroid *(27)*, subgroup analyses were performed to examine its effectiveness in women with hypertensive disorders in pregnancy.

Maternal outcomes

Severe maternal morbidity or death: In the subgroup of women with hypertensive disorders of pregnancy, there were no significant differences in maternal death (RR 0.98, 95% CI 0.06–15.50; 1 study, 218 women), chorioamnionitis (RR 2.36, 95% CI 0.36–15.73; 2 studies, 311 women), puerperal sepsis (RR 0.68, 95% CI 0.30–1.52; 1 study, 218 women) or maternal admission to intensive care unit (RR 0.74, 95% CI 0.26–2.05; 1 study, 218 women) between those who received corticosteroids and those who received placebo or no treatment.

Infant outcomes

Fetal and neonatal death: Among infants of mothers with hypertensive disorders exposed to antenatal corticosteroids, there were significant reductions in neonatal deaths (RR 0.50, 95% CI 0.29–0.87; 2 studies, 278 infants). No statistically significant differences were observed between groups for fetal death only (RR 1.73, 95% CI 0.91–3.28; 3 studies, 331 infants) or combined fetal and neonatal death (RR 0.83, 95% CI 0.57–1.20; 2 studies, 313 infants).

Severe neonatal morbidity: There were significant reductions in RDS (RR 0.50, 95% CI 0.35–0.72; 5 studies, 382 infants) and cerebroventricular haemorrhage (RR 0.38, 95% CI 0.17–0.87; 2 studies, 278 infants). No statistically significant differences were observed between groups for birth weight

(MD -131.72 g, 95% CI -319.68 to 56.24; 1 study, 95 infants).

RECOMMENDATION 1.7

Antenatal corticosteroid therapy is recommended for women at risk of imminent preterm birth of a growth-restricted fetus.
(Strong recommendation based on very low-quality evidence)

REMARKS

- The GDG noted the limited evidence on the benefits of antenatal corticosteroid in this subgroup of women. However, the group placed its emphasis on the overall benefits of antenatal corticosteroid, the potential benefits in terms of reduced handicap among surviving intrauterine growth-restricted (IUGR) infants, and evidence of reduced odds of adverse newborn mortality and morbidity outcomes, and therefore made a strong recommendation.
- The GDG acknowledged the concern about the effect of antenatal corticosteroids on fetal growth, but agreed that there is no evidence to suggest that steroids will perform differently in this subgroup compared to the overall preterm population.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (growth-restricted fetus and small-for-gestational-age infant) (EB Table 1j)

Evidence relating to the effectiveness and safety of antenatal corticosteroid therapy for reducing adverse newborn outcomes in women with small-for-gestational-age (SGA) infants, including intrauterine growth-restricted (IUGR) infants, was extracted from one systematic review of nine observational studies *(30)*. The studies included women who were pregnant with babies diagnosed with IUGR through confirmation of placental insufficiency and those identified as SGA (a total of 2846 mothers and infants). Three of the studies were specifically on IUGR only, five were on SGA infants only, and one study included both IUGR and SGA infants. The studies evaluated betamethasone or dexamethasone compared with no treatment (or incomplete treatment) in women expected to deliver at or before 35 weeks of gestation. All studies were conducted in high-resource countries: Canada (1 study), France (1 study), Italy (2 studies), the Netherlands (3 studies), Sweden (1 study) and the USA (1 study).

Maternal outcomes

Maternal morbidity: There were no significant differences in the rates of chorioamnionitis (OR 0.77, 95% CI 0.36–1.63; 1 study, 220 women) or caesarean section (OR 0.48, 95% CI 0.03–8.68; 1 study, 165 women) between women with SGA or IUGR infants exposed to antenatal corticosteroids versus no antenatal corticosteroids (or incomplete corticosteroid treatment).

Infant outcomes

Fetal and neonatal death: There was no observed difference in perinatal mortality (fetal or neonatal death) between groups in any of the IUGR studies (pooled OR 0.81, 95% CI 0.58–1.04; 4 studies, 504 babies), nor in the majority of reports on SGA infants (pooled OR 0.78, 95% CI 0.58–1.04; 6 studies, 958 babies).

Child death: No significant difference in childhood deaths was observed in the study that reported long-term follow-up (OR 0.79, 95% CI 0.20–3.08; 124 babies).

Severe neonatal morbidity: No significant difference was observed for RDS between treated and untreated groups in any of the IUGR studies (pooled OR 0.81, 95% CI 0.59–1.11; 4 studies, 504 babies), nor in the majority of reports on SGA infants, though pooled analyses showed a trend in favour of antenatal corticosteroid-exposed infants (pooled OR 0.83, 95% CI 0.66–1.05; 8 studies, 1126 babies). No difference was observed in the risk of major cerebral morbidity between corticosteroid-exposed compared with unexposed IUGR infants in two studies (pooled OR 0.86, 95% CI 0.35–2.10; 211 babies), but a reduction in brain lesions was observed for SGA infants who were exposed to antenatal corticosteroids (OR 0.57, 95% CI 0.41–0.78; 5 studies, 761 babies).

There was no significant difference noted in exposed versus control groups for other neonatal outcomes (neonatal sepsis, BPD, NEC, Apgar < 7 at 5 minutes, use of mechanical ventilation, chronic lung disease, or low birth weight defined as < 3rd percentile for gestational age).

Long-term morbidity: Only one study reported on long-term outcomes after antenatal corticosteroid treatment. Survival without handicap at two years was more likely in IUGR infants exposed to antenatal steroids (82% in the exposed versus 65% in the unexposed group: OR 2.55, 95% CI 1.11–5.87; 124 babies). However, physical growth beneath the 10th percentile appears more likely after antenatal steroid exposure (OR 5.20, 95% CI 1.38–19.62).

RECOMMENDATION 1.8

Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes who are at risk of imminent preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control. *(Strong recommendation based on very low-quality evidence)*

REMARKS

- The GDG acknowledged the paucity of evidence on the benefits of antenatal corticosteroid in this subgroup of women. However, the group placed its emphasis on the overall benefits of antenatal steroid in preterm, 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, and therefore made a strong recommendation.
- The group considered the concern about the maternal hyperglycaemic 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 glycaemic 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.
- Delay in fetal lung maturity is generally more frequent in pregnant diabetic women compared with the general obstetric population. Therefore, in pregnant women with poorly controlled diabetes, the use of corticosteroids should also be considered at > 34 weeks of gestation if there is laboratory evidence of fetal lung immaturity.

Summary of evidence

Antenatal corticosteroids versus placebo or no treatment (pre-gestational and gestational diabetes)

A systematic review of randomized and non-randomized studies evaluating the effectiveness of antenatal corticosteroid therapy compared with placebo or no treatment for reducing adverse outcomes in pre-gestational and gestational diabetic women at risk of preterm birth identified no eligible studies *(30)*. Importantly, previous trials on antenatal corticosteroids for reducing adverse outcomes in newborns have generally excluded women with gestational diabetes and diabetes mellitus.

One randomized trial conducted in Brazil compared antenatal betamethasone with no treatment in non-diabetic pregnant women with severe pre-eclampsia between 26 and 34 weeks of gestation *(33)*. This study showed increased risk of gestational diabetes mellitus among women receiving betamethasone compared with the controls (RR 2.71, 95% CI 1.14–6.46; 123 women). However, the reduction in RDS and other adverse outcomes in newborns among women receiving betamethasone in the same study was consistent with the findings of the Cochrane review that showed benefit of antenatal corticosteroids in preterm infants *(27)*.

Additionally, one observational study among 30 women in Mexico reported on glycaemic control following antenatal use of betamethasone in diabetic women at risk of premature rupture of the membranes *(34)*. The study showed that following antenatal betamethasone therapy, 40% of women with diet-treated diabetes required de novo insulin administration, while insulin dose was increased 39–112% in women with diet-plus-insulin-treated diabetes and increased 26–64% among women with type 2 diabetes treated with diet or diet and insulin. The greatest changes occurred between days 2 and 4 following betamethasone treatment.

RECOMMENDATION 1.9

Either intramuscular (IM) dexamethasone or IM betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice when preterm birth is imminent. *(Strong recommendation based on low-quality evidence)*

REMARKS

- The GDG noted that there is no conclusive evidence on the comparative efficacy of dexamethasone and betamethasone that would support a recommendation of one over the other. The group 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 and in WHO's *Managing complications in pregnancy and childbirth: a guide for midwives and doctors (11)*.
- 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 dexamethasone 6 mg IM 12 hours apart or two doses of betamethasone 12 mg IM 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 dose of steroid 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 steroids across settings and emphasized that local protocols on the type and dosing regimen of antenatal steroid should be informed by the preparations that are readily available in the setting. This will not only encourage uptake and ease their use by health-care providers but also avoid incorrect dosing and wastage of resources.
- The panel felt there might be important differences in pharmacological properties of dexamethasone and betamethasone dosage regimens and therefore considered this as a research priority.

Summary of evidence

Different corticosteroid regimens for women at risk of preterm birth (EB Table 1k)

Evidence on the effectiveness and safety of different corticosteroids and different drug regimens was extracted from a Cochrane systematic review that included 12 trials (1557 women and 1661 infants) evaluating antenatal corticosteroid therapy for preterm birth *(35)*.

Ten trials compared dexamethasone with betamethasone and two trials compared different regimens of the same drug in women at high risk of giving birth between 23 and 35 weeks of gestation. In the comparison between dexamethasone and betamethasone, both drugs were administered intramuscularly (IM); betamethasone was given as 24 mg in two to four divided doses 12–24 hours apart and dexamethasone was given as 24 mg (except in one trial which used 16 mg) in two to four divided doses 12 hours apart. However, 6 of the 10 studies in this comparison used two doses of 12 mg betamethasone 24 hours apart and four doses of 6 mg dexamethasone 12 hours apart.

In four of the trials, women may have received repeat doses of corticosteroid. Three of the trials were conducted in the USA, two in France and one trial each in Iran, Israel, the Netherlands, Poland, Taiwan and the United Kingdom, as well as a two-centre study in Italy and Israel.

Dexamethasone versus betamethasone (any dose or regimen)

Maternal outcomes

Pregnancy prolongation: Pregnancy prolongation was reported in only one trial with results reported separately for women with intact and ruptured membranes. For women with ruptured membranes, the mean interval between hospital admission and birth was identical (7.1 days) in the two groups (MD 0.00 days, 95% CI -0.99 to 0.99; 120 women). However, for women with intact membranes, pregnancy was prolonged for a mean difference of 7 days in the dexamethasone group compared with the betamethasone group (MD 7.0 days, 95% CI 5.56 to 8.44; 120 women).

Infant outcomes

There were no significant differences in most critical infant outcomes between groups receiving dexamethasone and those receiving betamethasone.

Neonatal death: Neonatal death was similar in the two groups (RR 1.41, 95% CI 0.54–3.67; 4 studies, 596 infants).

Severe neonatal morbidity: There were no significant differences in RDS (RR 1.06, 95% CI 0.88–1.27; 5 studies, 753 infants), neonatal sepsis (RR 1.30, 95% CI 0.78–2.19; 2 studies, 516 infants), NEC (RR 1.29, 95% CI 0.38–4.40; 3 studies, 598 infants), retinopathy of prematurity (RR 0.93, 95% CI 0.59–1.47; 2 studies, 516 infants), periventricular leukomalacia (RR 0.83, 95% CI 0.23–3.03; 4 studies, 703 infants) or BPD (RR 2.50, 95% CI 0.10–61.34; 2 studies, 464 infants). The use of dexamethasone was associated with a reduction in the frequency of any IVH (all grades) (RR 0.44, 95% CI 0.21–0.92; 4 studies, 549 infants), but no difference was observed between the drugs for severe IVH (RR 0.40, 95% CI 0.13–1.24; 4 studies, 549 infants).

There was no significant difference in the rate of low infant Apgar score (< 7) at 5 minutes after birth (RR 0.97, 95% CI 0.43–2.18; 2 studies, 207 infants) or admission to NICU (RR 1.72, 95% CI 0.44–6.72; 2 studies, 345 infants) between the groups. In one trial (70 infants), the mean duration of NICU stay was reduced by approximately 1 day in the dexamethasone group as compared to the betamethasone group (MD -0.91, 95% CI -1.77 to -0.05).

One trial reported the difference in low infant birth weight (< 2500 g) and identified no significant difference between groups (RR 0.89, 95% CI 0.65–1.24; 105 infants). In addition, in five trials, the mean birth weights in the dexamethasone and betamethasone groups were almost identical (MD 0.01 kg, 95% CI -0.11 to 0.12; 3 studies, 734 infants).

Long-term morbidity: Only one trial (with 12 children) reported assessment of neurosensory disability at 18 months. The trial did not have sufficient statistical power to detect meaningful differences between the comparison groups.

Subgroup analyses were conducted comparing different dosing regimens of dexamethasone and betamethasone. There were no differences between the different dosing regimens with regard to neonatal death or severe infant morbidity. For most outcomes, estimable data were only available for one subgroup, or low event rates meant that studies lacked statistical power to identify possible subgroup differences.

Oral versus intramuscular dexamethasone

One study with data for 183 women compared oral (32 mg 12-hourly) with intramuscular (24 mg 12-hourly) dexamethasone.

Maternal outcomes

No maternal outcomes were reported in this trial.

Infant outcomes

Neonatal death and severe neonatal morbidity: There were no significant differences between groups receiving oral or IM dexamethasone in terms of neonatal death, NEC, IVH or infant birth weight. Neonatal sepsis was increased in the oral compared with the IM dexamethasone group, and for this outcome the difference between groups was significant (RR 8.48, 95% CI 1.11–64.93).

Betamethasone 12 mg 12-hourly versus betamethasone 12 mg 24-hourly

One trial with data for 255 women compared 12 mg doses of betamethasone every 12 hours versus 24 hours.

Maternal outcomes

Maternal morbidity: Maternal postpartum hospital stay was reduced in the group receiving betamethasone 12-hourly as compared to the group receiving 24-hourly treatment, although the magnitude of this difference between groups may not be clinically significant (mean of 2.82 versus 3.55 days; MD -0.73 days, 95% CI -1.28 to -0.18). There was no significant difference observed in the rates of maternal fever > 100.4ºF (RR 0.71, 95% CI 0.25–2.02).

Infant outcomes

Neonatal mortality and early morbidity: There were no significant differences between the two regimens for all newborn critical outcomes reported, although the study lacked statistical power to identify differences between groups for most outcomes.

RECOMMENDATION 1.10

A single repeat course of antenatal corticosteroid is recommended if preterm birth does not occur within 7 days after the initial dose, and a subsequent clinical assessment demonstrates that there is a high risk of preterm birth in the next 7 days. *(Conditional recommendation based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes)*

REMARKS

- The GDG acknowledged the lack of evidence on further reduction of neonatal mortality with the use of repeat corticosteroids. However, the group placed its emphasis on the associated further reduction in the respiratory morbidity and less surfactant use (which could save costs) and placed lower value on the small reduction in neonatal birth weight, and therefore recommended a single repeat course of steroid. Given that there are likely to be variations in these values across health system settings, the GDG lowered the strength of the recommendation and made it conditional.
- A single course in this context refers to a full dose of antenatal corticosteroid as recommended in this guideline.
- This recommendation should only be applied to women between 24 and 34 weeks of gestation.
- 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 group also noted the variations in the number of courses and doses of betamethasone used, but agreed that the recommendation should align with the previous recommendation on antenatal corticosteroid regimens.

Repeat course(s) versus a single course of antenatal corticosteroids (EB Table 1l)

Data on repeat course(s) compared with a single course of antenatal corticosteroids were extracted from a Cochrane systematic review of 10 trials with data for 4733 women and 5700 babies *(36)*. The review evaluated the use of repeat doses of betamethasone compared with no repeat corticosteroid treatment in women who had received one course of corticosteroid at trial entry and remained at risk of preterm birth for 7 or more days after initial treatment. Studies were mainly conducted in high-resource settings: Australia and New Zealand, Canada, Finland and India (1 study each) and the USA (5 studies). One multicentre trial took place in 20 countries (including a number of middle-income countries): Argentina, Brazil, Bolivia, Canada, Chile, China, Columbia, Denmark, Germany, Hungary, Israel, Jordan, the Netherlands, Peru, Poland, Russia, Spain, Switzerland, the United Kingdom and the USA.

Additional comparisons included a subgroup of women with PPROM, and subgroup analysis compared different dosing regimens and intervals between initial treatment and repeat doses. Women included in the trials were between 23 and 34 weeks pregnant, though the specific criteria varied between studies.

Repeat course(s) of antenatal corticosteroids versus placebo or no treatment

Maternal outcomes

Prolongation of pregnancy: Repeat courses of corticosteroids were not associated with reduction in the rates of preterm birth before 28, 34 or 37 completed weeks of gestation (RR 1.07, 95% CI 0.83–1.38; 2 studies, 1632 women; RR 1.01, 95% CI 0.95–1.07; 4 studies, 2140 women; RR 0.97, 95% CI 0.92–1.02; 2 studies, 1181 women, respectively). Mean gestational age at delivery was not significantly different between comparison groups (MD -0.09 weeks, 95% CI -0.33 to 0.15; 8 studies, 3179 infants).

Maternal infectious morbidity: There were no significant differences between groups for rates of puerperal sepsis (RR 1.15, 95% CI 0.83–1.60; 5 studies, 3091 women) or maternal chorioamnionitis (RR 1.16, 95% CI 0.92–1.46; 6 studies, 4261 women).

Maternal side-effects: Maternal side-effects were not significantly different in the two groups (RR 0.97, 95% CI 0.24–3.90; 2 studies, 1474 women).

Infant outcomes

Fetal and neonatal death: There were no significant differences between groups in terms of fetal deaths (RR 0.82, 95% CI 0.24–2.84; 7 studies, 2755 fetuses), neonatal deaths (RR 0.91, 95% CI 0.62–1.34; 7 studies, 2713 infants) or fetal and neonatal deaths combined (RR 0.94, 95% CI 0.71–1.23; 9 studies, 5554 infants).

Severe neonatal morbidity: A repeat course of antenatal corticosteroids was associated with a reduction in RDS in infants compared with placebo or no treatment (RR 0.83, 95% CI 0.75–0.91; 8 studies, 3206 infants). A repeat course was also associated with a reduction in surfactant use in preterm infants (RR 0.78, 95% CI 0.65–0.95; 9 studies 5525 infants). There was no significant difference in the duration of respiratory support between the groups (MD 0.30 days, 95% CI -0.90 to 1.50; 1 study, 37 infants).

"Serious infant outcome", a composite outcome that variably included infant mortality and serious morbidity outcomes, was significantly reduced in infants of women treated with repeat courses of corticosteroids compared to controls (RR 0.84, 95% CI 0.75–0.94; 7 studies, 5094 infants). However, no significant differences were seen between comparison groups for individual severe infant morbidity outcomes: any grade of IVH (RR 0.94, 95% CI 0.75–1.18; 6 studies, 3065 infants), severe IVH (RR 1.13, 95% CI 0.69–1.86; 6 studies, 4819 infants), NEC (RR 0.74, 95% CI 0.51–1.08; 8 studies, 5394 infants), retinopathy of prematurity (RR 1.02, 95% CI 0.81–1.28; 7 studies, 4883 infants), chronic lung disease (RR 1.06, 95% CI 0.87–1.30; 8 studies, 5393 infants), periventricular leukomalacia (RR 0.77, 95% CI 0.43–1.37; 7 studies, 4888 infants) or systemic neonatal infection (RR 0.93, 95% CI 0.79–1.11; 3 studies, 1544 infants). Rates of admission to NICU were very similar in the two groups (RR 1.01, 95% CI 0.95–1.07; 2 studies, 3448 infants).

Infants whose mothers had received repeat courses of corticosteroids compared to those who had a single course had on average slightly lower birth weight (MD -75.79 g, 95% CI -117.63 to -33.96; 9 studies, 5626 infants). There was no significant difference between groups for frequency of SGA babies (RR 1.18, 95% CI 0.97–1.43; 7 studies, 3975 infants).

Long-term morbidity: Long-term outcomes were also similar in the two groups: survival free of any disability (RR 1.01, 95% CI 0.97–1.05; 2 studies, 3155 children); any neurosensory disability (RR 1.01, 95% CI 0.92–1.11; 2 studies, 1317 children); childhood disability at early childhood follow-up (RR 0.98, 95% CI 0.83–1.16; 1 study, 999 children); or development delay at early childhood follow-up (RR 0.97, 95% CI 0.84–1.13; 3 studies, 3202 children). Rates of blindness and deafness were very similar in the two

groups, as was the frequency of cerebral palsy at early childhood follow-up (RR 1.03, 95% CI 0.71–1.49; 5 studies, 3883 children).

Repeat course(s) of corticosteroids versus placebo or no treatment (PPROM, 7-day versus 14-day interval for repeat course, number of repeat courses)

Maternal and perinatal outcomes: One study with data for 160 women examined outcomes in women following PPROM. There were no significant differences between groups for most of the outcomes reported, including for puerperal sepsis, perinatal mortality, RDS and chronic lung disease. However, rate of chorioamnionitis was increased in women receiving the repeat course(s) of corticosteroids compared with those who received a single course (RR 1.56, 95% CI 1.05–2.31).

Subgroup analysis was conducted to examine whether the interval between one course and the repeat course made a difference (i.e. repeat course after 7 days versus repeat course after 14 days). There were no significant differences between subgroups for chorioamnionitis, fetal and neonatal mortality, or IVH. The results for RDS reflected the findings for the whole sample: both subgroups showed a reduction in RDS in the repeat course(s) group compared to the group receiving a single course of corticosteroids. Similarly, subgroup analysis reflected the findings for the whole sample for infant birth weight: the babies in the repeat course(s) group had slightly lower mean birth weights irrespective of the interval between the initial treatment and the repeat course(s).

Subgroup analysis was also conducted by the number of repeat courses of corticosteroids women in the repeat courses group received. Findings largely reflected the main analysis. For women receiving one repeat course of corticosteroids there were no significant differences between the repeat course and single course groups for most outcomes apart from RDS, which (as in the main analysis) was reduced in the repeat course group (RR 0.85, 95% CI 0.73–0.99; 2 studies, 399 infants). Data from one study indicated that babies exposed to four or more repeat courses of corticosteroids had an increase in the frequency of being small for gestational age compared with those who were exposed to a single course (RR 2.00, 95% CI 1.07–3.73; 368 infants). In the same study, repeat doses were also associated with reduced mean birth weight (MD -161.00 g, 95% CI -290 to -31.48).

Different dosing regimens were also compared. Subgroup interaction tests showed no significant differences between different dosing regimens for any of the outcomes reported, and findings largely reflected the overall findings for the whole sample.

3.1.2 Tocolysis for inhibiting preterm labour and improving newborn outcomes

RECOMMENDATION 2.0

Tocolytic treatments (acute and maintenance treatments) are not recommended for women at risk of imminent preterm birth for the purpose of improving newborn outcomes. *(Conditional recommendation based very low-quality evidence)*

REMARKS

- This recommendation was informed by the lack of substantive benefits of tocolytic treatment compared with no tocolytic treatment, in terms of reducing adverse perinatal and neonatal outcomes. The GDG agreed that prolongation of pregnancy for 2–7 days (which is achievable by few tocolytic agents) is an intermediate outcome that has not been demonstrated to improve critical neonatal outcomes.
- The GDG agreed that in women at risk of imminent preterm birth who have an otherwise uncomplicated pregnancy, the acute use of a tocolytic drug to prolong pregnancy (up to 48 hours) can be considered to provide a window for administration of antenatal corticosteroid and/or in-utero fetal transfer to an appropriate neonatal health-care setting, although there is currently no direct evidence to show that this measure improves neonatal outcomes.
  - When tocolysis is considered in this context, nifedipine (a calcium channel blocker) is the preferred agent. There is considerable variation in the nifedipine regimens used in relevant trials. The most common regimen used in trials for acute tocolytic treatment was 10–30 mg as an initial dose, followed by 10–20 mg every 4–8 hours until contractions ceased or for up to 48 hours. The GDG suggested an initial oral dose of 20 mg followed by 10–20 mg every 4–8 hours for up to 48 hours or until transfer is completed, whichever comes first.
  - Although betamimetics do appear effective in delaying birth for more than 48 hours, they should not be used for tocolysis because of the higher risk of adverse drug reactions, which may sometimes be life-threatening.

- There is no evidence of additional benefit of using a combination of tocolytic agents over single agents. Therefore, when tocolysis is considered, a combination of tocolytic agents should not be used.
- The available evidence regarding the potential risks and the lack of information on the long-term outcomes following tocolysis should be discussed with the woman and her partner in order for them to take an informed decision regarding the woman's care.
- Consideration of the use of tocolytics should be individualized and tocolytics should not be used when there is any obstetric or medical contraindication to prolonging the pregnancy. Specifically, tocolytics may be associated with harm and should not be used in the following conditions:
  - preterm prelabour rupture of membranes (PPROM)
  - chorioamnionitis
  - placenta abruption
  - cardiac disease.

- The GDG agreed that considerable uncertainty still exists around the value of tocolysis for newborns, particularly as it relates to taking advantage of the time gained for administration of antenatal corticosteroids and/or in-utero transfer, and whether a short prolongation of pregnancy of 2–7 days is more advantageous in one setting compared to another. The group considered studies on tocolytics (e.g. calcium channel blocker) + antenatal corticosteroids versus placebo + antenatal corticosteroids for improving neonatal outcomes a research priority. In addition, the GDG stressed the need for systematic collection of data on critical neonatal outcomes following tocolysis.

Summary of evidence

Any tocolytic agent versus placebo or no treatment

Evidence related to the use of tocolytic drugs versus no tocolysis for improving pregnancy outcomes in women with threatened preterm labour was extracted from eight Cochrane reviews examining the relative effects of tocolytic therapies *(37–44)*. Each systematic review originally examined the effectiveness of a particular class of tocolytic agent (as described below), rather than tocolysis as an intervention. Another systematic review examined the use of oral or intravenous (IV) hydration as a treatment for preterm labour *(45)*. The methodology of many of the tocolytic studies was limited by insufficient numbers of participants, lack of comparison with a placebo, and inconsistent use of glucocorticoids. For specific subgroups (e.g. women with multiple pregnancies, PPROM), evidence was sought from commissioned systematic reviews that considered both randomized and non-randomized studies. The summary of evidence for these subgroups is not included in this document as the overall recommendation is not in favour of tocolysis.

Betamimetics versus placebo or no treatment (EB Table 2a)

Twelve trials compared any betamimetics with placebo (1366 women). Eligible women were between 20 and 37 weeks of pregnancy, but the majority of women were recruited after 32 weeks. Three trials included women with PPROM and six included twin pregnancies in addition to singletons. Two trials administered steroids to women in both arms, use of steroids was not clear in one trial, and the remaining trials did not state whether or not women received steroids in addition to tocolytic therapy. Nine trials compared the betamimetic ritodrine with placebo, two compared terbutaline with placebo, and one trial compared isoxsuprine with placebo.

Maternal outcomes

Maternal death: There were no maternal deaths reported in trials that evaluated this outcome (2 studies, 907 women).

Pregnancy prolongation: While there was no observed effect on preterm birth before 37 weeks (RR 0.95, 95% CI 0.88–1.03; 10 studies, 1212 women), betamimetics reduced the chances of women in threatened preterm labour giving birth within 48 hours (RR 0.68, 95% CI 0.53–0.88; 10 studies, 1209 women) and within 7 days of entering the trial (RR 0.80, 95% CI 0.65–0.98; 5 studies, 911 women), compared with women who received placebo.

Adverse drug reaction and side-effects: More women on betamimetics stopped treatment due to adverse drug reaction (RR 11.38, 95% CI 5.21–24.86; 5 studies, 1081 women). Betamimetics were also associated with a number of maternal side-effects, including palpitation (RR 9.91; 95% CI 6.46–15.20; 5 studies, 1089 women) and chest pain (RR 11.29, 95% CI 3.81–33.46; 2 studies, 814 women). In addition, more women in the treatment group experienced headache (RR 4.07; 95% CI 2.60–6.35; 3 studies, 936 women), hyperglycaemia (RR 2.90, 95% CI

2.05–4.09; 1 study, 708 women), hypokalaemia (RR 6.07, 95% CI 4.00–9.20; 1 study, 708 women), dyspnoea (RR 3.86, 95% CI 2.21–6.77; 2 studies, 814 women), nausea or vomiting (RR 1.76, 95% CI 1.29–2.42; 3 studies, 932 women), nasal stuffiness (RR 2.90, 95% CI 1.64–5.12; 1 study, 708 women) and tremor (RR 10.74, 95% CI 6.20–18.59; 1 study, 708 women). There were no observed differences in women for pulmonary oedema, tachycardia, cardiac arrhythmias or hypotension. Myocardial infarction occurred in 6 out of 54 betamimetic-treated women compared with none among the 52 controls.

Infant outcomes

Perinatal, neonatal or infant death: There were no significant differences between comparison groups for perinatal death (RR 0.84, 95% CI 0.46–1.55; 11 studies, 1332 infants), neonatal death (RR 0.90, 95% CI 0.27–3.00; 6 studies, 1174 infants) or infant death (RR 0.51, 95% CI 0.05–5.64; 1 study, 750 infants).

Severe neonatal morbidity: There were no significant differences between comparison groups for any severe neonatal morbidity reported (RDS, NEC, neonatal sepsis or infection, neonatal hypoglycaemia or cerebral palsy). In a small trial, fetal tachycardia was significantly increased in the treatment group (RR 2.40, 95% CI 1.12–5.13; 30 infants).

Calcium channel blocker versus placebo or no treatment (EB Table 2b)

Only two studies (173 women) compared calcium channel blockers (nifedipine) with placebo and only three relevant outcomes were reported. One study included women carrying singleton pregnancies between 30 and 34 weeks of gestation and with intact membranes; the second included women between 28 and 35 weeks, with no further details given.

Maternal outcomes

Pregnancy prolongation: Both studies reported on the rate of preterm birth. In one study, birth before 37 weeks of gestation was significantly reduced in the calcium channel blockers group (RR 0.44, 95% CI 0.31–0.62; 84 women), while in another study, all but 2 of the 89 women included had given birth before 37 weeks (RR 0.96, 95% CI 0.89–1.03). Overall, there was no difference between groups (pooled average RR 0.65, 95% CI 0.18–2.43). Compared with placebo, calcium channel blockers were associated with a significant reduction in the number of women giving birth within 48 hours of recruitment (RR 0.30, 95% CI 0.21–0.43; 2 studies, 173 women).

Adverse drug reaction and side-effects: One study with 89 women reported maternal adverse drug reactions, and these were increased in the calcium channel blockers group compared with placebo: more than half of the women in the tocolysis group had side-effects (flushing, headache and vertigo) compared with none in the placebo group (RR 49.89, 95% CI 3.13–795.02).

Infant outcomes

Infant outcomes were not reported in these studies.

Cyclo-oxygenase (COX) inhibitors versus placebo or no treatment (EB Table 2c)

Three studies involving 106 women included comparisons of indomethacin (a COX inhibitor) with placebo. In two trials, indomethacin was administered orally and in the third as a rectal suppository. Women recruited to these trials were in labour between 23 and 35 weeks of gestation. Women with ruptured membranes were excluded from all three trials and those with multiple pregnancies from two of the trials.

Maternal outcomes

Pregnancy prolongation: In trials comparing COX inhibitors with placebo, findings on pregnancy prolongation were inconsistent. In one study with a small sample size, fewer women who received COX inhibitors gave birth before 37 weeks (RR 0.21, 95% CI 0.07–0.62; 36 women). There were no differences between treatment groups for delivery within 48 hours or within 7 days of initiation of treatment (RR 0.20, 95% CI 0.03–1.28, 2 studies, 70 women; RR 0.41, 95% CI 0.1–1.66, 2 studies, 70 women, respectively). Mean gestational age at birth was increased by 3.53 days in the COX inhibitors group compared with controls (95% CI 1.13–5.92; 2 studies, 67 women).

Maternal morbidity: No significant differences were observed between comparison groups for maternal infection (chorioamnionitis or endometritis: RR 1.94, 95% CI 0.44–8.60; 2 studies, 64 women).

Adverse drug reaction and side-effects: There were no significant differences between women receiving COX inhibitors versus placebo for maternal adverse drug reactions (RR 1.58, 95% CI 0.66–3.78; 3 studies, 101 women).

Infant outcomes

Perinatal death or severe neonatal morbidity: There were no significant differences between groups for perinatal mortality or serious infant morbidity including IVH, neonatal sepsis, NEC, RDS, persistent

pulmonary hypertension of the newborn, or chronic neonatal lung disease; for all of these outcomes, studies lacked sufficient power to demonstrate differences between groups. Admission to NICU was comparable in the two groups (RR 0.80, 95% CI 0.56–1.15; 1 study, 39 infants), as was low infant Apgar score (< 7) at 5 minutes (RR 0.53, 95% CI 0.05–5.34; 1 study, 39 infants).

In two studies with a total sample size of 67, mean infant birth weight was 716.34 g greater in the COX inhibitors group (95% CI 425.52–1007.16).

Magnesium sulfate versus placebo or no treatment (EB Table 2d)

Four trials compared magnesium sulphate with placebo or no tocolytic treatment (346 women). The loading dose of IV magnesium sulfate was 4–5 g and the maintenance dose was 2–4 g per hour. In two of the trials, women with ruptured membranes were explicitly excluded.

Maternal outcomes

Pregnancy prolongation: There was limited evidence that magnesium sulfate was effective in prolonging pregnancy, as compared with no treatment. There was no significant evidence that birth within 24 or 48 hours of trial entry was reduced in the magnesium sulfate group (RR 1.05, 95% CI 0.64–1.74, 1 study, 156 women; RR 0.57, 95% CI 0.28–1.15; 3 studies, 190 women, respectively). There was also no significant difference between groups for the mean interval between trial entry and birth (MD 0.08 days, 95% CI -4.08 to 4.24; 3 studies, 281 women). One trial with a small sample size (65 women) showed a reduction in preterm birth (before 37 weeks of gestation) in the group receiving magnesium sulfate (RR 0.62, 95% CI 0.46–0.83). However, the mean gestational age at birth was higher (approximately 5 days) in the group receiving no active treatment (MD -0.78 weeks, 95% CI -1.40 to -0.17; 3 studies, 281 women).

Maternal morbidity: Serious maternal complications were evaluated in one study and there were no events reported in either comparison group. Three studies reported the frequency of caesarean birth and there were no differences observed between the groups (RR 1.08, 95% CI 0.63–1.85; 280 women).

Adverse drug reaction and side-effects: Four trials reported maternal adverse effects leading to treatment discontinuation and there were no significant differences between groups (RR 1.31, 95% CI 0.01–221.68; 310 women). Maternal tachycardia and hypotension were assessed in one study (156 women) but no events were reported.

Infant outcomes

Perinatal death: Infant mortality was low in these trials and the trials lacked power to identify any possible differences between groups. There were no significant differences between groups receiving magnesium sulfate or no active treatment in terms of fetal deaths (RR 5.70, 95% CI 0.28–116.87; 2 studies, 257 infants), neonatal deaths (RR 1.37, 95% CI 0.48–3.97; 3 studies, 290 infants) or in terms of a composite outcome, including serious neonatal outcomes and death (RR 1.74, 95% CI 0.63–4.77; 3 studies, 292 infants). For all deaths (fetal, neonatal and infant) there was no significant difference between groups, although there was a trend towards fewer deaths in the group not receiving magnesium sulfate (RR 4.56, 95% CI 1.00–20.86; 2 studies, 257 infants).

Severe neonatal morbidity: There was no statistically significant difference between the group receiving magnesium sulfate and the group receiving no active treatment for any of the measures of serious infant morbidity reported: RDS (RR 1.09, 95% CI 0.98–1.22; 3 studies, 289 infants), proven neonatal infection (RR 6.25, 95% CI 0.32–121.14; 1 study, 34 infants), severe IVH (Grade 3 or 4) or periventricular leukomalacia (no events, 1 study, 90 infants), any grade IVH (RR 0.86, 95% CI 0.28 to 2.62; 3 studies, 289 infants), NEC (RR 1.19, 95% CI 0.33 to 4.29; 3 studies, 289 infants), respiratory arrest (RR 3.16, 95% CI 0.13–76.30; 2 study, 156 infants) or use of mechanical ventilation (RR 1.17, 95% CI 0.61–2.24; 2 study, 165 infants). There was also no significant difference between groups for admission to NICU (RR 0.49, 95% CI 0.18–1.32; 2 study, 165 infants).

Oxytocin receptor antagonists versus placebo or no treatment (EB Table 2e)

Three studies involving 691 women compared the use of the oxytocin receptor antagonist atosiban with placebo. The minimum gestational age at recruitment was 20 weeks in all three studies and the maximum varied between 34 and 36 weeks. All three studies excluded women with ruptured membranes and one excluded women with multiple pregnancies.

Maternal outcomes

Pregnancy prolongation: There was an observed reduction in extremely preterm birth, defined as birth before 28 weeks of gestation (RR 3.11, 95% CI 1.02–9.51; 1 study, 501 women), but not preterm birth, defined as birth before 37 weeks (RR 1.17, 95% CI 0.99–1.37; 1 study, 501 women). Compared with placebo there was no observed reduction in birth within 48 hours using oxytocin receptor antagonists for tocolysis (RR 1.05, 95% CI 0.15–7.43; 2 studies, 152 women).

Maternal morbidity or death: There were no maternal deaths reported in any of the studies.

Maternal adverse drug reaction: Maternal side-effects requiring cessation of treatment were significantly increased in those women using oxytocin receptor antagonists (RR 4.02, 95% CI 2.05–7.85; 2 studies, 613 women). There was also a significant increase in maternal drug reactions in the treated arm (RR 1.54, 95% CI 1.02–2.32; 2 studies, 613 women).

Infant outcomes

Perinatal or infant death: There was no difference between treatment groups for neonatal death (RR 4.10, 95% CI 0.88–19.13; 1 study, 583 infants). However, the use of the atosiban was associated with an increase in infant deaths (up to 12 months of age) in one study (RR 6.15, 95% CI 1.39–27.22; 583 infants).

Severe neonatal morbidity: There was no difference in adverse infant outcomes (RDS, IVF, NEC, admission to intensive care).

Nitric oxide donors versus placebo or no treatment (EB Table 2f)

Three trials compared nitric oxide donors with placebo (336 women). One trial used sublingual isosorbide dinitrate and two used glycerine trinitrate transdermal patches. In two of the trials, women with singleton pregnancies were recruited, and in two trials women with ruptured membranes were explicitly excluded. The lowest gestational age at recruitment in the trials was between 24 and 33 weeks and the maximum was between 32 and 36 weeks. For most outcomes a single trial contributed data.

Maternal outcomes

Prolongation of pregnancy: Use of nitric oxide donors was not associated with prolongation of pregnancy for more than 48 hours (RR 1.19, 95% CI 0.74–1.90; 2 studies, 186 women) nor reduced frequency of birth before 28, 34 or 37 completed weeks of gestation (RR 0.50, 95% CI 0.23 to 1.09, 1 study, 153 women; RR 0.93, 95% CI 0.61–1.41, 1 study, 153 women; RR 0.57, 95% CI 0.16 to 2.01, 2 studies, 303 women, respectively).

Adverse drug reaction and side-effects: Two studies (186 women) reported adverse drug reactions. Compared with controls, women in the nitric oxide donors group were more likely to experience adverse reactions (RR 1.49, 95% CI 1.14–1.94). Frequency of individual side-effects, including dizziness, flushing and hypotension, were similar in the two groups, although there was a higher incidence of headache in women in the nitric oxide donors group (RR 1.95, 95% CI 1.31–2.90; 1 study, 153 women).

Severe maternal morbidity: Other relevant outcomes reported included rate of caesarean section – which was not significantly different in women receiving nitric oxide donors (RR 0.47, 95% CI 0.14–1.57; 1 study, 33 women) – and whether women had completed a full course of antenatal corticosteroids – again, there was no significant difference between groups (RR 1.04, 95% CI 0.90–1.20).

Infant outcomes

Perinatal death or severe neonatal morbidity: There were no significant differences between groups for any outcomes relating to serious infant morbidity or mortality. One study with data for 153 infants reported stillbirths unrelated to congenital abnormalities and reported a single event with no significant difference between groups. The rate of neonatal death was also not significantly different in the nitric oxide and control groups (RR 0.43, 95% CI 0.06–2.89; 2 studies, 186 infants). For serious neonatal morbidity, there was no significant difference between groups for RDS (RR 0.47, 95% CI 0.14–1.57; 1 study, 33 infants), IVH (RR 2.14, 95% CI 0.20–23.06; 1 study, 153 infants) or chronic lung disease (RR 0.15, 95% CI 0.02–1.21; 1 study, 153 infants).

There was no significant difference between groups in terms of mean infant birth weight (MD 327.00 g, 95% CI -272.13 to 926.13; 1 study, 33 infants).

Progestational agents versus placebo or no treatment (EB Table 2g)

Four studies involving 300 women considered the effects of progestational agents on preterm labour and birth. Evidence for this question was extracted from a Cochrane systematic review that included eight studies, although four of these did not report the critical outcomes of interest. Women received adjuvant tocolysis in all trials; that is, a progestational agent was offered in addition to a tocolytic agent. The included studies varied in the form of progesterone used, dosage, method of administration, and additional tocolytic agents used.

Maternal outcomes

Prolongation of pregnancy: Fewer mothers who had received progestational agents delivered babies before 37 weeks of gestation (RR 0.62, 95% CI 0.39–0.98; 4 studies, 293 infants). There were no differences between groups for birth within 48 hours

of intervention (RR 0.76, 95% CI 0.38–1.50; 1 study, 110 women). There was no significant difference in the number of babies born before 34 weeks (RR 0.62, 95% CI 0.30–1.27; 1 study, 62 infants) or 35 weeks (RR 0.43, 95% CI 0.12–1.5; 1 study, 60 infants).

Infant outcomes

Perinatal death or severe neonatal morbidity: There were no significant differences in perinatal mortality (RR 0.31, 95% CI 0.01–7.41; 1 study, 83 infants), RDS (RR 0.93, 95% CI 0.06–14.38; 1 study, 83 infants), low birth weight (< 2500 g) (RR 1.01, 95% CI 0.61–1.65; 1 study, 105 infants) or admission to NICU (RR 1.08, 95% CI 0.59–1.97; 2 studies, 187 infants).

No differences were observed between groups for IVH (RR 3.12, 95% CI 0.13–74.76; 1 study, 104 infants), NEC (RR 1.04, 95% CI 0.07–16.18; 1 study, 104 infants), mechanical ventilation (RR 1.18, 95% CI 0.41–3.37; 2 studies, 187 infants) or oxygen requirement on day 7 and day 28 of life (RR 0.69, 95% CI 0.21–2.31, 1 study, 104 infants; and RR 0.42, 95% CI 0.08–2.05, 1 study, 104 infants, respectively).

Infants whose mothers had received progestational agents had a significantly higher average birth weight than those whose mothers had not (MD 324.7 g, 95% CI 155.05–494.34; 2 studies, 143 infants).

Relaxin versus placebo or no treatment (EB Table 2h)

Three studies (149 women) considered the effects of relaxin. All three were quasi-randomized trials and thus were at high risk of bias, had small sample sizes and low event rates. All studies recruited women in preterm labour but excluded women with any complications that necessitated immediate delivery.

Maternal outcomes

Prolongation of pregnancy: One trial reported a significant reduction in the number of women who went on to give birth within 7 days of treatment in the relaxin group (RR 0.50, 95% CI 0.29–0.87; 1 study, 30 women). There were no differences between groups in any of the other relevant outcomes reported, including preterm birth (0.92 95% CI 0.81–1.05; 1 study, 69 women).

Infant outcomes

Perinatal death or severe neonatal morbidity: There were no differences between groups for perinatal mortality (RR 0.83, 0.32–2.15; 1 study, 30 infants), neonatal death (RR 0.80, 0.27–2.41; 1 study, 30 infants), fetal death (RR 1.00, 95% CI 0.07–14.55; 1 study, 30 infants) or low birth weight (< 2500 g) (RR 2.0, 0.43 to 9.32; 1 study, 30 infants).

Intravenous or oral hydration versus bed rest alone or no treatment (EB Table 2i)

A Cochrane systematic review examined the evidence for the use of IV or oral hydration therapy as a treatment for preterm labour *(45)*. Included trials recruited women less than 37 weeks pregnant with intact membranes, preterm contractions and cervical changes to receive oral or IV hydration therapy versus bed rest alone. The review included two studies involving 228 women. Approximately 30% of women from both the intervention and control groups in these trials were treated with tocolytic drugs. There were no significant differences between groups for any relevant outcome reported.

Maternal outcomes

Pregnancy prolongation: There were no differences between groups for rates of preterm birth before 32, 34 or 37 weeks of gestation (RR 0.76, 95% CI 0.29–1.97, 1 study, 110 women; RR 0.72, 95% CI 0.20–2.56, 1 study, 118 women; RR 1.09, 95% CI 0.71–1.68, 2 studies, 228 women, respectively). Hydration had no significant effect on time to delivery in days (MD -0.99 days, 95% CI -7.85 to 5.87; 2 studies, 228 women).

Infant outcomes

Severe neonatal morbidity: For infants, the rates of NICU admission were comparable between the intervention and control groups (RR 0.99, 95% CI 0.46–2.16; 1 study, 118 infants). Other critical outcomes were not reported.

Tocolytic maintenance therapy for preterm labour after first-line tocolysis (EB Tables 2j to 2m)

Available evidence related to the use of tocolytic drugs as maintenance therapy to improve pregnancy outcomes after initial treatment of preterm labour consisted of five systematic reviews of 27 RCTs, each evaluating a particular class of tocolytic agent: oral betamimetics (13 RCTs, 1551 women) *(46)*, terbutaline pump (3 RCTs, 166 women) *(47)*, magnesium as magnesium sulfate, chloride or oxide (4 RCTS, 422 women) *(48)*, calcium channel blockers (6 RCTs, 794 women) *(49)* and oxytocin antagonists (1 RCT, 513 women) *(50)*. The interventions in these studies used different doses, regimens and drug, within each class of tocolytic agent. Most compared maintenance therapy with no treatment or placebo, while others conducted within-class and between-class comparisons of tocolytic agents. All studies were hospital based. Twenty-six were conducted in high-income countries (Croatia, Japan, Netherlands, New Zealand, Turkey, the United Kingdom and the USA) and one in a low-income country (Malaysia).

Tocolytic maintenance therapy versus placebo or no treatment

Maternal outcomes

Severe maternal morbidity or death: Maternal deaths were generally not reported and in those that did report maternal deaths, there were no deaths observed. Serious maternal morbidity was rare, and when reported there were no significant differences between groups for any of the maintenance therapies evaluated.

Pregnancy prolongation: There were no significant differences in the rates of preterm birth before 37 weeks of gestation for women receiving oral betamimetics, magnesium, nifedipine (calcium channel blocker) or atosiban (oxytocin antagonist) as maintenance therapy when compared with placebo or no treatment.

- betamimetics (ritodrine and terbutaline; 6 studies, 644 women): RR 1.11, 95% CI 0.91–1.35
- magnesium (2 studies, 99 women): RR 1.05, 95% CI 0.80–1.40
- calcium channel blockers (nifedipine; 5 studies, 681 women): RR 0.97, 95% CI 0.87–1.09
- oxytocin antagonists (atosiban; 1 study, 510 women): RR 0.89, 95% CI 0.71–1.12.

Compared with placebo or no treatment, none of the maintenance therapies led to a significant reduction in the rates of birth before 28 weeks or 32 weeks of gestation. There was no significant difference in mean gestational age at birth (weeks) for women receiving tocolytic maintenance therapy compared with placebo or no treatment (magnesium: MD -0.55, 95% CI -1.34 to 0.25, 2 studies, 183 women; nifedipine: MD 0.32, 95% CI -0.61 to 1.25, 5 studies, 681 women). Use of nifedipine maintenance therapy was associated with a prolongation of pregnancy after recruitment by 5.35 days on average (95% CI 0.49–10.21), but this therapy did not appear to affect any other measure of pregnancy prolongation. There were no significant effects on frequency of birth within 24 or 48 hours of commencing oral betamimetic maintenance therapy when compared with no active treatment or with nifedipine.

Adverse drug reaction and side-effects: Side-effects (tachycardia, tachypnea, hypotension and palpitations) were more likely to occur in women receiving oral betamimetics (RR 2.13, 95% CI 1.52–2.98, 4 studies, 414 women; RR 3.52, 95% CI 1.20–10.33, 2 studies, 260 women; RR 1.89, 95% CI 1.13–3.19, 2 studies, 166 women; and RR 5.67, 95% CI 1.32–24.40, 1 study, 140 women, respectively), although in two trials only 1 woman out of 141 stopped treatment due to severe side-effects. For other side-effects, no significant differences between groups were identified

Maternal morbidity: There was no difference in maternal readmission for a repeat episode of preterm labour in groups receiving active treatment.

Infant outcomes

Perinatal death or severe neonatal morbidity: There was no statistically significant difference in perinatal mortality between groups receiving maintenance tocolytic therapy and placebo or no treatment.

- betamimetics (ritodrine and terbutaline; 6 studies, 681 infants): RR 2.41, 95% CI 0.86–6.74
- magnesium therapy (1 study, 50 infants): RR 5.00, 95% CI 0.25–99.16
- calcium channel blockers (nifedipine; 2 studies, 466 infants): RR 1.48, 95% CI 0.45–4.86
- oxytocin antagonist (atosiban; 1 study, 512 infants): RR 0.77, 95% CI 0.21–2.83.

There was no observed reduction in severe morbidity for infants receiving any type of maintenance therapy (including rates of RDS, NEC, neonatal sepsis, periventricular haemorrhage, admission to NICU or mean length of NICU stay).

The frequency of low birth weight (< 2500 g) and mean birth weight were not significantly different for infants whose mothers had received maintenance therapy (betamimetics, magnesium sulphate, calcium channel blockers or oxytocin antagonists) compared with infants whose mothers had received placebo or no treatment.

3.1.3 Magnesium sulfate for fetal protection from neurological complications

RECOMMENDATION 3.0

The use of magnesium sulfate is recommended for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy in the infant and child. *(Strong recommendation based on moderate-quality evidence)*

REMARKS

- Evidence suggests that the protective effects of magnesium sulfate on neurological complications (neuroprotection) are likely to be increased at earlier gestational ages. The GDG is aware of an ongoing trial on the neuroprotective effects of magnesium sulfate at gestational ages below 34 weeks.
- Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours. The median time from

magnesium sulfate administration to birth was reported in only two of the trials that generated the evidence (1 hour 38 minutes and 3.7 hours). However, the GDG felt that administering magnesium sulfate at any time from immediately prior to birth, up to 24 hours prior to anticipated birth is appropriate.

- Three dosing regimens (IV 4 g over 20 minutes, then 1 g/hour until delivery or for 24 hours, whichever came first; IV 4 g over 30 minutes or IV bolus of 4 g given as single dose; and IV 6 g over 20–30 minutes, followed by IV maintenance of 2 g/hour) have been tested in the available studies, which – on meta-analysis – show effect on cerebral palsy, and death or cerebral palsy. There was insufficient evidence to recommend one specific dosing regimen over others. The GDG is aware that an individual patient data analysis of these studies is underway, which may affect this guidance in the future.
- This recommendation applies to women carrying either singleton or multiple pregnancies.
- In women at imminent risk of preterm birth, magnesium sulfate should be considered as the preferred option whenever there is a valid obstetric indication (e.g. pre-eclampsia) and where it is considered safe and effective.
- There is a need for further research to establish whether repeated treatment with magnesium sulfate for neuroprotection is appropriate (i.e. in the event that delivery does not occur).

Summary of evidence

Magnesium sulfate versus placebo or no treatment for fetal neuroprotection

Evidence on the use of magnesium sulfate for neuroprotection in preterm infants was extracted from a Cochrane systematic review (five studies including 6145 infants) investigating whether the administration of magnesium sulfate to women at risk of preterm labour conferred neuroprotective advantage to the fetus *(51)*. One trial was conducted in Australia and New Zealand, one in France, two in the USA, and the fifth was a multicentre study conducted in countries across the world. The final "Magpie" study was designed to prevent eclampsia by magnesium sulfate administration, but data relevant to the effect on preterm infants were included in the analysis. All studies were placebo controlled. The gestational age at recruitment to these trials ranged from below 30 weeks up to 37 weeks. Corticosteroids were given to more than 50% of women in three of the trials.

Magnesium sulfate versus no active treatment (all women and babies) (EB Table 3a)

Maternal outcomes

Maternal morbidity or death: There were no significant differences between women receiving magnesium sulfate versus placebo or no active treatment in terms of maternal mortality or serious maternal morbidity in four studies with a total of more than 5000 women. Risks of maternal death, cardiac arrest, respiratory depression or arrest, and admission to intensive care were not significantly different between groups. The cases of maternal deaths and serious morbidity that were recorded were largely confined to the study that recruited women with severe pre-eclampsia rather than those studies that randomized women with preterm labour. There were no significant differences between the groups for rates of postpartum haemorrhage, caesarean births or length of maternal hospital stay.

Maternal adverse effects: Cessation of therapy as a result of maternal adverse effects was increased in the magnesium sulfate group compared with the placebo group (RR 3.26, 95% CI 2.46–4.31; 3 studies, 4847 women). Maternal hypotension (RR 1.51, 95% CI 1.09–2.09; 2 studies, 1626 women) and maternal tachycardia (RR 1.53, 95% CI 1.03–2.29; 1 study, 1062 women) were also more frequent in women who had received magnesium sulfate.

Infant outcomes

Fetal and infant death: For overall infant mortality (including fetal mortality), there was no significant difference between women who had received magnesium sulfate and controls (RR 1.02, 95% CI 0.90–1.15; 5 studies, 6039 infants). Rates for other measures of fetal and infant mortality were also comparable in both groups (i.e. fetal death, infant death during hospitalization, infant death), to the latest age of follow up.

Severe neonatal morbidity and long-term morbidity: There were also no significant differences between groups for a range of composite outcomes (i.e. death or cerebral palsy, death or neurological impairment, death or serious motor dysfunction, and death or major neurological disability). There were no significant differences between women who received magnesium sulfate and those in the control group with regard to infant IVH, periventricular leukomalacia, major or any neurological impairment, blindness or deafness, or developmental delay or

intellectual impairment. There were no significant differences between groups for neonatal convulsions, neonatal hypotonia or requirement for ongoing respiratory support, although there was a trend towards reduced risk in the magnesium sulfate group for the latter outcome (RR 0.94, 95% CI 0.89–1.00; 3 studies, 4387 infants). There was no clear difference in length of infant hospital stay, nor in the incidence of chronic lung disease requiring oxygen at 28 days and at 3 months.

Infants exposed to magnesium sulfate were at reduced risk (39%) of substantial gross motor dysfunction compared to controls (RR 0.61, 95% CI 0.44–0.85; 4 studies, 5980 infants). The risk of cerebral palsy was also significantly reduced (by 30%) in the magnesium sulfate group (RR 0.70, 95% CI 0.55–0.89; 5 studies, 6039 infants).

Magnesium sulfate versus placebo or no treatment (single versus multiple pregnancy) (EB Table 3b)

For all comparisons, the sample size and event rate for multiple pregnancies compared with those for singleton pregnancies were smaller (2 studies, 527 women). There were no clear differences between singleton and multiple pregnancies for most of the critical outcomes reported.

The positive effects of magnesium sulfate on risk of cerebral palsy in singleton pregnancies was not observed in multiple pregnancies (RR 0.52, 95% CI 0.21–1.25; 2 studies, 527 babies), although the point estimate favoured benefit. The effects of magnesium sulfate on overall death rates, on composite outcomes (i.e. death or serious impairment) and on major neurological impairment were comparable for singleton and multiple pregnancies.

Magnesium sulfate versus placebo or no treatment (gestational age at administration) (EB Table 3c)

Subgroup analysis was performed according to gestational age at administration (< 30 weeks versus < 34 weeks at randomization). The evidence on the use of magnesium sulfate at < 30 weeks of gestation as opposed to < 34 weeks was not clear. Although statistical significance was more likely to be demonstrated for outcomes in the trials recruiting women up to 34 weeks of gestation, this was partly due to increased sample size and statistical power. Overall, the subgroup analysis findings largely reflected the findings in the main analysis. However, cerebral palsy was reduced in women randomized to magnesium sulfate versus placebo or no treatment at < 34 weeks of gestation (RR 0.69, 0.54–0.88; 4 studies, 5192 women) but not in women randomized at < 30 weeks (RR 0.86, 0.56–1.31; 2 studies, 1537 women), although the point estimate favoured a reduction in cerebral palsy with the use of magnesium sulfate in this population.

Magnesium sulfate versus placebo or no treatment (with the intention to prevent preterm birth-related neurologic complications) (EB Table 3d)

When the Magpie study (where magnesium sulfate was aimed at preventing eclampsia in women with severe pre-eclampsia) was excluded from the analysis, the findings of the meta-analysis remained consistent for most critical outcomes. When confined to studies where the intention of the treatment was explicitly for neuroprotection, there were no significant differences between groups for overall paediatric mortality, fetal death or infant death. The composite outcome of death or cerebral palsy was significantly reduced in the treated group (RR 0.85, 95% CI 0.74–0.98; 4 studies, 4446 infants). Similarly, the reduction in risk of moderate/severe cerebral palsy in the treated group remained consistent (RR 0.64, 95% CI 0.44–0.92; 3 studies, 4837 infants). For another composite outcome – death or gross motor dysfunction – there was a trend towards reduction in the group receiving magnesium sulfate (RR 0.84, 95% CI 0.71–1.00; 3 studies, 4387 infants).

Regimens of magnesium sulfate for fetal neuroprotection (EB Table 3e)

The route of administration and dose of magnesium sulfate varied in these trials: (i) IV 4 g over 20 minutes, then 1 g/hour until delivery or for 24 hours, whichever came first; (ii) IV 4 g over 10–15 minutes, followed by either IV 1 g/hour for 24 hours, or by IM 5 g every 4 hours for 24 hours; (iii) single dose of IV 4 g over 30 minutes; (iv) single IV bolus of 4 g; and (v) IV 6 g over 20–30 minutes, followed by maintenance infusion of 2 g/hour for 12 hours, with retreatment permitted whenever birth was imminent. All trials with neuroprotective intent used the intravenous route of administration.

There were no clear differences between the various regimens for most of the critical outcomes reported. However, the reduction in cerebral palsy only reached statistical significance for the following subgroups: 4–6 g loading dose plus any maintenance; and 6 g loading dose and higher-dose (2 g/hour) maintenance.

In the subgroup analysis according to whether retreatment was allowed or not after completing a course of therapy, the only trial that used high loading and maintenance doses showed a statistically significant reduction in the incidence of cerebral palsy (RR 0.59, 95% CI 0.40–0.85). This study was responsible for the overall point estimate related

to cerebral palsy in the review. For the composite outcome of death or cerebral palsy, the results were consistent across the two subgroups: retreatment allowed (RR 0.90, 95% CI 0.73–1.10) and retreatment not allowed (RR 0.91, 95% CI 0.74–1.13).

Maternal adverse effects related to magnesium sulfate appear to be dose dependent. However, the available evidence also points to better neuroprotection with higher dosing. Importantly, there is evidence to suggest that a maintenance dose is essential in order to observe an effect. It is unclear whether the effects on cerebral palsy of higher loading and higher maintenance dosing with a repeat treatment are due to the dosage regimen or a reflection of the size of the trial. However, as this protective effect was not demonstrated in terms of incidence of death or cerebral palsy, the relationship to dose is unlikely to be strong.

3.1.4 Antibiotics for women in preterm labour (with and without prelabour rupture of membranes)

RECOMMENDATION 4.0

Routine antibiotic administration is not recommended for women in preterm labour with intact amniotic membranes and no clinical signs of infection. *(Strong recommendation based moderate-quality evidence)*

REMARKS

- It is important that women with any diagnostic or clinical signs of infection are treated accordingly with antibiotics.
- Management of group B streptococcal colonization is not within the scope of this recommendation.
- The GDG placed its emphasis on the potential risk of harm to the baby and placed less value on the minimal benefit to mothers, and therefore recommended against the intervention.

Summary of evidence

Prophylactic antibiotics for women in preterm labour with intact amniotic membranes

Evidence on the use of antibiotics for women in preterm labour with intact amniotic membranes was extracted from a Cochrane systematic review of 14 RCTs involving more than 7800 women *(52)*. Studies were mainly conducted in high-resource settings: six trials in the USA, and one trial each in Canada, Chile, Denmark, Germany, Iran, South Africa and Uruguay, as well as a large multicentre trial with data predominantly from women in the United Kingdom.

Most of the results of meta-analysis were dominated by the findings of this latter placebo-controlled trial with data for more than 6000 women (the ORACLE II trial) *(53)*.

All studies recruited women with uterine contractions and cervical dilatation, with intact membranes and no clinical signs of infection. The mean gestational age at recruitment was between 30 and 32 weeks. Women received only oral antibiotics in three trials, only IV antibiotics in another three trials, and IV followed by oral antibiotics in eight trials. Antibiotics examined included ampicillin (with or without sulbactam or clavulanic acid), amoxicillin (with or without sulbactam or clavulanic acid), erythromycin, clindamycin, mezlocillin, ceftizoxime or metronidazole, mostly as combinations. The duration of treatment varied from 3 to 10 days. In 13 of the 14 trials, antibiotics were administered alongside tocolytic therapy to women in both intervention and control groups, according to local protocol at the study sites. Women participating in most of the trials conducted in the mid-1990s also received corticosteroids.

Any prophylactic antibiotic versus placebo or no antibiotics (EB Table 4a)

Maternal outcomes

Pregnancy prolongation: Overall, there was no clear evidence that prophylactic antibiotics prolong pregnancy. No statistically significant differences were observed in birth prior to 36 or 37 weeks (RR 0.98, 95% CI 0.92–1.05; 10 studies, 7387 women), birth within 48 hours of randomization (RR 1.04, 95% CI 0.89–1.23; 4 studies, 6800 women), birth within 7 days of randomization (RR 0.98, 95% CI 0.87–1.10; 8 studies, 7053 women) or gestational age at birth (MD 0.53 weeks, 95% CI 0.00–1.06; 10 studies, 986 women). However, the interval between randomization and birth was on average 5 days longer among women receiving prophylactic antibiotics (MD 5.59 days, 95% CI 0.31–10.87; 6 studies, 2499 women).

Maternal morbidity: There was a significant reduction in the frequency of maternal infection in the group receiving antibiotics (RR 0.74, 95% CI 0.63–0.86; 10 studies, 7371 women).

Adverse effects: There was no significant difference between groups for maternal adverse drug reaction requiring cessation of treatment (RR 1.32, 95% CI 0.92–1.89; 5 studies, 626 women).

Infant outcomes

Perinatal death: There were no significant differences between groups for perinatal death (RR 1.22, 95% CI 0.88–1.69; 10 studies, 7304 infants),

stillbirth (RR 0.73. 95% CI 0.43–1.26; 8 studies, 7080 infants) or infant death after 28 days (RR 1.06, 95% CI 0.68–1.67; 1 study, 4654 infants). Neonatal death, however, was increased in infants of women receiving antibiotics (RR 1.57, 95% CI 1.03–2.40; 9 studies, 7248 infants).

Severe neonatal morbidity: Overall, there was no evidence that prophylactic antibiotics significantly reduced serious infant morbidity. No significant differences were observed between comparison groups with regard to RDS (RR 0.99, 95% CI 0.84–1.16; 9 studies, 7200 infants), NEC (RR 1.06, 95% CI 0.64–1.73; 6 studies, 6880 infants), neonatal sepsis (RR 0.86, 95% CI 0.64–1.16; 10 studies, 7386 infants), IVH (RR 0.76 95% CI 0.48–1.19; 5 studies, 6813 infants), chronic neonatal lung disease (on ultrasound before hospital discharge) (RR 1.17, 95% CI 0.78–1.76; 1 study, 6241 children) or mechanical ventilation (RR 1.02, 95% CI 1.02, 95% CI 0.84–1.24; 1 study, 6241 infants). Admissions to NICU were comparable in the two groups (RR 0.82, 95% CI 0.62–1.10; 5 studies, 6875 infants).

Antibiotics were not associated with a significant reduction in the incidence of low birth weight (< 2500 g) (RR 0.97, 0.81–1.15; 5 studies, 6628 infants). There was also no significant difference between groups in mean infant birth weight (MD 58.38 g, 95% CI -26.24 to 143.00; 12 studies, 7531 infants).

Long-term morbidity: One study in the United Kingdom followed up women and infants for 7 years. At age 7 years, there was no significant difference between children whose mothers had received antibiotics compared with those whose mothers had received placebo with respect to moderate or severe functional impairment (RR 1.07, 95% CI 0.89–1.28; 3052 children). There was a trend towards an increase in any functional impairment (including mild impairment) at age 7 (RR 1.10, 95% CI 0.99–1.23; 3052 children) and cerebral palsy (RR 1.82, 95% CI 0.99–3.34; 3173 children) for those children whose mothers had received antibiotics for preterm labour.

Specific classes of antibiotics versus no antibiotics (EB Table 4b)

The review also examined subgroups comparing different types of antibiotics:

- betalactam antibiotics (e.g. ampicillin, amoxicillin, co-amoxiclav) alone versus no antibiotics
- macrolide antibiotics (e.g. erythromycin) alone versus no antibiotics
- combined macrolide and betalactam antibiotics versus no antibiotics
- antibiotics active against anaerobic bacteria (e.g. clindamycin) versus no antibiotics.

Pregnancy prolongation: There was no statistically significant evidence that any specific class of antibiotics reduced the number of preterm births (< 37 weeks), or delayed birth by 48 hours compared with no antibiotics. While macrolide and betalactam antibiotics had no significant impact on the interval between randomization and birth, three small trials indicated that the mean interval between randomization and birth was increased in women receiving antibiotics active against anaerobic bacteria (MD 10.50 days, 95% CI 4.95–16.06; 293 women).

Adverse effects: There was no evidence that maternal adverse drug reactions were significantly increased with the use of any particular class of antibiotic.

Perinatal or infant death: For stillbirth, perinatal, neonatal and infant death, there were no statistically significant subgroup differences, although there were few events in some subgroups and many effect estimates were imprecise.

Severe neonatal morbidity: There was no evidence of subgroup differences for RDS, NEC or IVH.

Long-term morbidity: Long-term morbidity outcomes were measured in a single factorial study; there was no evidence that different antibiotics had a differential impact on moderate or severe functional impairment, or any functional impairment when children were 7 years of age. Compared with placebo, there was an increased risk of cerebral palsy observed at 7 years in association with macrolide and betalactam antibiotics combined (erythromycin plus co-amoxiclav) (RR 2.83, 95% CI 1.02–7.88; 1 study, 1052 children).

RECOMMENDATION 5.0

Antibiotic administration is recommended for women with preterm prelabour rupture of membranes. *(Strong recommendation based moderate-quality evidence)*

REMARKS

- In order to avoid inadvertent antibiotics administration to women with intact amniotic membranes, antibiotics should not be prescribed unless a definite diagnosis of preterm prelabour rupture of membranes (PPROM) has been made. Therefore, a policy of prescribing antibiotics for women with PPROM should be accompanied by a protocol for reliably diagnosing PPROM.
- Women should be monitored for signs of clinical chorioamnionitis.

Summary of evidence

Prophylactic antibiotics for women with preterm prelabour rupture of membranes

Evidence on the use of antibiotics for women with PPROM was extracted from a Cochrane review that included 22 RCTs and a total of more than 7000 women *(54)*.

Data were mainly for women cared for in high-resource settings: 14 trials in the USA, and one trial each in Denmark, Finland, Germany, Spain, Turkey, Zimbabwe, as well as two multicentre trials, one mostly recruiting women from Chile and the other one from the United Kingdom. Most of the results were dominated by the findings of the United Kingdom trial with data for more than 4800 women (the ORACLE I trial) *(55)*.

Most women recruited into the trials were not in active labour. Trials recruited women between 20 and 37 weeks of gestation. For the 16 placebo-controlled trials, women received oral antibiotics in three trials, IV antibiotics in four trials, and IV therapy followed by oral antibiotics in the remaining trials. Ten of these trials examined broad-spectrum antibiotics and five compared macrolide antibiotics (erythromycin) with placebo. In some trials combinations of different drugs were used. The duration of the course of antibiotics varied considerably across trials, from two doses through to continued antibiotic therapy until delivery.

Any prophylactic antibiotic versus placebo or no antibiotics (EB Tables 5a)

Maternal outcomes

Pregnancy prolongation: Compared with placebo, there was no statistically significant evidence that antibiotics reduced the likelihood of preterm birth (< 37 weeks) (RR 1.00, 95% CI 0.98–1.03; 3 studies, 4931 women). Antibiotics were associated with a reduction in the chances of women giving birth within 48 hours (RR 0.71, 95% CI 0.58–0.87; 7 studies, 5927 women) and within 7 days (RR 0.79, 95% CI 0.71–0.89; 7 studies, 5965 women).

Maternal death: There were no maternal deaths in any of the three trials that reported this outcome (763 women).

Maternal infectious morbidity: Fewer women in the group receiving antibiotics developed chorioamnionitis (RR 0.66, 95% CI 0.46–0.96; 11 studies, 1559 women). Four studies with data for 5547 women reported on maternal infection following delivery (before hospital discharge); there was no significant difference between groups for this outcome (RR 0.91, 95% CI 0.8–1.02).

Maternal adverse effects: No women were reported to have suffered a major adverse drug reaction (3 studies, 5487 women).

Infant outcomes

Perinatal death: There was no significant difference between groups in terms of perinatal death (RR 0.89, 95% CI 0.74–1.08; 18 studies, 6872 infants). In a sensitivity analysis including only placebo-controlled trials, the difference between groups remained non-significant (RR 0.93, 95% CI 0.76–1.14; 12 studies, 6301 infants).

Severe neonatal morbidity: Infants whose mothers received antibiotics had a reduced risk of infection, including pneumonia (RR 0.67, 95% CI 0.52–0.85; 12 studies, 1680 infants), and a reduced risk of having a positive blood culture (RR 0.79, 95% CI 0.63–0.99; 3 studies, 4961 infants). Infants whose mothers received antibiotics were also at reduced risk of major cerebral abnormality (RR 0.81, 95% CI 0.68–0.98; 12 studies, 6289 infants). In one study, antibiotics slightly reduced the risk of the infant requiring treatment with a surfactant (RR 0.83, 95% CI 0.72–0.96; 1 study, 4809 infants). There were no significant differences between groups receiving or not receiving antibiotics with regard to RDS (RR 0.95, 95% CI 0.83–1.09; 12 studies, 6287 infants), NEC (RR 1.09, 95% CI 0.65–1.83; 11 studies, 6229 infants) or need for mechanical ventilation (RR 0.90, 95% CI 0.80–1.02; 2 studies, 4924 infants). There were no instances of neonatal encephalopathy in one trial with a small sample size reporting this outcome.

Admissions to the NICU were similar in the two groups (RR 0.98, 95% CI 0.84–1.13; 4 studies, 5023 infants). Data on length of NICU stay were reported in three trials with small sample sizes; infants in the group whose mothers received antibiotics, on average, had five fewer days in special care (MD -5.05 days, 95% CI -9.77 to -0.33; 225 infants). Antibiotics were not associated with a reduction in the incidence of low birth weight (< 2500 g) (RR 1.00, 0.96–1.04; 2 studies, 4876 infants). Mean birth weight was slightly increased in those infants whose mothers had received antibiotics (MD 53.83 g, 95% CI 7.06–100.60; 12 studies, 6374 infants).

Long-term morbidity: One study followed up women and infants for seven years. At age 7, there were no significant differences in serious disability between children whose mothers had received antibiotics in pregnancy versus placebo (RR 1.01, 95% CI 0.91–1.12; 3171 children).

RECOMMENDATION 5.1

Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes *(Conditional recommendation based on moderate-quality evidence)*

REMARKS

- The GDG acknowledged the paucity of evidence from the subgroup analysis to demonstrate comparative effectiveness of different classes and regimens of antibiotics used for prophylaxis in women with preterm prelabour rupture of membranes (PPROM). However, the choice of erythromycin was based on the findings of a study (the ORACLE I trial) with over 2000 women, which showed that erythromycin lessens the risk of necrotizing enterocolitis (NEC) in the newborn compared to co-amoxiclav. The recommendation was made conditional because antibiotic choice may be dependent on local availability of the drug and sensitivities of prevalent organisms.
- For antibiotic prophylaxis in women with PPROM, oral erythromycin 250 mg four times a day for 10 days (or until delivery) should be used. The choice of this regimen was informed by the regimen used in the ORACLE I trial.
- The management of group B streptococcal colonization is outside the scope of this guideline. However, when considering colonization with group B streptococcus, management decisions should be taken based on adequate microbiological coverage and sensitivities.

RECOMMENDATION 5.2

The use of a combination of amoxicillin and clavulanic acid ("co-amoxiclav") is not recommended for women with preterm prelabour rupture of membranes. *(Strong recommendation based moderate-quality evidence)*

REMARKS

- This recommendation was based on the increased risk of NEC with co-amoxiclav when compared with placebo and with erythromycin.
- Where organisms are sensitive to other antibiotics, it would seem sensible to avoid using co-amoxiclav during pregnancy.
- Penicillins (excluding amoxiclav) were used in the pooled trials that showed benefits of antibiotics in this context. Therefore, where erythromycin is not available, penicillin (such as amoxicillin) can be used.

Summary of evidence

Regimens of prophylactic antibiotics for women with PPROM (EB Tables 5b to 5d)

The Cochrane review *(54)* also examined subgroups comparing different types of antibiotics:

- all penicillins (except co-amoxiclav) versus placebo
- beta-lactam antibiotics (including co-amoxiclav) versus placebo
- macrolide antibiotics (including erythromycin) versus placebo
- other antibiotics versus placebo
- erythromycin versus co-amoxiclav
- 3-day versus 7-day regimens of ampicillin.

Perinatal death: There was no statistically significant evidence that the type of antibiotic used had an impact on perinatal death compared with placebo (i.e. there were no significant differences between groups for any of the subgroups examined).

Severe neonatal morbidity: While there were no significant differences between groups for most types of antibiotics compared with placebo, risk of NEC was increased for those infants whose mothers had received beta-lactam antibiotics (including co-amoxiclav) (RR 4.72, 95% CI 1.57–14.23; 2 studies, 1880 infants). The risk of other neonatal infections, including pneumonia, appeared to be reduced in the infants whose mothers received broad-spectrum penicillins (excluding co-amoxiclav) compared with placebo (RR 0.30, 95% CI 0.13–0.68; 5 studies, 521 infants), but differences were not significant for other subgroups. Similarly, all penicillins (excluding co-amoxiclav) were associated with reduced occurrence of major cerebral abnormality on ultrasound, but the differences were not significant for other subgroups.

When erythromycin was compared with co-amoxiclav in one study with data for more than 2000 women and infants, there were no significant differences for perinatal mortality or for the most serious neonatal morbidity outcomes (i.e. perinatal death, RDS, treatment with surfactant, major cerebral abnormality on ultrasound before discharge, NICU admission and serious childhood disability at 7 years). However, women in the erythromycin group were at slightly increased risk of birth within 48 hours of receiving the antibiotic (RR 1.14, 95% CI 1.02–1.28; 1 study, 2395 women). However, birth before 37 weeks of gestation was comparable between the erythromycin and co-amoxiclav groups. Infants whose mothers had received erythromycin rather than co-amoxiclav were at significantly reduced risk of NEC (RR 0.46, 95% CI 0.23–0.94; 1 study, 2395 women).

One trial with data for 82 women compared 3- versus 7-day regimens. The study did not have sufficient statistical power to identify any significant differences for most outcomes.

The overall quality of the evidence varied across the subgroup comparisons. For comparisons of all penicillins (except co-amoxiclav) versus placebo, and for other antibiotics versus placebo, the quality of evidence was rated as low to high. The quality was rated as moderate for all outcomes reported in the comparison of macrolide antibiotics (including erythromycin) versus placebo and for most outcomes reported in the comparison of beta-lactam antibiotics (including co-amoxiclav) versus placebo. For the comparison between erythromycin versus co-amoxiclav, the quality of evidence was rated as moderate to high, while for 3- versus 7-day regimen comparisons, it was mostly rated as low.

3.1.5 Optimal mode of birth for women in refractory preterm labour

RECOMMENDATION 6.0

Routine delivery by caesarean section for the purpose of improving preterm newborn outcomes is not recommended, regardless of cephalic or breech presentation. *(Conditional recommendation based very low-quality evidence)*

REMARKS

- There is insufficient evidence to support the routine delivery of preterm infants by caesarean section instead of vaginal delivery, regardless of fetal presentation.
- Caesarean section should only be performed for obstetric indications.

Summary of evidence

Planned immediate caesarean section versus vaginal delivery for preterm birth (EB Table 6a)

Evidence on the optimal mode of delivery for the preterm infant was extracted from one Cochrane systematic review of four trials involving a total of 116 women *(56)*. These trials compared two policies for delivery of the preterm infant: planned immediate caesarean section (CS) versus vaginal delivery for women with refractory preterm labour with singleton pregnancies. One trial was conducted in Singapore, one in the United Kingdom and two in the USA. One of the trials included women with cephalic presentation only, while three included women with breech presentation only. All women were in labour (experiencing regular contractions) at recruitment, and all were less than 37 weeks pregnant. All four trials were stopped early, due to difficulties with recruitment.

Maternal outcomes

Severe maternal morbidity: Women with breech presentation were more likely to experience major postpartum complications in the immediate CS group compared to those in the vaginal delivery group (RR 7.21, 95% CI 1.37–38.08; 3 studies, 78 women). Women with breech presentation and in the CS group were at higher risk of puerperal pyrexia (RR 2.98, 95% CI 1.18–7.53; 2 studies, 51 women). No woman with cephalic presentation (by either mode of delivery) had major complications or any reported maternal morbidity (1 study, 38 women).

Overall, there was no significant difference between groups for rates of maternal wound infection (RR 1.16, 95% CI 0.18–7.70; 3 studies 103 women), although for women with breech presentation, the risk of other maternal infection was increased among women in the CS group (RR 2.63, 95% CI 1.02–6.78; 2 studies, 65 women). Another outcome reported in these trials was length of maternal hospital stay: there was no difference between women in the two trial arms in the proportion of women with a hospital stay longer than 10 days (RR 1.27, 95% CI 0.35–4.65; 3 studies, 78 women).

Timing of birth after trial entry: Two trials (both recruiting women with breech presentation) reported delivery within 7 days of entry to trials: out of 51 women, all but one had delivered within this time.

Infant outcomes

Perinatal death: Perinatal mortality was reported in three trials comparing immediate CS versus vaginal delivery, with data for 89 infants. There was no statistically significant difference between groups (RR 0.29, 95% CI 0.07–1.14).

Severe neonatal morbidity: There were no cases of head entrapment in any of the trials, and event rates were low for cord prolapse, with no significant differences between women randomized to immediate CS versus vaginal delivery for this outcome (RR 0.25, 95% CI 0.03–1.92; 4 studies, 116 women). One study with a small sample size reported rates of birth asphyxia: there was no significant difference between groups (RR 1.63, 95% CI 0.84–3.14; 12 infants). There were no significant differences between groups in rates of RDS (RR 0.55, 95% CI 0.27–1.10; 3 studies, 103 women) or neonatal seizures (RR 0.22, 95% CI 0.01–4.32; 3 studies, 77 infants). There were few data on hypoxic ischemic encephalopathy and intracranial pathology and no significant differences between groups for

either outcome (RR 4.0, 95% CI 0.2–82.01, 1 study, 12 infants; RR 0.92, 95% CI 0.27–3.14, 4 studies 110 infants, respectively). One study reported birth injury following breech presentation: there was no significant difference between groups for this outcome (RR 0.56, 95% CI 0.05–5.62; 38 infants).

There were no significant differences between immediate CS and vaginal delivery for rates of NEC (RR 6.67, 95% CI 0.39–114.78; 1 study, 12 infants), proven neonatal infection (RR 0.76, 95% CI 0.12–4.66; 3 studies, 103 women) or neonatal jaundice (RR 0.92, 95% CI 0.57–1.48; 3 studies, 103 women), although these outcomes were reported infrequently.

The number of infants requiring mechanical ventilation and the mean number of days infants used mechanical ventilation were not significantly different (RR 1.87, 95% CI 0.71–4.88 and MD 18.26 days, 95% CI -19.90 to 56.42, respectively; 1 study, 12 infants).

There was no significant difference between groups for low infant Apgar score (< 7) at 5 minutes (RR 0.83, 95% CI 0.43–1.6; 4 studies, 115 infants).

Long-term morbidity: Abnormal childhood follow-up (not defined) was reported in one trial: there were no significant differences between groups (RR 0.65, 95% CI 0.19–2.22; 38 children).

Optimal mode of birth by gestational age

Subgroup analysis by gestational age was not performed in the Cochrane systematic review due to small sample sizes. Two of the included trials recruited pregnant women up to 36 weeks of gestation (66 infants), while the other two had upper limits of 32 weeks (12 infants) and 33 weeks (38 infants).

Severe maternal morbidity: No differences were observed between caesarean and vaginal birth groups for major postpartum complications according to gestational age.

Perinatal death: There were no significant differences in perinatal deaths in infants delivered by planned CS or vaginal birth between 26 and 32 weeks of gestation (12 infants, breech presentation: RR 0.50, 95% CI 0.02–10.34), between 26 and 33 weeks (38 infants, cephalic presentation: RR 0.33, 95% CI 0.03–3.29) or between 28 and 36 weeks (38 infants, breech presentation: RR 0.22, 95% CI 0.03–1.73).

3.2 Newborn interventions

3.2.1 Thermal care for preterm newborns

RECOMMENDATION 7.0

Kangaroo mother care is recommended for the routine care of newborns weighing 2000 g or less at birth, and should be initiated in health-care facilities as soon as the newborns are clinically stable. *(Strong recommendation based on moderate-quality evidence)*

REMARKS

- The definition of Kangaroo mother care (KMC) is care of preterm infants carried skin-to-skin with the mother. Its key features include early, continuous and prolonged skin-to-skin contact between the mother and the baby, and exclusive breastfeeding (ideally) or feeding with breastmilk.
- Evidence for this recommendation was based on facility-based studies, mainly from low- and middle-income countries.
- There is insufficient evidence to make a recommendation to provide KMC to unstable neonates.
- Health system issues relating to KMC – such as health system requirements, human resources and their competencies, criteria for discharge and follow-up – should be included in the manual or guidance for implementation.
- Given that there is currently no evidence suggesting the need for any change in the recommendation, the existing criteria for discharge should continue to be applied.

Summary of evidence

Kangaroo mother care (KMC) versus conventional care for routine care of stable newborns (EB Table 7a)

Evidence on the effectiveness of KMC was extracted from an updated Cochrane review (13, 16). The review included 18 trials that evaluated the effects of KMC versus conventional care on neonatal mortality and morbidity outcomes. Thirteen of these trials were conducted in low- and middle-income countries (LMICs) while five were conducted in high-income countries (HICs). Five studies included babies born following multiple pregnancies (in addition to singletons) while six trials provided KMC only to babies weighing < 1500 g at birth. The review examined the effects of KMC practiced either intermittently or continuously with a view to answering specific questions: whether KMC can be started early before stabilization of the baby; for what

minimum duration per day KMC should be practiced; at what level of care and what resources are needed for effective KMC; what criteria have been used for discharge of babies initiated on KMC in the facility; and what is the optimum frequency of follow-up contact after discharge.

Neonatal death: Compared with conventional care, KMC was associated with a 40% lower risk of mortality at discharge or 40–41 weeks postmenstrual age (RR 0.60, 95% CI 0.39–0.92; 8 studies, 1736 babies). A comparable result was obtained when analysis was limited to the seven trials conducted in LMICs. In these seven trials, KMC was associated with a 43% reduction in mortality at discharge or 40–41 weeks postmenstrual age, compared to conventional care (RR 0.57, 95% CI 0.37–0.89). The only study from HICs that evaluated this outcome found no protective effect for KMC compared with conventional care.

KMC, as compared with conventional care, was also associated with a 33% lower risk of all-cause mortality for infants at the latest follow-up (RR 0.67; 95% CI 0.48–0.95; 11 studies, 2167 babies). Nine studies conducted in LMICs showed that KMC resulted in a 35% reduction in the risk of mortality at the latest follow-up (RR 0.65, 95% CI 0.45–0.93; 2036 babies). In the two trials from HICs (with 131 preterm newborns), the evidence of an effect on mortality was inconclusive, with confidence intervals consistent with a possible 71% reduction as well as over five-fold higher risk of mortality at the latest follow-up (RR 1.25, 95% CI 0.29–5.42).

Severe neonatal morbidity: Compared with conventional care, KMC was associated with a 44% reduction in the risk of severe infection at the latest follow-up (RR 0.56, 95% CI 0.40–0.78; 7 studies, 1343 babies). The intervention was also associated with a 55% lower risk of nosocomial infection at the time of discharge or at 40–41 weeks postmenstrual age (RR 0.45, 95% CI 0.27–0.76; 3 studies, 913 babies). All the studies that reported on the risk of hypo- and hyperthermia implemented intermittent rather than continuous KMC. Six studies (with 698 babies) showed that KMC was associated with a 66% lower risk of hypothermia at the time of discharge or at 40–41 weeks postmenstrual age (RR 0.34, 95% CI 0.17–0.67). There was inconclusive evidence on the risk of hyperthermia at the time of discharge or at 40–41 weeks postmenstrual age. The point estimate of data from two studies also suggested a possible reduction in the risk of readmission at the latest follow-up for babies that were provided with KMC (RR 0.60, 95% CI 0.34–1.06).

RECOMMENDATION 7.1

Newborns weighing 2000 g or less at birth should be provided as close to continuous Kangaroo mother care as possible. *(Strong recommendation based on moderate-quality evidence)*

RECOMMENDATION 7.2

Intermittent Kangaroo mother care, rather than conventional care, is recommended for newborns weighing 2000 g or less at birth, if continuous Kangaroo mother care is not possible. *(Strong recommendation based on moderate-quality evidence)*

Summary of evidence

Continuous or intermittent Kangaroo mother care (KMC) versus conventional care

The Cochrane review summarized data on effectiveness by subgroups of studies that had used either continuous or intermittent KMC *(13)*. Continuous KMC is defined as the practice of skin-to-skin care continuously throughout the day without breaking the contact between mother and baby, while intermittent KMC is the practice of skin-to-skin care alternated with the use of either a radiant warmer or an incubator care for the baby.

Continuous KMC practice versus conventional care (EB Table 7b)

Five trials evaluated the effect of continuous KMC practice on neonatal mortality or severe neonatal morbidity.

Neonatal death: Continuous KMC was associated with a 40% lower risk of mortality at the time of discharge or at 40–41 weeks postmenstrual age compared to conventional care (RR 0.60, 95% CI 0.39–0.92; 3 studies, 1117 babies). Continuous KMC was also associated with a 33% reduction in the risk of mortality at the latest follow-up contact, compared with conventional care (RR 0.67, 95% CI 0.46–0.98; 4 studies, 1384 babies).

Severe neonatal morbidity: Only one trial (663 babies) reported the effects of continuous KMC on severe infection at the latest follow-up and the finding was inconclusive (RR 0.69, 95% CI 0.43–1.12). One study reported on the risk of nosocomial infections until the time of discharge or 40–41 weeks postmenstrual age: there was a 51% lower risk with continuous KMC compared to conventional care (RR 0.49, 95% CI 0.25–0.93). The evidence of effectiveness of continuous KMC in terms of reducing the risk of readmission was inconclusive (RR 0.60, 95% CI 0.34–1.06).

Intermittent KMC practice versus conventional care (EB Table 7c)

Thirteen of the 18 identified trials in the main review implemented intermittent KMC.

Neonatal death: From five studies involving 619 babies, there was inconclusive evidence regarding the benefit of intermittent KMC for reducing mortality up to the time of discharge or 40–41 weeks postmenstrual age, compared with conventional care (RR 0.59, 95% CI 0.19–1.81). Seven trials with 783 preterm babies also showed inconclusive evidence of reduction in the risk of mortality at the latest follow-up (RR 0.68, 95% CI 0.26–1.77).

Severe neonatal morbidity: All the studies that reported the effects of KMC on hypo- and hyperthermia used intermittent KMC. There was a 66% lower risk of hypothermia at the time of discharge or at 40–41 weeks postmenstrual age (RR 0.34, 95 CI 0.17–0.67), but no significant reduction in the risk of hyperthermia (RR 0.79, 95% CI 0.59–1.05). Compared with conventional care, intermittent KMC was associated with a 55% lower risk of severe infection at the latest follow-up visit (RR 0.45, 95% CI 0.28–0.73; 6 studies, 680 babies) and 61% lower risk of nosocomial infections at the time of discharge or at 40–41 weeks postmenstrual age (RR 0.39, 95% CI 0.16–0.67; 2 studies, 250 infants).

RECOMMENDATION 7.3

Unstable newborns weighing 2000 g or less at birth, or stable newborns weighing less than 2000 g who cannot be given Kangaroo mother care, should be cared for in a thermo-neutral environment either under radiant warmers or in incubators. *(Strong recommendation based on very low-quality evidence)*

REMARKS

- A thermo-neutral environment was considered to be environmental conditions under which a baby maintains temperature in a normal range at minimum metabolic rate.
- There is insufficient evidence to support superiority of either radiant warmers or incubators over the other for the care of preterm babies. In making any choice between the two devices, the health-care providers' preferences and costs should be considered.
- The selection of a device for creating the thermo-neutral environment, and the strategy for its use, should be carefully assessed in the relevant context, i.e. the patient population (including size, maturity and concurrent illnesses), the physical environment, personnel, cost and other resources.

Summary of evidence

Radiant warmer versus incubator for sick or unstable neonates (EB Table 7d)

Evidence related to the comparative effects of radiant warmers and incubators was obtained from one Cochrane review that compared nursing preterm newborns in radiant warmers (with the baby either naked or clothed) with controls *(57)*. In the control group, the infant was either naked (except for nappies) or clothed and was nursed in an air-heated, single or double-walled incubator, controlled manually or by servo-mechanism. Eight trials involving 156 preterm babies were included in the review and all were conducted in neonatal intensive care units (NICUs) in HICs. Infants recruited into the studies had gestational ages of 28–32 weeks and weighed 1.1–1.6 kg at birth. Exposure to the intervention varied between 1 hour and 3 days in six trials and between 7 and 35 days after birth (or until the baby weighed 1.8 kg) in the remaining trials. In some trials, additional interventions such as humidification or heat shields for the incubators were employed for babies in the control groups, and phototherapy was also provided to some babies in the intervention group. No additional relevant studies after the publication of the Cochrane review were found. Overall the data were limited and the quality of evidence was very low.

Neonatal death: Two trials involving 94 preterm newborns yielded inconclusive evidence on the risk of neonatal mortality for babies nursed under radiant warmers compared with those nursed in incubators (absolute risks: 2.1% versus 10.6%; RR 0.27, 95% CI 0.05–1.59).

Severe neonatal morbidity: One study involving 60 preterm newborns reported risks of sepsis and bronchopulmonary dysplasia (BPD), but there were very few events and the confidence interval was very wide. Two studies (with 90 preterm newborns) showed no significant impact of the intervention on rates of severe intraventricular haemorrhage (IVH) (0% versus 2.2%). The mean time taken to regain birth weight was similar in both trials (MD 0.86 days, 95% CI -1.49 to 3.10 days).

RECOMMENDATION 7.4

There is insufficient evidence on the effectiveness of plastic bags/wraps in providing thermal care for preterm newborns immediately after birth. However, during stabilization and transfer of preterm newborns to specialized neonatal care wards, wrapping in plastic bags/wraps may be considered as an alternative to prevent hypothermia. *(Conditional recommendation based on low-quality evidence)*

Summary of evidence

Plastic wraps or bags before stabilization for thermal care versus conventional thermal care for preterm infants (EB Table 7e)

A systematic review that addressed this question identified 24 hospital-based studies *(58)*. Twenty of these studies involved preterm babies exclusively while the other four had results for term babies. Sixteen of the 20 studies with preterm babies involved very preterm babies with either birth weight < 1500 g or gestational age below 32 weeks, while two included moderately preterm babies (32–34 weeks of gestation) and two involved late preterm babies (34–37 weeks). Nine of the 24 studies were conducted in LMICs. The intervention consisted of wrapping of the neonate in a plastic bag, wrap or cap immediately following vaginal birth or caesarean section (prior to drying), and keeping the bag, wrap or cap on until the neonate had been stabilized or had a normal body temperature. Materials used for wrapping included saran wraps (a transparent polythene film or sheet), shopping bags and other manufactured plastic sheets. In the control group, thermal care was provided using incubators or radiant warmers, or by keeping the baby wrapped in clothes in a warm room. No study compared this intervention with provision of KMC.

Neonatal death: Five trials involving 341 very preterm neonates (< 29 weeks) from HICs showed no significant difference in terms of all-cause neonatal mortality when plastic wrapping was compared with wrapping in a blanket (absolute risks: 16.3% versus 19.4%; RR 0.84, 95% CI 0.54–1.30). When the analysis was restricted to three studies where radiant warmers were used for the control group, the overall effect on neonatal mortality was similar in the intervention and control groups (RR 0.86; 95% CI 0.49–1.49; 290 neonates). A study from Zambia, among 104 newborns born at 26–36 weeks or weighing < 2500 g, found absolute mortality risks of 14.3% versus 5.5% for wrapping versus conventional thermal care although the study lacked sufficient power to detect a statistically significant difference in mortality (RR 2.62, 95% CI 0.72–9.58). Another small trial conducted in Malaysia, among 110 neonates born at 24–34 weeks of gestation admitted to the NICU, showed absolute mortality risks of 10.0% versus 16.7% for wrapping versus conventional thermal care (RR 0.60, 95% CI 0.22–1.64). There were six observational studies that evaluated mortality outcomes comparing plastic wrapping with wrapping in a blanket; the results were again similar (RR 1.10, 95% CI 0.84–1.46; 849 neonates).

Severe neonatal morbidity: Three studies, including one randomized controlled trial (RCT) and two observational studies, examined the impact of wrapping in plastic bags compared with conventional care on the risk of necrotizing enterocolitis (NEC). The RCT involving 110 preterm newborns (born at 24–34 weeks of gestation) had only two reported events – both in the intervention group – and thus lacked power to detect meaningful differences between the groups (RR 5.98, 95% CI 0.29–121.80). Similarly, results from the two observational studies did not demonstrate any significant difference with regard to the risk of NEC in neonates < 1500 g (RR 1.29, 95% CI 0.85–1.97; 273 neonates).

Four studies (including two RCTs from Malaysia and Uruguay) examined the impact of the intervention on severe IVH (grade 3–4). The results from the RCTs showed no statistically significant effects of the intervention on the risk of IVH. The study from Malaysia, which involved 110 preterm newborns < 1000 g, showed no significant difference in the risk of IVH when wrapping in plastic bags was compared to keeping the baby under a radiant warmer (RR 0.30, 95% CI 0.03–2.60). In the study from Uruguay, which compared the intervention with every other means of thermal care, there was a trend towards a reduction in the incidence of IVH (RR 0.38, 95% CI 0.15–1.02; 77 neonates).

Two RCTs conducted in HICs assessed the impact of the intervention on other major brain injuries in preterm neonates born at ≤ 29 weeks of gestation: no evidence of an effect was found (RR 1.10, 95% CI 0.41–2.98; 152 neonates).

An RCT of plastic bags used for neonates with gestational ages of 24–34 weeks in Malaysia found no evidence of a difference in incidence of respiratory distress syndrome (RDS) between the intervention and control groups (RR 1.04, 95% CI 0.78–1.38; 110 neonates). Similarly, an observational study of neonates < 1000 g showed no evidence of a reduced risk of BPD (RR 0.98, 95% CI 0.57–1.69; 209 neonates).

Three RCTs involving 229 very preterm neonates (≤ 29 weeks) showed a 42% reduction in the risk of hypothermia (temperature < 36.5 °C) with plastic bag use compared to controls (absolute risks: 46.0% versus 79.0%; RR 0.58, 95% CI 0.46–0.72). Plastic wraps were also associated with a reduction in risk of hypothermia in more mature preterm neonates: one RCT of preterm neonates born at 24–34 weeks reported a 21% reduction in the risk of hypothermia (RR 0.79, 95% CI 0.67–0.93; 110 neonates). Two RCTs in neonates ranging in gestational age from 26 to 36 weeks showed a 46% reduction in the

risk of hypothermia (RR 0.54, 95% CI 0.36–0.79; 194 neonates). Ten observational studies reporting the risk of hypothermia estimated impacts ranging from no effect to 85% reduction in hypothermia. The results of these observational studies were not pooled because of differences in the definition of hypothermia.

Hyperthermia, defined as temperature ≥ 37.5 °C or 38.0 °C, was reported in nine RCTs but was a rare outcome in all the studies. It was reported in only eight cases out of 286 infants in the intervention group, and none of 312 infants in the control group.

3.2.2 Continuous positive airway pressure and surfactant administration for newborns with respiratory distress syndrome

RECOMMENDATION 8.0

Continuous positive airway pressure therapy is recommended for the treatment of preterm newborns with respiratory distress syndrome. *(Strong recommendation based on low-quality evidence)*

REMARKS

- The GDG felt strongly that the technological context of care, including the ability to monitor oxygen saturation and cardiorespiratory status, must be considered prior to instituting any respiratory intervention (supplemental oxygen, continuous positive airway pressure [CPAP] or ventilator support) to critically ill neonates in less-developed medical settings, as these interventions have the potential to lead to more harm than benefit.
- This recommendation should be implemented in health-care facilities that can provide quality supportive care to newborns.
- If oxygen therapy is to be delivered with CPAP, low concentrations of blended oxygen should be used and titrated upwards to maintain targeted blood oxygen saturation levels (see Recommendation No. 10.1). Where blenders are not available, air should be used; 100% oxygen should never be used because of demonstrable harms.
- Respiratory distress syndrome can be diagnosed on the basis of clinical or radiological criteria.

Summary of evidence

Any continuous positive airway pressure (CPAP) therapy versus oxygen therapy by head box, facemask or nasal cannula for respiratory distress syndrome (RDS) in preterm newborns (EB Table 8a)

Evidence for this recommendation was extracted from a Cochrane review *(59)*. An updated literature search in May 2014 found no additional relevant studies. The review included six trials from HICs, five of which were randomized trials and one quasi-randomized. The trials enrolled preterm babies with radiological or clinical features of RDS, and the interventions included continuous distending pressure (CDP), CPAP using nasal prongs, nasopharyngeal/endotracheal tubes or continuous negative pressure. These were compared with oxygen delivered by head box, facemask or nasal cannula. Antenatal corticosteroids were additionally used in two of the trials and surfactants were used in one.

Neonatal death: Compared to the comparison arm, CPAP was associated with a 48% reduction in overall in-hospital neonatal mortality (17.9% versus 9.1%; RR 0.52, 95% CI 0.32–0.87; 6 studies, 355 preterm babies). There was also a 35% reduction in the risk of the combined outcome of death or the need for assisted ventilation in preterm babies with RDS (RR 0.65, 95% CI 0.52–0.81). Subgroup analysis by gestational age (28–32 weeks and 32–36 weeks) showed no significant differences in RDS-specific in-hospital mortality.

Severe neonatal morbidity: CPAP, as compared to oxygen therapy, was associated with a significantly lower risk of respiratory failure requiring assisted ventilation, but was also associated with a higher risk of pneumothorax and air leaks. In five trials with 314 preterm neonates, respiratory failure requiring assisted ventilation occurred in 36.4% on CPAP compared to 52.5% on oxygen therapy (RR 0.72, 95% CI 0.56–0.91). However, the risk of pneumothorax in the CPAP-treated neonates increased more than two-fold (RR 2.64, 95% CI 1.39–5.04). Similarly, the risk of air leaks was also increased among preterm neonates on CPAP (14.5% versus 6.1% in controls; RR 2.42, 95% CI 1.26–4.65). There was no evidence of significant differences between the groups treated with CPAP or standard oxygen therapy in terms of the need for surfactant therapy (RR 0.43, 95% CI 0.12–1.48) or BPD (RR 1.22, 95% CI 0.44–3.39; 3 studies, 260 preterm neonates).

RECOMMENDATION 8.1

Continuous positive airway pressure therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made. *(Strong recommendation based on very low-quality evidence)*

REMARKS

- In view of the high proportion of neonatal deaths that are caused by respiratory distress syndrome, the GDG made a strong recommendation despite the low quality of the evidence showing the benefits of early continuous positive airway pressure (CPAP) therapy.

Summary of evidence

Early versus late initiation of continuous positive airway pressure (CPAP) therapy for respiratory distress syndrome (RDS) in preterm infants (EB Table 8b)

Evidence on the timing of initiation of CPAP therapy for preterm newborns with RDS was derived from a Cochrane review by Ho et al. *(59)*. This review included five randomized trials and one quasi-randomized trial, all from HICs. The included studies were conducted between the mid-1970s and the early 1980s, before the era of surfactant treatment. Criteria for enrolment differed somewhat between trials but essentially all preterm babies with radiological or clinical features of RDS were included. The intervention involved initiation of CPAP therapy (either with continuous distending pressure or continuous negative pressure) immediately following the diagnosis of RDS, and these neonates required fraction of inspired oxygen (FiO2) between 0.3 and 0.7. In the comparison arm, CPAP was initiated only when RDS was worsening and babies required relatively higher FiO2 (between 0.5 and 1.0). An updated search in May 2014 identified one additional RCT *(60)*, conducted in Iran in 2013. In the study, early CPAP was defined as CPAP initiated within 5 minutes of birth, and late CPAP was that initiated at least 30 minutes after birth. This trial was the largest of all the seven studies included and contributed over 30% of the total preterm newborns in the review.

Neonatal death: Only two trials (involving 61 preterm babies) reported mortality in the neonatal period. The trials suggested no evidence of a reduction in neonatal mortality with early initiation of CPAP as compared to delayed initiation (RR 0.93, 95% CI 0.13–6.81). All seven trials reported the effect of early initiation of CPAP on in-hospital neonatal mortality. However, with a total of only 237 preterm babies included in this analysis, the evidence for mortality reduction from the pooled results was inconclusive: 13.8% of those initiated early on CPAP died in-hospital, as compared to 18.8% of those receiving delayed CPAP (RR 0.70, 95% CI 0.40–1.24).

Severe neonatal morbidity: Six studies (involving 165 neonates) showed that early rather than delayed initiation of CPAP therapy was associated with reduced risk of respiratory failure requiring mechanical ventilation (17.8% versus 31.5%; RR 0.55, 95% CI 0.32–0.96). Only one study *(60)* reported on the need for surfactant therapy and the incidence of sepsis in neonates on early or late CPAP. Early initiation was associated with a 36% lower risk of complications requiring surfactant therapy (RR 0.64, 95% CI 0.44–0.93) and a 54% lower incidence of sepsis (RR 0.46, 95% CI 0.27–0.79). Finally, the incidence of IVH was also lower with the use of early CPAP compared with delayed CPAP (58.3 versus 83.0%, P = 0.037). However, there was no conclusive evidence of reduction in the risks of BPD (RR 0.70, 95% CI 0.12–3.98) or air leaks (RR 0.84, 95% CI 0.37–1.91).

RECOMMENDATION 9.0

Surfactant replacement therapy is recommended for intubated and ventilated newborns with respiratory distress syndrome. *(Conditional recommendation [only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available] based on moderate-quality evidence)*

REMARKS

- The GDG members were of the opinion that the benefits of the intervention in reducing mortality clearly outweighed the possible increased risk of pulmonary haemorrhage.
- The recommendation should be used in higher-level health-care facilities because it applies to preterm newborns with respiratory distress syndrome who have access to intubation and mechanical ventilation.
- In high-income countries, surfactant treatment may reduce overall hospital costs, but this might not be the case in low- and middle-income countries (LMICs).
- In many LMICs, resource implications (both human and material) may make the use of surfactant a lower priority.

Summary of evidence

Surfactant replacement therapy (SRT) for preterm neonates with clinical and/or radiologically established respiratory distress syndrome (RDS)

Two Cochrane reviews that evaluated the effects of SRT on neonatal mortality and morbidity provided evidence for this recommendation. The first, by Seger et al. *(61)*, evaluated the effects of the use of animal-derived surfactants, whilst the second, by Soll *(62)*, focused on the use of protein-free synthetic surfactants; both reviews included studies that compared the treatment to placebo or no treatment. An updated search conducted for both reviews found no additional relevant studies. All included studies were conducted in intensive care units within hospitals in HICs. The interventions included the administration of a single dose or multiple doses of exogenous animal-derived or synthetic surfactants by endotracheal tube for babies with clinical or radiological features of RDS. The comparison groups included babies receiving placebo or no treatment. The results of the two Cochrane reviews were not pooled because of the differences in the source of the surfactants used (animal-derived versus synthetic) and because protein-free synthetic surfactants are no longer commercially available in most countries.

Animal-derived surfactants (EB Table 9a)

The review by Seger et al. *(61)* included 13 RCTs in which preterm neonates with clinical or radiological evidence of RDS were either treated with surfactants from bovine, porcine or amniotic fluid sources or received no surfactant therapy.

Neonatal death: SRT using animal-derived surfactants was found to be associated with lower overall and in-hospital neonatal mortality. Ten trials involving 1469 preterm babies showed a 32% lower risk of overall neonatal mortality, compared with no SRT (19.5% versus 28.4%; RR 0.68, 95% CI 0.57–0.82). SRT with animal-derived surfactants also showed a 37% lower risk of in-hospital neonatal mortality compared with controls (RR 0.63, 95% CI 0.44–0.90; 7 studies, 421 neonates).

Severe neonatal morbidity: Animal-derived surfactant for SRT was associated with a 53% reduction in the risk of air leaks as compared to no surfactant (14.7% versus 31.0%; RR 0.47, 95% CI 0.39–0.58; 7 studies, 1380 neonates). However, no significant differences in the effects on the risks of sepsis (RR 1.14, 95% CI 0.87–1.48), pulmonary haemorrhage (RR 1.29, 95% CI 0.77–2.15), BPD (RR 0.95, 95% CI 0.84–1.08) or severe IVH (RR 0.93, 95% CI 0.79–1.10) were observed between those receiving SRT versus no SRT.

Protein-free synthetic surfactants (EB Table 9b)

In the review by Soll *(62)*, six trials that compared protein-free synthetic surfactants for SRT with no SRT were included. Five of these trials used a surfactant formulation whose production has been discontinued and the other used dry 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine and phosphatidylglycerol preparation.

Neonatal death: Six trials involving 2352 preterm neonates showed that SRT using synthetic surfactants was associated with a 27% lower risk of overall neonatal death when compared to no SRT (RR 0.73, 95% CI 0.61–0.88). These results also demonstrated a 21% lower risk of in-hospital neonatal mortality (RR 0.79, 95% CI 0.68–0.92).

Severe neonatal morbidity: Five trials showed that SRT using synthetic surfactants resulted in a significant 36% lower risk of air leaks (RR 0.64, 95% CI 0.55–0.76; 2328 neonates) and a 25% lower risk of BPD (RR 0.75, 95% CI 0.61–0.92; 2248 neonates). However, synthetic surfactant therapy was not associated with a significantly lower risk of severe IVH when compared to no SRT (RR 0.84, 95% CI 0.63–1.12; 2328 neonates).

RECOMMENDATION 9.1

Either animal-derived or protein-containing synthetic surfactants can be used for surfactant replacement therapy in ventilated preterm newborns with respiratory distress syndrome. *(Conditional recommendation [only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available] based on moderate-quality evidence)*

REMARKS

- The GDG noted that protein-free synthetic surfactants increase the risk of pneumothorax when compared with animal-derived surfactant. This type of synthetic surfactant is no longer commercially available.

Summary of evidence

Synthetic surfactants versus natural (animal-derived) surfactants for preterm neonates with clinical and/or radiologically established respiratory distress syndrome (RDS)

The evidence for this recommendation was derived from two Cochrane reviews that directly compared the effects of a single dose or multiple doses of synthetic versus natural surfactants for SRT in preterm babies at risk of RDS or with radiological/

clinical features of RDS. The surfactants were administered by the intra-tracheal route. The first review by Soll et al. *(63)* evaluated the effects of SRT with protein-free synthetics whilst the second, by Pfister et al. *(64)*, evaluated the use of protein-containing synthetic surfactants, both compared to natural surfactants.

Protein-free synthetic versus natural surfactants (EB Table 9c)

The review by Soll et al. *(63)* included 11 studies that used protein-free synthetic surfactant in the intervention group and compared its effects with the use of natural surfactants. These studies were conducted within intensive care units of hospitals in HICs. An updated search found two additional studies, which were included in the pooled analysis.

Neonatal death: Neonates who received protein-free synthetic surfactant had similar risk of overall neonatal mortality compared to natural surfactants (RR 1.07, 95% CI 0.99–1.17; 12 studies, 5447 babies).

Severe neonatal morbidity: The risk of pneumothorax (including pneumo-mediastinum and pneumo-pericardium) was 49% higher with the use of the protein-free synthetic surfactants compared with the use of natural ones (RR 1.49, 95% CI 1.26–1.77; 5381 neonates). There were no significant differences in the risks of BPD (RR 1.00, 95% CI 0.92–1.10; 7 studies, 4006 preterm neonates), IVH (RR 0.95, 95% CI 0.83–1.09; 9 studies, 4969 neonates) or sepsis (RR 0.99, 95% CI 0.90–1.08; 10 studies, 5244 neonates) between the groups receiving the two types of surfactants.

Protein-containing synthetic versus natural surfactants (EB Table 9d)

The systematic review by Pfister et al. *(64)* included two studies that compared the effects of the newer generation of protein-containing surfactants with those of natural surfactants on mortality and morbidity outcomes when used in newborns with clinical or radiological features of RDS or at risk of RDS. An updated search identified no additional studies eligible for inclusion.

Neonatal death: There was no significant difference in the risk of mortality between the use of protein-containing synthetic surfactant compared to natural surfactants (RR 0.79, 95% CI 0.61–1.02; 2 studies, 1028 neonates).

Severe neonatal morbidity: Among preterm babies with RDS, use of protein-containing synthetic surfactants was associated with a lower risk of NEC compared with natural surfactants (RR 0.60, 95% CI 0.42–0.86). There was inconclusive evidence of differences in the risks of pulmonary haemorrhage (RR 0.73, 95% CI 0.51–1.06; 1028 neonates), BPD (RR 0.99, 95% CI 0.84–1.18; 1028 neonates), air leaks (RR 1.00, 95% CI 0.73–1.37; 1028 neonates), sepsis (RR 1.01, 95% CI 0.85–1.19; 785 neonates) and IVH (RR 1.52, 95% CI 0.73–3.13; 243 neonates).

RECOMMENDATION 9.2

Administration of surfactant before the onset of respiratory distress syndrome (prophylactic administration) in preterm newborns is not recommended. *(Strong recommendation based on low-quality evidence)*

REMARKS

- The GDG did not recommend prophylactic administration of surfactants despite evidence of benefit in older studies because:
  - the control group in these older studies did not receive continuous positive airway pressure (CPAP), which is now part of standard care; and
  - recent studies in which CPAP was given to control group did not show any evidence of benefit for prophylactic surfactant administration, and a possibility of harm could not be ruled out.

Summary of evidence

Prophylactic versus rescue surfactant therapy for respiratory distress syndrome (RDS) in preterm neonates (EB Tables 9e to 9g)

Evidence for this recommendation was based on a Cochrane review that evaluated the effects of prophylactic administration of surfactants compared with selective rescue therapy on mortality and morbidity in preterm newborns with or without evidence of RDS *(65)*. The review included 11 studies, all from intensive care units of hospitals in HICs, and all using animal-derived surfactants. Surfactants were administered with or without CPAP; two studies routinely administered CPAP to stabilize babies in the comparison arm, whereas the other nine were conducted in the pre-CPAP era.

Neonatal death: The use of prophylactic surfactant administration was not associated with benefit in terms of neonatal death (RR 0.89, 95% CI 0.76–1.04; 10 studies, 4507 preterm neonates). However, there was substantial heterogeneity among studies depending on whether the control group receive CPAP or not. In recent studies in which CPAP was given to control infants, prophylactic administration of surfactants did not reduce neonatal death (RR 1.24, 95% CI 0.97–1.58; 2 studies, 1746 neonates).

However, in eight older studies where CPAP was not administered to control infants, the mortality reduction was significant (RR 0.69, 95% CI 0.56–0.85; 2761 neonates). The findings were similar for in-hospital mortality outcomes as reported in five studies. There was a trend towards a reduction in risk of in-hospital mortality with the use of prophylactic surfactant administration compared to selective therapy (RR 0.79, 95% CI 0.63–1.00; 5 studies, 1458 neonates). One of these five studies used CPAP for control infants, and reported a relative risk of 1.76 (95% CI 0.79–3.94; 428 neonates).

Severe neonatal morbidity: The pooled effect across all 11 studies that reported morbidity outcomes did not provide evidence of a difference between intervention and control groups for air leaks (RR 0.86, 95% CI 0.71–1.04), sepsis (RR 0.83, 95% CI 0.64–1.08) or severe IVH (RR 0.87, 95% CI 0.74–1.04). However, the nine older studies in which control group infants did not receive CPAP showed a reduced risk of air leaks (RR 0.79, 95% CI 0.63–0.98; 8 studies, 2760 neonates) and sepsis (RR 0.1, 95% CI 0.03–0.33; 5 studies, 2013 neonates) in the intervention group.

RECOMMENDATION 9.3

In intubated preterm newborns with respiratory distress syndrome, surfactant should be administered early (within the first 2 hours after birth) rather than waiting for the symptoms to worsen before giving rescue therapy. *(Conditional recommendation [only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available] based on low-quality evidence)*

Summary of evidence

Early (within the first 2 hours after birth) versus delayed selective surfactant therapy (given after 2 hours with worsening RDS) for preterm neonates intubated for clinically or radiologically established RDS (EB Tables 9h)

Evidence for this recommendation was extracted from a Cochrane review that evaluated the effects of early surfactant administration (within the first 2 hours of birth) for preterm newborns intubated for radiological and/or clinical features of RDS requiring assisted ventilation *(66)*. The comparison group had delayed selective surfactant therapy administered only when they developed established RDS. The review included six studies – five from HICs and one from Brazil. Four studies used animal-derived surfactants and the other two used a synthetic surfactant. An updated search for the Cochrane review did not find any additional studies that met the eligibility criteria.

Neonatal death: In six trials (3577 babies), early surfactant administration within the first 2 hours of birth for preterm newborns intubated for RDS was associated with lower risk of overall and in-hospital neonatal mortality compared to controls (RR 0.84; 95% CI 0.74–0.95; RR 0.88; 95% CI 0.78–0.99, respectively). There was inconclusive evidence on mortality risk with early surfactant administration compared with delayed therapy in the only study conducted in an LMIC (RR 0.76, 95% CI 0.46–1.26; 75 neonates).

Severe neonatal morbidity: Early surfactant administration was associated with a lower risk of BPD (RR 0.67, 95% CI 0.54–0.84; 4 studies, 3082 neonates) and air leaks (RR 0.64, 95% CI 0.48–0.78; 2 studies, 463 neonates). No association was observed in the risk of severe IVH or confirmed bacterial sepsis, which were only reported in the single study from Brazil *(67)*.

3.2.3 Oxygen therapy for preterm newborns

RECOMMENDATION 10.0

During ventilation of preterm babies born at or before 32 weeks of gestation, it is recommended to start oxygen therapy with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen. *(Strong recommendation based on very low-quality evidence)*

RECOMMENDATION 10.1

The use of progressively higher concentrations of oxygen should only be considered for newborns undergoing oxygen therapy if their heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation with 30% oxygen or air. *(Strong recommendation based on very low-quality evidence)*

REMARKS

- These recommendations are the same as those in the *WHO guidelines on basic newborn resuscitation (68)*.
- Oxygen concentration should be guided by blood oxygen saturation levels. However, measurement of these saturation levels should not supersede early efforts at resuscitation of the preterm newborn and hence saturation-level monitoring should be initiated 2 minutes after birth.

- The target oxygen saturation levels are as follows:

Time (after birth)	All preterm infants
2 minutes	55% - 75%
3 minutes	65% - 80%
4 minutes	70% - 85%
5 minutes	80% - 90%
10 minutes	85% - 95%

- The adjustment of the concentration of oxygen levels should be by 10% (FiO2=0.1) per 30 seconds and must be guided by oxygen saturation levels reached.

Summary of evidence

Lower oxygen concentration (room air to ≤50%) versus higher oxygen concentrations (>50%) for positive pressure ventilation (PPV) of preterm neonates at birth

Evidence related to the starting and progression of oxygen concentration during ventilation was extracted from a systematic review of six RCTs involving 484 newborns. *(69)*. An updated literature search did not identify any additional eligible studies. Five of the included trials were conducted among neonates born at a gestational age less than 32 weeks in HICs. The sixth was a multicentre trial that was conducted among preterm and term neonates in high- and low-income countries. Most of the studies had serious methodological limitations that affected the overall quality of the evidence. Low oxygen concentration was defined as receiving room air (21% oxygen concentration, 4 studies), 30% (1 study) or 50% (1 study) oxygen concentration. High oxygen concentration was defined as receiving 100% (4 studies), 90% (1 study) or 80% (1 study) oxygen concentration.

Neonatal death: There was significant benefit of using low oxygen concentrations for resuscitation in terms of overall and in-hospital neonatal mortality: eight trials demonstrated that the use of low oxygen concentration or air for preterm babies resuscitated with PPV immediately after birth was associated with a 37% lower risk of overall or in-hospital mortality (RR 0.63, 95% CI 0.44–0.92).

Severe neonatal morbidity: There was no association between ventilation with low oxygen concentrations for neonatal resuscitation and severe morbidities, including BPD, retinopathy of prematurity, NEC, severe IVH, the proportion of infants reaching target oxygen saturation by 10 minutes after birth, the duration (in days) of mechanical ventilation or the need for endotracheal intubation during resuscitation.

Subgroup analysis (preterm babies born at 32–36 weeks versus <32 weeks of gestation)

Except for two of the studies – Saugstad et al. *(70)* and Kapadia et al. *(71)* – all other studies in the review enrolled preterm babies born before 32 weeks of gestation. Saugstad et al. included both term and preterm neonates, with approximately 95% of enrolled neonates being born at 32 weeks or later. For the purpose of this review, the results of the study were stratified into those born at 32–36 weeks and those born before 32 weeks, and low versus high oxygen concentrations were compared. Kapadia et al. enrolled preterm infants born before 35 weeks of gestation (the mean gestation being 30 weeks) but was excluded because of non-availability of data for the two subgroups of interest.

Preterm babies born at 32–36 weeks of gestation: There was a 42% lower risk of in-hospital mortality observed in the lower oxygen concentration group compared to the higher oxygen concentration group (RR 0.58, 95% CI 0.34–0.97). No morbidity outcomes were available from the Saugstad et al. study.

Preterm babies born at <32 weeks of gestation: There was inconclusive evidence regarding the risk of mortality (RR 0.69, 95% CI 0.39–1.22) and the same was true for all the critical outcomes, including BPD, NEC, IVH, retinopathy of prematurity (ROP), and the proportion reaching target saturation by 5 or 10 minutes after birth.

4. Research implications

The Guideline Development Group identified important knowledge gaps that need to be addressed through primary research. The quality of evidence was rated as "low" or "very low" for a number of recommendations, particularly those relating to questions about sub-populations. According to GRADE methodology, evidence quality that was rated as "low" or "very low" implies that further research is likely to have an impact on the corresponding recommendation(s). Conversely, further research is not a priority for those recommendations based on evidence of "moderate" or "high" quality. The knowledge gaps identified based on this concept were prioritized by considering whether such research would be original and innovative, feasible to implement, likely to promote equity, and likely to contribute to improvements in care for mothers and infants at risk of preterm birth. The priority research questions are listed as they relate to maternal and newborn interventions.

4.1 Maternal research priorities

Antenatal corticosteroids

- What are the long-term outcomes of all infants exposed to antenatal corticosteroids (including term infants)?
- What strategies can effectively and safely increase the use of corticosteroids in low- and middle-income country (LMIC) settings to improve outcomes?
- What are the effects of antenatal corticosteroid at different gestational ages at birth (using independent patient data analysis)?
- Assessment of coverage of antenatal corticosteroids before and after guideline implementation (and associated reduction in neonatal mortality).
- Assessment of implementation strategies and monitoring of adverse events (in LMIC settings).
- What are the effects of antenatal corticosteroid administration in women undergoing prelabour caesarean section in late preterm?
- What are the effects of task shifting in the context of antenatal corticosteroid administration (e.g. using the first dose in the community followed by referral to a health-care facility)?
- Are there differences in the pharmacokinetic properties of betamethasone acetate versus betamethasone phosphate (consider using available data in settings where they are routinely used)?
- What is the impact of antenatal corticosteroid administration among mothers with evidence of infection who also receive appropriate antibiotic therapy on both maternal and neonatal outcomes?
- What is the minimum effective dose of corticosteroids to achieve fetal lung maturation and other improved outcomes? What is the minimum effective dose required for repeat courses of antenatal corticosteroids?
- What is the most effective regimen and dose for antenatal corticosteroids?
- In what contexts can antenatal corticosteroids be used safely and effectively in low-income countries?

Tocolysis

- What are the effects on neonatal mortality and morbidity, and on maternal mortality and morbidity, of tocolytics in combination with antenatal corticosteroids versus placebo + antenatal corticosteroids? (Consider calcium channel blockers versus placebo to improve outcomes, including dosing regimens)

Magnesium sulfate for fetal neuroprotection

- Are repeated doses of magnesium sulfate safe for fetal neuroprotection in the event that birth does not occur after completing the first dose?
- What is the minimum effective dose of magnesium sulfate for fetal neuroprotection?
- What is the comparative effectiveness of alternative regimens of magnesium sulfate when used for fetal neuroprotection (including effectiveness of intramuscular regimen)?
- What are the effects of task shifting in the context of magnesium sulfate administration (e.g. using the first dose in the community followed by referral to a health-care facility)?
- What are the effects of magnesium sulfate on the newborn in the immediate postpartum period (particularly on resuscitation)?

Antibiotic prophylaxis

- What is the appropriate dose and regimen that should be used for prophylaxis (particularly in relation to combination therapy with betalactam and macrolide)?

Optimal mode of delivery for the preterm infant

- What are the comparative effects and safety of vaginal versus caesarean delivery by gestational age and presentation?

4.2 Newborn research priorities

Kangaroo mother care (KMC)

- What is the optimal frequency of follow-up for mothers providing KMC after discharge from the health-care facility?
- What is the minimum threshold of KMC exposure needed to achieve an impact on neonatal mortality and other important outcomes?
- Can KMC be effectively initiated in the community setting in LMICs?

Continuous positive airway pressure (CPAP) and surfactant administration

- What is the best modality for providing CPAP? e.g. nasal intermittent positive pressure ventilation, nasal flow cannulas, etc.
- What is the role of CPAP for babies with apnoea of prematurity that persists despite giving methylxanthines/caffeine?

- What is the efficacy of surfactants in a context where antenatal corticosteroids and early CPAP is provided (without immediate obligatory mechanical ventilation) for babies who are at risk of respiratory distress syndrome (e.g. InSURE – intubation, surfactant replacement therapy and extubation)?

Infection treatment

- What is the role of emollient therapy in reducing infections and mortality among preterm infants?

Nutrition

- What are the optimal feeding methods for preterm infants with birth weight < 1200 grams?
- Is there a role for total parenteral nutrition in the management of preterm infants?

Growth and development

- Are there effective interventions for the care and development of preterm infants and what are these?

5. Dissemination and implementation of the guideline

The ultimate goal of this guideline is to improve the quality of care and health outcomes related to preterm birth. The dissemination and implementation of this guideline are therefore crucial steps that should be undertaken by the international community as well as by national and local health services. In this context, the WHO Department of Reproductive Health and Research has adopted a formal knowledge-to-action framework for the dissemination, adaptation and implementation of guidelines *(72)*. In addition to this framework, a list of priority actions and events, advocacy and promotion opportunities identified during the WHO Technical Consultation will be used by WHO and other partners to facilitate the dissemination and implementation of this guideline.

5.1 Guideline dissemination and evaluation

The recommendations in this guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies, and nongovernmental organizations. After the final approval of the guideline, technical meetings will be held at WHO within the Department of Maternal, Newborn, Child and Adolescent Health and the Department of Reproductive Health and Research to share the recommendations and other related products with the teams responsible for policy and programme implementation. The recommendations will be published on the websites of these two WHO departments, as well as in the WHO Reproductive Health Library, where they will be accompanied by an independent critical appraisal based on the AGREE instrument (Appraisal of Guidelines Research and Evaluation)[1]. Evidence briefs will also be developed for a wide range of policy-makers, programme managers and clinicians, and then disseminated through WHO regional and country offices.
The executive summary of the guideline will be translated into the six United Nations languages and disseminated through the WHO regional offices and during meetings organized by or attended by relevant WHO staff. Technical assistance will be provided as needed to any WHO regional office willing to translate the full guideline into any of the six United Nations languages. To also increase awareness of the guideline, the recommendations will be published as commentaries in peer-reviewed journals, in compliance with WHO's open access and copyright policies.

5.2 Guideline implementation

The successful introduction of evidence-based policies related to the interventions 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 the development or revision of existing national guidelines or protocols based on this document. The Department of Maternal, Newborn, Child and Adolescent Health and the Department of Reproductive Health and Research at WHO will support national and subnational subgroups to adapt and implement the guideline based on existing strategies.

Within this context, the WHO Department of Reproductive Health will involve its international partnership called the GREAT Network (Guideline-driven, Research priorities, Evidence synthesis, Application of evidence, and Transfer of knowledge) to adapt and implement guidelines particularly in LMICs *(72)*. The GREAT Network uses a unique evidence-based knowledge translation approach to

[1] Available at: http://www.agreecollaboration.org/instrument

support LMICs in the adaptation and implementation of guidelines relating to reproductive, maternal, perinatal and newborn health, and has been successfully employed for other WHO guidelines in many countries. Specifically, the GREAT Network brings together relevant stakeholders of the health care system to identify and assess the priorities, barriers and facilitators to guideline implementation, and supports the efforts of stakeholders to develop guideline adaptation and implementation strategies tailored to the local context. This includes technical support for local guideline implementers in the development of training manuals, flowcharts and quality indicators, as well as participation in stakeholder meetings.

The recommendations contained in the present guideline should be adapted into locally appropriate documents that are able to meet the specific needs of each country and its health service. Modifications to the recommendations, where necessary, should be limited to conditional recommendations, and justifications for any changes should be made in an explicit and transparent manner.

An enabling environment should be created for the use of these recommendations (e.g. ensuring that antenatal corticosteroids are available at hospitals), including changes in the behaviour of health-care practitioners and managers to enable the use of evidence-based practices. Local professional societies may play important roles in this process and an all-inclusive and participatory process should be encouraged.

6. Applicability issues

6.1 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 the following:

- Non-availability or irregular supply of essential medicine (e.g. antibiotics, corticosteroids, magnesium sulfate, and surfactant) and lack of equipment and supplies (e.g. oxygen, masks for oxygen administration, pulse oximeter, incubators, and radiant warmers);
- Lack of human resources with the necessary expertise and skills to implement the recommended practices and monitor recipients' clinical response (e.g. application of continuous positive airway pressure, intubation, oxygen therapy);
- Low certainty of gestational age estimation particularly in the obstetric population in low-resource countries;
- Lack of effective referral mechanisms and care pathways that ensure management of women with preterm labour and preterm infants within a continuum.

In order to overcome these barriers, the Guideline Development Group (GDG) noted that the following issues should be considered before the recommendations made in this guideline are applied:

- Local protocols should be developed that integrate the management of women at risk of imminent preterm birth and preterm infants 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 imminent preterm birth.
- Local arrangements should be made to ensure ample and consistent supplies of antenatal corticosteroids (dexamethasone or betamethasone), magnesium sulfate and antibiotics (macrolide or penicillin).
- 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 (KMC).
- Clear referral pathways for women at risk of imminent preterm birth should be established within the health-care facility.

6.2 Monitoring and evaluation of guideline impact

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. At the Technical Consultation in May 2014, 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 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 the interventions contained in this guideline. Clearly defined review criteria and indicators are needed and these could be associated with locally agreed targets. In this context, the following indicators are suggested:

- The proportion of all babies at risk of being born from 24 to < 34 weeks of gestation who were exposed to antenatal corticosteroids (numerator: all babies at risk of being born from 24 to < 34 weeks whose mothers received antenatal corticosteroids; denominator: all babies at risk of being born from 24 to < 34 weeks in the facility).
- The proportion of all babies at risk of being born at ≥ 34 weeks of gestation who were exposed to antenatal corticosteroids (numerator: all babies at risk of being born at ≥ 34 weeks of gestation whose mothers received antenatal corticosteroids; denominator: all babies at risk of being born at ≥ 34 weeks in the facility).
- The proportion of all babies born before 32 weeks of gestation and exposed in-utero to magnesium sulfate for fetal neuroprotection (numerator: all babies born before 32 weeks whose mothers received magnesium sulfate for fetal neuroprotection; denominator: all babies born before 32 weeks in the facility).
- The proportion of women with preterm prelabour rupture of membranes (PPROM) who received prophylactic antibiotics (numerator: all women with PPROM who received antibiotic prophylaxis; denominator: all women with PPROM giving birth in the facility).
- The proportion of clinically stable neonates weighing ≤ 2000 g at birth who received KMC (numerator: clinically stable neonates weighing ≤ 2000 g at birth who received KMC; denominator: all clinically stable neonates weighing ≤ 2000 g managed in the facility).

7. Updating the guideline

In accordance with the guidance of the WHO Guidelines Review Committee, which ensures a systematic and continuous process of identifying and bridging evidence gaps following guideline implementation, this guideline will be updated in five years after publication, unless new evidence emerges which necessitates earlier revision. WHO welcomes suggestions regarding additional questions for inclusion in the updated guideline. Please e-mail your suggestions to: mpa-info@who.int. The WHO Steering Group will continue to follow the research developments in the area of preterm birth, particularly those relating to questions for which no evidence was found and those that are supported by low-quality evidence, where new recommendations or a change in the published recommendation may be warranted, respectively. Following publication and dissemination of the guideline, any concern about validity of any recommendation will be promptly communicated to the guideline implementers in addition to plans to update the recommendation.

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Annex 2. Considerations related to the direction and strength of the recommendations

Recommendation. 1: Antenatal corticosteroid therapy is recommended for women at risk of preterm birth from 24 weeks to 34 weeks of gestation when the following conditions are met:

- gestational age assessment can be accurately undertaken;
- preterm birth is considered imminent;
- there is no clinical evidence of maternal infection;
- adequate childbirth care is available (including the capacity to recognize and safely manage preterm labour and birth);
- the preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment and safe oxygen use).

FACTOR	DECISION	EXPLANATION
Quality of the evidence	☐ High ☒ Moderate (newborn) ☒ Low (mother) ☐ Very low	Based on the main analysis, the overall quality of evidence for maternal outcomes was mostly rated as low, whereas for newborn severe morbidity and mortality outcomes it was rated as moderate or high. Long-term outcomes during childhood and adulthood were rated as low. The quality of evidence from the subgroup analyses based on gestational age at first dose was rated low for most newborn morbidity and mortality outcomes due to few trials and small sample sizes. However, it was rated as moderate or high for categories between 26 and 34^{+6} weeks for respiratory distress syndrome (RDS). The quality of evidence from the subgroup analyses based on gestational age at birth was quite variable, ranging from low to high across the different age categories for severe neonatal morbidity and mortality outcomes. However, it was moderate to high for RDS for babies born < 30 weeks, < 32 weeks, < 34 weeks and < 36 weeks. The Guideline Development Group (GDG) acknowledged the differences in the quality of evidence between maternal and early newborn critical outcomes and between early and late newborn critical outcomes. The panel interpreted the overall quality of evidence within the context of the recommendation question and the main review findings, and favoured a distinction between the quality of evidence for the mother and the newborn. Thus, the overall quality of evidence was rated as moderate for newborn outcomes and low for maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of a preterm newborn without residual morbidity. The GDG is confident that there is no variation in this value among mothers, health-care providers and policy-makers in low-, middle- and high-income settings.

Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Antenatal corticosteroid reduces the risk of death and serious short-term morbidities and is probably beneficial in reducing long-term adverse neurological outcomes for preterm infants. For the mother, there is no evidence of benefits or harms. While the Cochrane systematic review demonstrated these benefits across a broad range of gestational ages (largely from 24 to 36 weeks), the subgroup analyses for the most part lack sufficient power to show consistent statistically significant results for specific gestational age categories. These inconsistencies were more pronounced at the two extremes of prematurity (< 26 weeks and > 34 weeks) because the sample sizes were even smaller. Nevertheless, the subgroup analyses showed consistent evidence of reduction in neonatal death when the infant is born before 34 weeks of gestation. Likewise, the data indicated that corticosteroid does not reduce infant mortality when born after 34 weeks and there is an increasing likelihood of fetal and newborn death when born at 36 weeks or after. With regard to the lower end of gestational age limit, corticosteroid may likely reduce neonatal mortality for infants born as early as 23 weeks of gestation, but the overall rate of survival without residual morbidity is generally low among infants born before 24 weeks. Overall, the desirable consequences for preterm infants whose mothers receive antenatal corticosteroid between 24 and 34 weeks are substantial (including reduction in the risks of death and serious short-term morbidities and possibly better long-term neurological outcomes) and highly valued. For eligible mothers, these benefits are achievable without increased harm to mother and baby. Beyond this gestational age range, the undesirable consequences for the preterm infant (including survival with residual long-term morbidity and increased risk of death) outweigh the potential benefits.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols that are designed to manage women at imminent risk of preterm birth with minimal costs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The moderate-to-high confidence in the magnitude of effects of a relatively cheap intervention on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the benefits to the preterm infants in terms of reducing severe morbidity and mortality outcomes, the low cost and wide availability of corticosteroid globally, the feasibility of implementing the intervention and the potential impact on health-care resource use across settings, and therefore made a strong recommendation.

Recommendation 1.1: For eligible women, antenatal corticosteroid should be administered when preterm birth is considered imminent within 7 days of starting treatment, including within the first 24 hours.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	The quality of evidence was variable for critical outcomes reported, ranging from low to high across the different categories of intervals between first dose of corticosteroid and preterm birth. Overall, the quality of evidence was rated low for both newborn and maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the benefits of an intervention with the potential to reduce the risk of newborn death and serious morbidity even when given at short interval before birth. The GDG is confident that mothers, health-care providers and policy-makers in any setting will invariably place a higher value on these benefits compared to any inconvenience that incomplete dosing of steroids might cause to the mother or the health system.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There is evidence of benefit in terms of reduction in neonatal death for infants born within 24 hours and within 48 hours after the first corticosteroid dose. This benefit was not clearly demonstrated in those born between 1 and 7 days and after 7 days of first steroid dose. However, there is a 54% reduction in the likelihood of RDS among those born within 1 and 7 days after the first dose of corticosteroid. Overall, there is variable evidence of benefits regarding newborn death and RDS for infants born within 7 days of receiving the first corticosteroid dose, while there is consistently no evidence of benefits for these outcomes in infants born 7 days after the first dose. The risk of intrapartum maternal infection is independent of the time interval between the first corticosteroid dose and birth. Overall, the desirable consequences for preterm infants whose mothers receive antenatal corticosteroids and who are born within 7 days after the first dose are substantial. Even for preterm infants born within 24 hours of exposure to steroid, the balance is in the favour of these benefits, as they are not associated with any inconvenience or harm to the mother.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. Available preparations of dexamethasone and betamethasone are often compatible with standard dosing regimen and inability to complete a full course is unlikely to result in waste of health resources.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The magnitude of beneficial effects of a relatively cheap intervention on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG acknowledged the limitations and potential bias of evidence derived from the subgroup analysis according to the interval between steroid administration and preterm birth, which led to low quality evidence for critical outcomes. Nevertheless, the group made a strong recommendation on the basis of the balance in favour of benefits of antenatal steroids (in terms of reducing respiratory morbidity and mortality for babies born within 24 hours and up 7 days of starting treatment), the low resource requirements, and feasibility of implementing the intervention.

Recommendation 1.2: Antenatal corticosteroid therapy is recommended for women at risk of preterm birth irrespective of whether a single or multiple birth is anticipated.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	The overall quality of evidence was rated low for both newborn and maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the modest benefits of antenatal steroids on the risk of newborn death and serious morbidities, particularly because of higher baseline risk of preterm birth in multiple pregnancy. The GDG is confident that mothers, health-care providers and policy-makers in any setting will invariably place a higher value on these benefits, even if modest, and will chose to use the intervention.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	The positive effects of corticosteroids on preterm infants resulting from multiple pregnancies are not as clear as in singleton pregnancies. It is uncertain whether the lack of a statistical difference was only related to the small sample size of this subgroup in the systematic review or as a result of different pharmacokinetic properties leading to sub-therapeutic levels of steroids in multiple pregnancies. However, for the outcomes reported, the point estimates were consistent for risk reduction in both singleton and multiple pregnancies. Given that the evidence base demonstrating benefits of antenatal corticosteroids was extracted from studies that included women with multiple pregnancies, it is plausible for corticosteroids to also improve survival and reduce the risk of morbidity of preterm infants resulting from multiple pregnancies. Overall, the desirable consequences for preterm infants whose mothers receive antenatal corticosteroids are likely to be substantial. Appropriate use in eligible mothers is not known to constitute any inconvenience or harm among populations of women carrying either singleton or multiple pregnancies.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. The same dosage is required for treatment of a woman with a multiple pregnancy as for a woman with a singleton pregnancy.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The potential beneficial effects of a relatively cheap intervention on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG acknowledged the lack of clarity on the benefits of antenatal steroids in this subgroup of women, but felt there is no reason to suggest that antenatal corticosteroids are not beneficial, given that the point estimates were all in favour of reduced risks of adverse critical outcomes reported. The group considered the impact of any benefit, albeit modest, on the critical outcomes in this group of women, who are inherently more likely to deliver preterm, on the overall preterm newborn survival and morbidity rates, and therefore made a strong recommendation.

Recommendation 1.3: Antenatal corticosteroid therapy is recommended in women with preterm prelabour rupture of membranes and no clinical signs of infection.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate (newborn) ☒ Low (mother) ☐ Very low	The quality of evidence was variable for the reported critical outcomes for preterm prelabour rupture of membranes as a group, and for prolonged rupture of membranes for more than 24 hours and 48 hours. However, for preterm prelabour rupture of membranes as a subgroup, the quality of evidence was generally low for maternal infectious morbidity and moderate for early newborn death and infectious morbidity. The overall quality of evidence was rated moderate for newborn outcomes and low for maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the reduction in the risk of newborn death and serious morbidity and less value on the potential for increased risk of maternal infection. The panel is confident that mothers, health-care providers and policy-makers in any setting will invariably place a higher value on these benefits, and will chose to use the intervention.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Corticosteroid administration is associated with reduction in the risk of neonatal death and serious short-term morbidity in women with preterm prelabour rupture of membranes at the time of the first dose without increasing the risk of maternal or neonatal infection. While it is unclear whether these benefits remain consistent for women with ruptured membranes for more than 24 or 48 hours, the risk of intrapartum infection was not any worse even in these women.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing health structures and protocols that are designed to manage women at risk of imminent preterm birth with minimal costs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	In spite of the low confidence in the magnitude of effects, the overall balance is in favour of benefits.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG noted the paucity of evidence on benefits around the duration of membrane rupture due to the lack of such information from trials included in the review. However, the group placed its emphasis on the overall balance of benefits versus harm of using antenatal steroids in terms of reducing severe adverse neonatal outcomes without evidence of increased risk of infection to the mother or the baby, and with consideration that a substantial proportion of women at risk of imminent preterm birth would present with ruptured membranes, and therefore made a strong recommendation.

Recommendation 1.4: Antenatal corticosteroid therapy *is not* recommended in women with chorioamnionitis who are likely to deliver preterm.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	Available evidence on newborn critical outcomes was obtained from observational studies with some design limitations. No maternal outcomes were reported.
Values and preferences	☐ No significant variability ☒ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in high-income settings might place a higher value on the potential benefits of antenatal steroids in terms of reduction in RDS and neonatal mortality (regardless of the limited evidence on benefits in this context) over concerns about exacerbation of maternal infections, and therefore chose not to adhere to the recommendation in all women; whereas those in low- and middle-income settings might put a higher value on the potential risk of increasing maternal infectious morbidity over unclear benefits for clinical chorioamnionitis and thus chose to adhere to the recommendation in the majority of women.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☒ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Corticosteroids are known to suppress the immune system, and so the concern that their use may activate latent infections is reasonable. In a pregnant woman with ongoing infection, it may theoretically suppress the natural immune response and exacerbate infectious morbidities. However, there is no direct evidence from randomized and observational studies on the effects of corticosteroid therapy on mothers with chorioamnionitis who are at risk of giving birth to preterm neonates to either confirm or refute this theory. Evidence from the reviewed observational studies from high-income countries suggests that in women with histological chorioamnionitis, there are some benefits for the preterm neonates without increasing potential harm of steroid therapy, particularly neonatal sepsis. However, no convincing evidence of benefits was shown for neonatal mortality and RDS in women with clinical chorioamnionitis. In view of the evidence from low-income settings showing a significant 67% increase in suspected maternal infections among mothers of preterm infants who received antenatal corticosteroid, the potential harm of worsening infectious morbidities may outweigh the potential benefits, especially in settings where the baseline risk of maternal infection is high. This concern is further supported by a 35% increased risk of puerperal sepsis (albeit not statistically significant) among all women receiving corticosteroid compared with placebo as shown in the main Cochrane review of antenatal corticosteroid for improving adverse neonatal outcomes. It is unclear whether the desirable consequences (possible reduction in mortality and severe morbidity) for the preterm newborn associated with corticosteroid use outweigh the potential harm for the mother (in terms of puerperal sepsis and other infection-related severe maternal morbidity).
Resource use	☐ Less resource intensive ☒ More resource intensive	Although it is feasible to administer antenatal corticosteroid, it might not be cost–effective if it has adverse impact on maternal infectious morbidity.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The GDG acknowledged that while there might be some benefits for the newborn, there might also be harm to the mother. The decision to recommend against the intervention was based on the lack of clear evidence on the benefits for the baby in clinical chorioamnionitis which could be outweighed by potential harm to the mother in the majority of the population that will use the guideline.

Recommendation 1.4: Antenatal corticosteroid therapy *is not* recommended in women with chorioamnionitis who are likely to deliver preterm *(continued)*.		
FACTOR	**DECISION**	**EXPLANATION**
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG reviewed the concern about risk of exacerbating maternal infection, particularly in low- and middle-income settings where baseline risks of maternal infectious morbidity is higher than those of settings where the current evidence was generated. The group acknowledged the variability in the balance between benefits and harms according to context and the variation in clinical practice, and chose to make a conditional recommendation against the intervention.

Recommendation 1.5: Antenatal corticosteroid therapy *is not* recommended in women undergoing planned caesarean section at late preterm gestations (34–36^{+6} weeks).		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	Current evidence comes from a single study without major methodological concerns apart from its non-blind design. However, indirectness was a major issue as the population studied (i.e. mothers undergoing elective caesarean section at term) differs from the population of interest. The quality of the evidence was graded as very low across all critical outcomes.
Values and preferences	☐ No significant variability ☒ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in high-income settings might place a higher value on the potential cost saving of antenatal steroids in terms of reduction in neonatal intensive care unit (NICU) admission and therefore chose the intervention regardless of the lack of evidence on mortality outcomes; whereas those in low- and middle-income settings might put a higher value on the potential maternal harm related to caesarean section and lower value on modest reduction in NICU admission – which may not be available in such settings. As a result of variability in these values and preferences across settings, clinical practice and choice made by women and their families are likely to vary across settings.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☒ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There is insufficient evidence to conclude on the benefits or harms of using antenatal corticosteroids in women undergoing elective caesarean section in late preterm. There may be some benefits with regard to reducing NICU admission for respiratory complications, although this was not supported by the comparable frequencies of respiratory complications reported in the review. In view of the lower risk of respiratory complications for babies born in late preterm, much larger sample sizes and longer follow-up would be needed to examine the potential differences regarding benefits or harms of antenatal corticosteroid. Given that the overall evidence on the effectiveness of antenatal corticosteroid suggests possible harm to preterm infants born after 34 weeks, it is unclear whether the desirable consequences of administering corticosteroid outweigh the potential harm for the preterm infant born through elective caesarean section after 34 weeks.
Resource use	☐ Less resource intensive ☒ More resource intensive	Although it is feasible to administer antenatal corticosteroid, it might not be cost–effective if it has little or no impact on serious adverse newborn outcomes.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The GDG acknowledged that while there might be some benefits, there might also be harm. The decision was based on the potential for harm as suggested by the overall evidence on antenatal corticosteroid.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG made a conditional recommendation based on the very low quality of evidence, the variability in the values and preferences across settings, and the lack of clear benefits or harms. The group considered this to be a research priority, but chose to recommend against the practice until further evidence becomes available.

Recommendation 1.6: Antenatal corticosteroid therapy is recommended in women with hypertensive disorders in pregnancy who are at risk of imminent preterm birth.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate (newborn) ☒ Low (mother) ☐ Very low	The quality of evidence was rated as low for all maternal critical outcomes reported, but was rated as moderate to high for most mortality and serious early newborn morbidities. Therefore, the overall quality of evidence was rated as moderate for newborn outcomes and low for maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of a preterm baby born to a mother with a hypertensive disorder during pregnancy. The GDG is confident that there is little or no variation of this value among mothers, health-care providers and policy-makers in low-, middle- and high-income settings, particularly because hypertensive disorders pose further risk of morbidity and mortality for the preterm newborn.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Antenatal corticosteroid therapy in women with hypertension during pregnancy is associated with reduction in both neonatal mortality and serious short-term morbidities, without any evidence of harm to the mother or the baby. Overall, the desirable consequences of administering antenatal corticosteroids to hypertensive mothers are substantial and highly valued.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing structures and protocols for the management of women with hypertensive disorders and at imminent risk of preterm birth at minimal cost.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The moderate-to-high confidence in the magnitude of effects of a relatively cheap intervention on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the benefits to the preterm infants in terms of reducing mortality and serious early morbidities, the low cost and wide availability of corticosteroid globally, the feasibility of implementing the intervention and the potential impact on health-care resource use across settings, and therefore made a strong recommendation.

Recommendation 1.7: Antenatal corticosteroid therapy is recommended for women at risk of imminent preterm birth of a growth-restricted fetus.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	The overall quality of evidence was rated very low for both newborn and maternal outcomes. Evidence was extracted from observational studies that had some design limitations.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the potential benefits of antenatal steroids on babies' survival without handicap and less value on potential effect on physical growth. The GDG is confident that mothers, health-care providers and policy-makers in any setting will invariably place a higher value on these benefits in the light of overall benefits of antenatal steroids for preterm population, and will chose to use the intervention.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	The potential benefits in terms of reduced handicap among surviving intrauterine growth-restricted (IUGR) preterm infants at the age of two years, evidence of reduced likelihood of newborn mortality and morbidity outcomes outweigh the potential adverse effects on physical growth.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. It is feasible to include antenatal corticosteroid therapy into existing protocols for the management of women at imminent risk of giving birth preterm to a growth-restricted fetus at minimal costs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	In spite of the low confidence in the magnitude of effects, the overall balance is in favour of benefits.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	There is limited evidence on the use antenatal corticosteroids in growth-restricted fetuses. However, in light of the considerable beneficial effects of antenatal corticosteroids for preterm infants overall, coupled with lack of clear evidence of harm in growth-restricted fetuses, the GDG made a strong recommendation.

Recommendation 1.8: Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes who are at risk of imminent preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	Only indirect evidence was available. The quality of the evidence was graded as very low.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of preterm newborns who are at higher risk of respiratory morbidities from maternal diabetes. The panel is confident that there is little or no variation of this value among mothers, health-care providers and policy-makers in low-, middle- and high-income settings.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There is insufficient evidence to conclude on the benefits or harms of antenatal corticosteroid in pre-gestational or gestational diabetic women at risk of imminent preterm birth. However, in diabetic women, preterm birth and RDS are both more frequent than in the general obstetric population. The need for antenatal corticosteroid therapy is thus likely to be greater in women with pre-gestational and gestational diabetes. While there is no evidence to clearly demonstrate the benefits of antenatal corticosteroid in this subgroup of women, available evidence suggests hyperglycaemic effect of corticosteroids in pregnant women. It is known that maternal hyperglycaemia can adversely affect fetal lung maturity and therefore it is possible that any benefit of corticosteroids to the baby could be offset by corticosteroid-induced hyperglycaemia, although there is no direct evidence. In particular, corticosteroid-induced hyperglycaemia may be greater in insulin-treated women with gestational or type 2 diabetes, with the potential for abnormal glucose metabolism and risk of ketoacidosis if the insulin dose is not adjusted accordingly. Overall, the desirable consequences for preterm infants of women with gestational diabetes are substantial and highly valued.
Resource use	☐ Less resource intensive ☒ More resource intensive	Antenatal corticosteroids are relatively cheap, easy to administer, and readily available in at least one preparation in all settings. Monitoring and maintaining normal blood glucose in mothers during antenatal corticosteroid administration will increase the demand on health resources. However, these added costs are outweighed by the cost savings for managing the respiratory morbidities and ensuring survival among preterm babies of women with abnormal glucose metabolism.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The potential beneficial effects of a relatively cheap intervention on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG acknowledged the paucity of evidence on the benefits of antenatal corticosteroid in this subgroup of women. However, the group placed its emphasis on the overall benefits of antenatal steroid in preterm, the potential benefits in terms of reducing the higher risk of newborn respiratory morbidity posed by maternal diabetes, and potential impact on the overall newborn survival, and therefore made a strong recommendation.

Recommendation 1.9: Either intramuscular (IM) dexamethasone or IM betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice when preterm birth is imminent.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	The quality of evidence was based on the comparison of any dose or regimen of dexamethasone and betamethasone. In spite of the total number of trials included, few of them reported on critical maternal and newborn outcomes. Overall, the quality of the evidence was rated as low.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a higher value on the overall clinical benefits of either drug as well-tested corticosteroids (in terms of reduction preterm morbidity and mortality) over subtle pharmacological differences that might exist, and therefore chose to adhere to the recommendation. The GDG is confident that there is no variation of this value among mothers, health-care providers and policy-makers in low-, middle- and high-income settings.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☒ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	From the available evidence, it appears there are no major differences in the effectiveness and safety of dexamethasone and betamethasone, although dexamethasone may be slightly advantageous with regard to all grades of intraventricular haemorrhage (IVH) and duration of stay in NICU. There is insufficient evidence on tested dosing regimens to draw conclusions on their effectiveness and safety although one small trial suggested that 12-hour and 24-hour dosing regimens of betamethasone may be equally effective. Another small study suggested that IVH and neonatal sepsis may be reduced with IM as opposed to oral dexamethasone. There is a paucity of data to assess the long-term benefits or harms of the two commonly used antenatal corticosteroids. No proof of efficacy exists for any other steroids or regimen.
Resource use	☒ Less resource intensive ☐ More resource intensive	Both steroid preparations are already available and used in one form or the other in all countries and implementing this recommendation is not expected to increase current health-care costs. However, as dexamethasone is cheaper than betamethasone, health systems switching from betamethasone to dexamethasone based on this recommendation are likely to save costs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The lack of significant differences in clinical benefits of either preparation on highly valued critical newborn outcomes favoured the use of either intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG acknowledged the low quality of evidence on the comparative benefits of the two popular corticosteroid preparations with one another. However, it placed its emphasis on the overall evidence of clinical benefits of antenatal corticosteroids (which was based on both preparations), the lack of safety concerns when one is compared with the other, and the potential impact of recommending either preparation on uptake of antenatal corticosteroids, and therefore made a strong recommendation.

Recommendation 1.10: A single repeat course of antenatal corticosteroid is recommended if preterm birth does not occur within 7 days after the initial dose, and a subsequent clinical assessment demonstrates that there is a high risk of preterm birth in the next 7 days.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate (newborn) ☒ Low (mother) ☐ Very low	The quality of evidence was rated as low to moderate for reported maternal critical outcomes, but was rated as moderate to high for newborn critical outcomes (mortality and serious early and late newborn morbidities). Therefore, the overall quality of evidence was rated as moderate for newborn outcomes and low for maternal outcomes.
Values and preferences	☐ No significant variability ☒ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in high-income settings might place a higher value on the potential cost saving of antenatal corticosteroids in terms of further reduction in newborn RDS and surfactant use, and therefore chose the intervention regardless of the lack of further benefits on newborn mortality outcomes; whereas those in low- and middle-income settings might place a higher value on the concern about potential harm to the mother and lower value on reducing surfactant use – which is often not part of standard care in such settings.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There are short-term benefits for infants exposed to repeat course(s) of corticosteroids in terms of less respiratory distress (17% reduction) and surfactant use (22% reduction), and fewer serious morbidities (when considered as a composite) compared to infants exposed to a single course. However, these apparent short-term benefits do not translate into a reduction in neonatal death. The downside of repeat course is a reduction in the weight at birth, which is independent of whether the interval before the repeat course is 7 or 14 days. While there seems to be no apparent long-term benefits, available data did not show any increase in harm during childhood. Although this evidence supports the concern about restriction of growth of the preterm infants with repeat corticosteroid from animal studies, it neither confirms nor refutes the concern regarding brain developmental delay and behavioural abnormalities. For women with preterm prelabour rupture of membranes, there may be no added benefits, but the risk of intrapartum infection may be increased with repeat courses of corticosteroids. Overall, the desirable consequences of a repeat course of corticosteroid for the newborn outweigh the undesirable effect on newborn birth weight or concern about childhood development. However, antenatal exposure to four or more repeat courses may likely nullify these benefits as the undesirable effects become more frequent and clinically significant.
Resource use	☐ Less resource intensive ☒ More resource intensive	Additional course of steroid for women who are likely to give birth preterm is likely to increase human resource needs and supply costs. However, this interventions is likely to be cost–effective in settings where standard neonatal support attracts significant health-care costs (e.g. for surfactant or other interventions relating to RDS in the newborn).
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The overall balance of desirable versus undesirable effects is in favour of a single repeat course of antenatal corticosteroids.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG placed its emphasis on further reduction in the respiratory morbidity and less surfactant use (which could save costs) and lower value on the concern about reduction in neonatal birth weight, and therefore recommended the intervention. As there are likely to be significant variations in these values across countries and health-system settings, the group lowered the strength of the recommendation and made it conditional.

Recommendation 2.0: Tocolytic treatments (acute and maintenance treatments) *are not* recommended for women at risk of imminent preterm birth for the purpose of improving neonatal outcomes.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	There were design limitations and insufficient data on critical maternal and neonatal outcomes for many of the studies comparing first-line tocolytic or maintenance therapy with placebo.
Values and preferences	☐ No significant variability ☒ Significant variability	Health-care providers, policy-makers and pregnant women and their families in high-income settings are likely to place a higher value on the potential harms (maternal adverse effects) that are associated with tocolytic therapy; and less value on the benefit of short delay in preterm birth which does not improve neonatal outcomes and therefore chose to adhere to the recommendation in most women; whereas those in low- and middle-income settings are likely to place a higher value on the potential benefits of delaying birth to complete corticosteroids and in-utero fetal transfer and thus chose not to adhere to the recommendation in most women.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☒ Disadvantages outweigh benefits	There is no convincing evidence that first-line tocolysis improve substantive perinatal outcomes as there is no clear reduction in perinatal death or neonatal morbidities associated with preterm birth (e.g. RDS and IVH). Compared with no tocolytic treatment, betamimetics and calcium-channel blockers appear beneficial in delaying birth for more than 48 hours, whereas for other tocolytics, the evidence on pregnancy prolongation is inconclusive. Most tocolytics are associated with side-effects that are often dependent on their class and mechanism of action. These side-effects are very frequent, more disturbing and have important medical implications particularly with betamimetics, but are also considerable for calcium-channel blockers, oxytocin-receptor antagonists and nitric-oxide donors. There are no data to assess long-term benefits or harms of tocolytic therapy compared with no tocolytic therapy. Similarly, there is no consistent evidence that any tocolytic maintenance therapy prolonged pregnancy duration or had any positive effect on maternal and infant outcomes. Some maintenance therapies were associated with considerable side-effects. Overall, the undesirable consequences (maternal side-effects and life-threatening adverse reactions, inconvenience of administration to the mother) outweigh the benefit of short prolongation of the time of birth for the newborn.
Resource use	☒ Less resource intensive ☐ More resource intensive	The implementation of this recommendation is likely to save health-care costs.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The decision to recommend against the intervention was based on the lack of substantive benefits in terms of neonatal critical outcomes; the benefits are outweighed by potential harm to the mother.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG considered the quality of the evidence and the variability in values and preferences of mothers, health-care providers and policy-makers across different settings, and chose to make a conditional recommendation.

Recommendation 3.0: The use of magnesium sulfate is recommended for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy in the infant and child.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The quality of the evidence was moderate to high for critical outcomes relating to infant mortality and serious morbidity and maternal outcomes. Overall, the quality of evidence was rated as moderate.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the survival of a preterm newborn without cerebral palsy. The panel is confident that there is little or no variation of this value among mothers, health-care providers and policy-makers in low-, middle- and high-income settings.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Magnesium sulfate was associated with reductions in cerebral palsy and gross motor dysfunction. Magnesium sulfate increased the risk of minor maternal adverse effects, including hypotension and tachycardia, and in some cases adverse effects led to cessation of treatment. None of the potential harms (including death and serious morbidity) for the fetus, infant or child were increased with antenatal exposure to magnesium sulfate. The neuroprotective benefit of magnesium sulfate was demonstrated in infants up to 33 weeks and 6 days, but the available evidence regarding fetuses less than 30 weeks is less clear. Considering the fact that the risk of neurodevelopmental delay is inversely proportional to the gestational age at birth, it is likely that fetuses less than 30 weeks also benefit. Although the evidence regarding benefits is less clear in the subgroup of women carrying a multiple pregnancy, it is likely that magnesium sulfate would have similar neuroprotective effects in infants resulting from multiple pregnancies as in those of singletons, given the point and direction of the effect estimate. Overall, the desirable consequences for preterm infants whose mothers receive magnesium sulfate at gestation of less than 32 weeks are substantial. These benefits outweigh the potential risk of maternal adverse effects. Beyond 32 weeks, the undesirable consequences for the mother are likely to outweigh the potential benefits.
Resource use	☐ Less resource intensive ☒ More resource intensive	Implementation of this recommendation is likely to increase costs where it is not currently in practice. However, the application of the intervention is likely to be cost–effective.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The moderate-to-high confidence in the magnitude of effects on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the long-term benefits to the preterm infants in terms of reducing gross motor dysfunction and cerebral palsy, the feasibility of implementing the intervention where it is already being used for other maternal indications (e.g. pre-eclampsia), and the potential long-term impact on resource use across settings, and therefore made a strong recommendation.

Recommendation 4.0: Routine antibiotic administration *is not* recommended for women in preterm labour with intact amniotic membranes and no clinical signs of infection.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The overall quality of the evidence was graded as moderate for newborn and maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on preterm infant survival without long-term morbidity and less value on clinical benefits in terms of reduction in maternal infection. The panel is confident that there is no variation of this value among mothers, health-care providers and policy-makers in any setting.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☒ Disadvantages outweigh benefits	Compared with placebo or no treatment, prophylactic antibiotics did not appear to have a significant impact on most of the critical outcomes examined in the review, including severe infant morbidity. Antibiotic prophylaxis appears to reduce maternal infection; however, it may be associated with an increase in neonatal death, and poorer long-term outcomes in children. Although the observed differences between groups were not statistically significant for cerebral palsy or any functional impairment at 7 years, there was a trend towards increased risk in children whose mothers had received antibiotics. Overall, the undesirable consequences for preterm infants considerably outweigh the desirable consequences for the mother.
Resource use	☒ Less resource intensive ☐ More resource intensive	Implementation of this recommendation is likely to reduce costs where routine antibiotic prophylaxis is currently the norm.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The moderate-to-high confidence in the magnitude of effects on highly valued critical newborn outcomes is against the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the considerable short- and long-term harm this intervention could cause to the preterm infant, and the need to curb the widespread use of routine antibiotic prophylaxis globally, and therefore made a strong recommendation.

Recommendation 5.0: Antibiotic administration is recommended for women with preterm prelabour rupture of membranes.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The overall quality of the evidence for the main comparison was graded as moderate for newborn and maternal outcomes.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the benefits in short-term outcomes for the mother and infant (reduction in maternal and neonatal infection). The GDG is confident that there is no variation of this value among mothers, health-care providers and policy-makers in any setting.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Compared with placebo, antibiotics for preterm prelabour rupture of membranes (PPROM) reduced the risk of women giving birth within 48 hours and 7 days, and reduced the risk of chorioamnionitis in the mother. Antibiotics also reduced the risk of neonatal infections including pneumonia, and cerebral abnormality, and were associated with a shorter stay in NICU. On the other hand, antibiotics did not appear to have an impact on other infant mortality or severe morbidity or on longer-term outcomes. Overall, there are desirable short-term benefits for the mother and preterm infants without evidence of harms in the short or long term.
Resource use	☒ Less resource intensive ☐ More resource intensive	Antibiotics are widely available in oral and parenteral forms in all settings. It is feasible to include prophylactic antibiotic therapy into existing health structures that are designed to manage women at risk of imminent preterm birth with minimal costs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The moderate confidence in the magnitude of effects on highly valued critical maternal and newborn outcomes is in favour of the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the short-term benefits to the mother and preterm infants in terms of reducing infection without evidence of harm, the moderate quality of evidence, an even stronger argument for antibiotic use in low-income settings, and wide availability of the recommended antibiotics globally, and therefore made a strong recommendation.

Recommendation 5.1: Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The overall quality of the evidence was graded as moderate.
Values and preferences	☐ No significant variability ☒ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in different settings may choose different types of antibiotics based on costs, availability and many other considerations.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	The desirable consequences for preterm infants whose mothers receive erythromycin for PPROM are substantial without increased risk of harm (such as necrotizing enterocolitis) and highly valued.
Resource use	☐ Less resource intensive ☒ More resource intensive	It is feasible to include erythromycin treatment into existing protocols but at extra costs to the health systems.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The moderate confidence in the magnitude of protective effects on highly valued newborn outcomes (necrotizing enterocolitis) is in favour of the intervention.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG considered the variability in values and preferences of mothers, health-care providers and policy-makers across different settings and chose to make a conditional recommendation.

Recommendation 5.2: The use of a combination of amoxicillin and clavulanic acid ("co-amoxiclav") *is not* recommended for women with preterm prelabour rupture of membranes.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The overall quality of the evidence was graded as moderate.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers, policy-makers, and pregnant women and their families in all settings are likely to place a high value on the risk of harms to the preterm infant (increased risk of necrotizing enterocolitis). The GDG is confident that there is no variation of this value among mothers, health-care providers and policy-makers in any setting.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Broad-spectrum penicillins (excluding co-amoxiclav) are beneficial in reducing neonatal infection (including pneumonia) and major cerebral abnormality detected on ultrasound before discharge. There is a high risk of necrotizing enterocolitis in infants whose mothers received co-amoxiclav compared with either placebo or erythromycin. The undesirable consequences associated with co-amoxiclav outweigh its benefits as an antibiotic for PPROM.
Resource use	☒ Less resource intensive ☐ More resource intensive	It is feasible to exclude co-amoxiclav from the choice of antibiotics for PPROM since other suitable and less harmful options exist. Other penicillins (excluding co-amoxiclav) are readily available and could be easily incorporated into existing protocols for management of women at risk of imminent preterm birth at minimal costs.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The moderate confidence in the magnitude of effects on highly valued critical newborn outcomes is against the use of the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the very high risk of necrotizing enterocolitis among infants of mothers treated with co-amoxiclav, when compared with placebo or erythromycin, the moderate confidence in the effect size, and global availability of other antibiotics that are effective without harm, and therefore made a strong recommendation.

Recommendation 6.0: Routine delivery by caesarean section for the purpose of improving preterm newborn outcomes *is not* recommended, regardless of cephalic or breech presentation.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	The overall quality of evidence was rated as very low for maternal and newborn critical outcomes mainly because of the small sample sizes of the studies in the review.
Values and preferences	☐ No significant variability ☒ Significant variability	Health-care providers, policy-makers, pregnant women and their families in different settings are likely to prefer different mode of birth for preterm infants as this choice is likely to be influenced by health system, social and cultural considerations. With the uncertainty of benefits to the preterm infants, pregnant women and their families in low- and middle-income settings are likely to prefer vaginal birth over caesarean section. Pregnant women in settings where there are fewer cultural restrictions to caesarean birth and good perinatal outcomes for preterm infants may prefer caesarean section over vaginal birth.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☒ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	Women with breech presentation and planned vaginal birth were less likely to experience major postpartum complications, puerperal pyrexia and other maternal infections. For other critical outcomes, including neonatal mortality and serious neonatal morbidity, there was insufficient evidence to assess the harms and benefits of planned caesarean versus vaginal birth for preterm infants. The small sample sizes in the studies meant that they generally lacked statistical power to detect clinically important differences. Overall, there is insufficient evidence to assess the harms and benefits of planned caesarean versus vaginal birth for preterm infants. However, there are known undesirable consequences associated with caesarean birth for the mother irrespective of gestational age at birth.
Resource use	☐ Less resource intensive ☒ More resource intensive	A policy of routine caesarean birth rather than vaginal birth for all preterm infants will significantly increase health-care costs, not just to perform the intervention but also to manage potential maternal morbidities. Additionally, it will further contribute to the rising global rates of caesarean section.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The overall balance of desirable versus undesirable effects is against a policy of routine caesarean birth for all preterm infants.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG considered the very low confidence in the quality of evidence and the variations in values and preferences relating to the interventions across settings, and therefore chose to make a conditional recommendation.

Recommendation 7.0: Kangaroo mother care is recommended for the routine care of newborns weighing 2000 g or less at birth, and should be initiated in health-care facilities as soon as the newborns are clinically stable.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The quality of evidence for most of the critical outcomes, including that for mortality, neonatal infections and hypothermia, was high. However, the GDG decided to rate the overall quality of evidence as moderate because the quality of evidence was moderate for hyperthermia and re-admission to hospital.
Values and preferences	☒ No significant variability ☐ Significant variability	Kangaroo mother care (KMC) provides a very simple-to-implement method for care of low-birth-weight babies. Mothers can be taught to practise at facilities and even continue at home upon discharge. The benefits of KMC go beyond just mortality and morbidity and include improved breastfeeding practices and bonding between mother and baby. These are desired values with known health and social benefits for families, communities as a whole, health-service providers and policy-makers.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was conclusive evidence that, compared to conventional care, KMC reduces mortality, prevents severe infections and nosocomial infections, and reduces the risk of hypothermia; there was some evidence, though inconclusive, of a reduced risk of hyperthermia. No clear harms have been demonstrated with KMC compared to conventional care.
Resource use	☒ Less resource intensive ☐ More resource intensive	Apart from initial set-up costs, the cost of the maintaining implementation of KMC could be low in terms of finance but may require some amount of health workers' time to educate mothers to initiate KMC and maintain the practice.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The moderate-to-high confidence in the magnitude of effects of a relatively cheap intervention on highly valued critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Weak recommendation	The GDG made a strong recommendation considering the moderate- to high-quality evidence, the benefits outweighing the risks, the lack of variability in the values and preferences which were all in favour of the intervention, the low cost, the feasibility of implementing the intervention and the potential impact on health-care resource use across all settings.

Recommendation 7.1: Newborns weighing 2000 g or less at birth should be provided as close to continuous Kangaroo mother care as possible.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The quality of evidence for most of the critical outcomes, including that for mortality, neonatal infections and hypothermia, was high. However, the GDG decided to rate the overall quality of evidence as moderate, because the quality of evidence was moderate for hyperthermia and re-admission to hospital.
Values and preferences	☒ No significant variability ☐ Significant variability	Providing KMC for low-birth-weight and preterm newborns is crucial for thermoregulation. When KMC is practised continuously, the newborn maintains a uniform body temperature, which reduces stress and promotes growth and survival. It may, however, require the mother/carer to carry the baby for all activities. If initiated within facilities, where mothers/carers do not engage in any activity except caring of their baby, the inconvenience may be minimal. Knowing that their baby needs their thermal support for survival and the feeling of being involved in the care of the baby continually may be of value to mothers/carers. The benefits of increased survival will be valued by health-service providers and policy-makers.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	The evidence from the review suggests that providing continuous KMC has benefits in reducing mortality and morbidity for the preterm newborn. There was no evidence of harmful effects of continuous KMC practice.
Resource use	☒ Less resource intensive ☐ More resource intensive	The cost of providing continuous KMC depends on the human resources of the facility invested in the care. That said, it is a relatively cheap intervention and may not cost more than practising intermittent KMC. In the latter, with interspersed use of incubators and radiant warmers, staff time and resource use may be much more.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The confidence in the positive of effects of the continuous KMC (with no added costs to the health systems between continuous or intermittent KMC practice, but the potential for less morbidity which will reduce facility resource use) on highly critical newborn outcomes favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Weak recommendation	The GDG emphasized the moderate- to high-quality evidence, the benefits outweighing the risks, the lack of variability in the values and preferences which were all in favour of the intervention, the fact that there will be no additional costs in implementing continuous compared to intermittent KMC, the feasibility of implementing the intervention and the potential impact on health-care resource use across settings, and therefore made a strong recommendation.

Recommendation 7.2: Intermittent Kangaroo mother care, rather than conventional care, is recommended for newborns weighing 2000 g or less at birth, if continuous Kangaroo mother care is not possible.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The quality of evidence was moderate for neonatal mortality and hyperthermia, but high for all other critical outcomes. The GDG rated the overall quality of evidence as moderate because of imprecision around the mortality effect estimates.
Values and preferences	☒ No significant variability ☐ Significant variability	Providing KMC for low-birth-weight and preterm newborns is crucial for thermoregulation. The benefits and absence of harm with intermittent KMC will be particularly valued by mothers/carers since it will enable them to carry out many of their routine activities. If initiated within facilities, where mothers/carers do not engage in any activity except caring of their baby, the inconvenience may be minimal. It also maintains the satisfaction these mothers/carers will derive from knowing that they are being directly involved in the care of their baby. These benefits will be valued by the mothers/carers, health-care providers and policy-makers.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	While the evidence suggests some benefits of intermittent KMC practice with respect to morbidity reduction, the overall evidence was inconclusive for mortality benefits. There was, however, no clear evidence of harm.
Resource use	☒ Less resource intensive ☐ More resource intensive	The cost of providing intermittent KMC depends on the human resources of the facility invested in the care. That said, it is a relatively cheap intervention. However, if intermittent KMC is interspersed with the use of incubators and radiant warmers, staff time and facility resource use may be relatively more.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG considered that there was enough confidence in the positive of effects of the intermittent KMC (with relatively low costs to the health systems and potential for increased compliance and less morbidity, which will reduce facility human resource use) on highly critical newborn outcomes and therefore favoured the intervention.
Overall strength of the recommendation	☒ Strong recommendation ☐ Weak recommendation	The GDG made a strong recommendation, based on the moderate- to high-quality evidence suggesting that the benefits to the preterm newborn in terms of reducing morbidity and mortality outcomes outweighs the risks. The group also considered the low cost and feasibility of implementing the intervention, as well as the lack of suitable alternatives, across many low- and middle-income settings.

Recommendation 7.3: Unstable newborns weighing 2000 g or less at birth, or stable newborns weighing less than 2000 g who cannot be given Kangaroo mother care, should be cared for in a thermo-neutral environment either under radiant warmers or in incubators.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	The evidence was from only one study conducted in a high-income setting and the mortality effect estimates were imprecise. The overall quality of evidence was rated very low.
Values and preferences	☒ No significant variability ☐ Significant variability	Given the very low quality of evidence and, more importantly, the paucity of data on the relative benefits and harms in sick preterm neonates, health-care providers and policy-makers from both high-income countries (HICs) and low- and middle-income countries (LMICs) are likely to consider the relatively cheaper costs of radiant warmers (compared to incubators) as well as the relative safety in terms of water loss with the incubators. It is very difficult to determine what their choice would be between incubators and radiant warmers and either may be valued on the basis of other factors. The GDG thought incubators are neither superior nor inferior to radiant warmers for the provision of routine thermal care for stable preterm neonates weighing < 2000 g and both will be of value.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was very low-quality evidence suggesting no difference in morbidity and mortality between nursing under radiant warmers or in incubators for these unstable preterm newborns. The risk of insensible water losses increased with the use of radiant warmers compared to incubators. The generalizability of the effects is very low as (a) all the included studies were from HIC settings, and (b) all the studies had enrolled relatively stable preterm infants who were on enteral feeds and gaining weight, and excluded sick infants with respiratory distress. Only one study included infants from day of birth.
Resource use	☒ Less resource intensive ☐ More resource intensive	Incubators are more expensive than radiant warmers. They may not be easily available and may be difficult to maintain in many resource-restricted settings where reliable power supply and adequate human resources to check the proper functioning may be serious challenges.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG considered the paucity of evidence, the urgency in attending to the health of unstable preterm babies and recommended the thermo-neutral environment and thought both radiant warmers and incubators could be used to provide such an environment.
Overall strength of the recommendation	☒ Strong recommendation ☐ Weak recommendation	Based on the benefits to sick or unstable preterm newborns, even though the quality of the evidence was very low, the GDG made a strong recommendation. The group considered that the benefits outweigh the risks and the intervention will be valued in all settings because KMC cannot be practised for these babies.

Recommendation 7.4: There is insufficient evidence on the effectiveness of plastic bags/wraps in providing thermal care for preterm newborns immediately after birth. However, during stabilization and transfer of preterm newborns to specialized neonatal care wards, wrapping in plastic bags/wraps may be considered as an alternative to prevent hypothermia.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	The evidence was derived from component studies that had methodological biases, with inconsistent and imprecise effect estimates or were conducted in high-income settings; hence the GDG graded the overall evidence quality as low.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers and policy-makers in developing-country settings are likely to accept the intervention or value the benefits on hypothermia reduction because it is cheap and easy to apply. Other forms of thermal care such as incubators are not affordable or readily available in these settings and, even where they are, unreliable power supply and poor maintenance as well as difficulty in ensuring aseptic conditions makes these less pragmatic. No study reported a comparison with KMC, but plastic wraps could have competed as another cheap alternative for thermal care. However, with preterm babies already having relatively higher mortality rates, it will be difficult to manage perceptions of mothers/carers and community members that babies placed in these plastic bags are being considered as moribund. This will impact on the acceptability of the intervention.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was a significant reduction in the risk of hypothermia for preterm babies, irrespective of the gestational age, who were wrapped in plastic bags compared with controls. No conclusive evidence of mortality reduction was shown, as most of the trials that assessed the outcome lacked sufficient power to show statistical significance; however, the effect was in the direction of mortality reduction. The only reported adverse outcome with the intervention was hyperthermia, but this was resolved when the wrap was taken off. There was, however, a non-significant increase in the risk of necrotizing enterocolitis.
Resource use	☒ Less resource intensive ☐ More resource intensive	The intervention is low cost, and would be easily accessible and feasible to implement in all settings, including low- and middle-income settings.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The GDG considered the paucity of evidence and decided against the intervention. There was a conditional recommendation specific for facility settings where specialized neonatal care can be provided.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG could not make a recommendation for the routine use of the plastic bags/wraps. It did, however, make a conditional recommendation for the use of the plastic bags and wraps within hospitals to prevent hypothermia in situations where KMC cannot be applied.

Recommendation 8.0: Continuous positive airway pressure therapy is recommended for the treatment of preterm newborns with respiratory distress syndrome.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	The GDG rated the quality of evidence as low because of methodological biases and imprecise effect estimates in the component studies. The studies were also conducted mainly in high-income settings.
Values and preferences	☒ No significant variability ☐ Significant variability	In spite of the low-quality evidence, the reduction in mortality with the use of continuous positive airway pressure (CPAP) is likely to be valued by health-care providers and policy-makers. CPAP may be more expensive than oxygen therapy, but the cost would be justifiable to policy-makers. It presents a potential life-saving intervention and will be preferred to oxygen therapy or might be used and augmented with oxygen therapy.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was low-quality evidence of reduction in in-hospital mortality as well as the need for mechanical ventilation. There was also inconclusive evidence of a possible reduction in the need for surfactant therapy. However, the intervention increased the risk of pneumothorax and air leaks, as well as a possible increase in the risk of bronchopulmonary dysplasia (BPD) for which the evidence was inconclusive.
Resource use	☐ Less resource intensive ☒ More resource intensive	The treatment with CPAP will require more resources – human and material as well as time – than just oxygen by face mask or nasal prongs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG recommendation was in favour of the use of the intervention. This was informed by its potential to save many lives in spite of the costs.
Overall strength of the recommendation	☒ Strong recommendation ☐ Weak recommendation	The GDG acknowledged the low quality of evidence for this recommendation, but considered that the potential for the intervention to improve newborn outcomes was substantial and outweighs the risks. The group felt that though the costs may be high, the intervention will be highly valued in settings where it can be implemented, and were unanimous in making a strong recommendation.

Recommendation 8.1: Continuous positive airway pressure therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	The GDG rated the overall quality of evidence as very low because there were only few trials conducted in high-income settings which had methodological biases and their effect estimates were imprecise.
Values and preferences	☒ No significant variability ☐ Significant variability	Policy-makers and health-care providers will likely place value on the effects of early initiation of CPAP on severe morbidity even if there was inconclusive evidence of a benefit on mortality because of the paucity of data.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was no conclusive evidence for mortality effects in early versus delayed initiation of CPAP because of lack of sufficient data. There was a significant benefit with early therapy in that it showed a lower risk of respiratory failure requiring mechanical ventilation, the need for surfactant therapy and a lower risk of sepsis. These effects could be linked to later mortality benefits. There was no evidence of harm with early initiation of CPAP.
Resource use	☒ Less resource intensive ☐ More resource intensive	Treatment with CPAP will require more resources – human and material as well as time – than just oxygen by face mask or nasal prongs, but starting early or late does not change the material input; rather the evidence of reduced morbidity will mean less facility resources in the long term.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG recommendation was in favour of the use of early rather than delayed CPAP. This was informed by its potential to save many lives.
Overall strength of the recommendation	☒ Strong recommendation ☐ Weak recommendation	In spite of the very low quality of evidence, the GDG considered the potential for the intervention to improve newborn outcomes and the fact that, if CPAP can be administered, there will be no additional cost in starting it early or late and therefore made a strong recommendation.

Recommendation 9.0: Surfactant replacement therapy is recommended for intubated and ventilated newborns with respiratory distress syndrome.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The GDG rated the overall quality of evidence as moderate. The evidence quality was moderate for the mortality outcomes, but low for morbidity outcomes. The trials either were conducted mainly in high-income settings or had imprecise effect estimates.
Values and preferences	☒ No significant variability ☐ Significant variability	Health-care providers and policy-makers will place value on the significant one third reduction in the risk of mortality from the animal-derived surfactants. Since preterm birth is one the most important contributors to neonatal mortality and RDS is a significant contributor to this, this significant effect is especially noteworthy. In many LMICs, the scale of preference and other resource implications may make the surfactant a lower priority. Synthetic surfactants are not commercially available and there are differences in the quality of those available. While new research will be identifying more refined synthetic ones, the benefits of the animal-derived ones overall will make them a preferred option in settings where they can be used.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was conclusive evidence of reduced mortality in preterm babies with RDS who are given surfactant replacement therapy (SRT) whether with synthetic or animal-source surfactants. The emphasis of the balance of benefits versus harms was placed on the animal-derived surfactants because of the non-availability of the synthetic products used in this review. There was also evidence of reduction in the incidence of air leaks with SRT compared with no SRT. However, the evidence was inconclusive on the beneficial effects of the animal-derived surfactants on severe morbidities such as IVH, BPD and sepsis. That said, there was no clear evidence of harm to the preterm even though there were suggestions of a possible increase in the risk of pulmonary haemorrhage.
Resource use	☒ Less resource intensive ☐ More resource intensive	The cost of surfactants is relatively high, especially the synthetic ones. The GDG noted that In HIC settings, surfactant treatment may reduce overall hospital costs, but this might not be the case in LMICs.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG recommendation was in favour of the use of SRT, whether animal derived or synthetic, since the intervention has the potential of improving newborn outcomes.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG considered the potential for the intervention to improve newborn outcomes, and the value that health-care providers and policy-makers will place on its use, to make recommendation conditional on the availability of the right environment and resources (human and other) for implementation.

Recommendation 9.1: Either animal-derived or protein-containing synthetic surfactants can be used for surfactant replacement therapy in ventilated preterm newborns with respiratory distress syndrome.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low	The GDG rated the overall quality of evidence as moderate because all the evidence was derived from trials conducted solely in HICs.
Values and preferences	☒ No significant variability ☐ Significant variability	The results of the review indicate no value in using synthetic surfactants over animal-derived ones in preterm newborns with RDS. The evidence for the newer-generation protein-containing synthetic surfactants was very scanty and the fact that there are already suggestions of protection from severe morbidities like NEC is promising, but the higher costs of these newer-generation surfactants would not make them preferable to natural ones at this time.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There was insufficient evidence of mortality benefits for preterm babies treated with synthetic surfactants compared with those treated with animal-derived ones even though the very low-quality evidence suggested possible mortality benefits from the protein-containing surfactants compared to animal-derived ones. However, protein-containing synthetic surfactants are not available in many countries. There was also evidence that the protein-containing surfactants offered some protection against the incidence of necrotizing enterocolitis in preterm infants. Determinations of differences in the effects of the synthetic surfactants compared to the natural ones on other morbidities were inconclusive.
Resource use	☒ Less resource intensive ☐ More resource intensive	The cost of surfactants is relatively high, especially the synthetic ones.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG recommendation was in favour of the use of either animal-derived or synthetic surfactants since the intervention has the potential of improving newborn outcomes.
Overall strength of the recommendation	☐ Strong recommendation ☒ Conditional recommendation	The GDG considered the potential for the intervention to improve newborn outcomes and placed emphasis on the basic requirements in any setting that will enable the use of SRT. The group thought the recommendation should be conditional and should only be implemented in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available.

Recommendation 9.2: Administration of surfactant before the onset of respiratory distress syndrome (prophylactic administration) in preterm newborns *is not* recommended.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	The GDG considered there were methodological biases in the studies and many were conducted in HICs, and therefore rated the overall quality of evidence as low.
Values and preferences	☒ No significant variability ☐ Significant variability	In settings where CPAP can be routinely administered to preterm newborns for stabilization, the evidence suggests that there will be no value in routine prophylaxis with surfactants. Where CPAP cannot be given, there will be value in routinely administering prophylactic surfactants to preterm babies even before the onset of RDS, but considerations of the costs, the resource requirement and the invasiveness of the procedure compared to CPAP will guide provider preferences and hence policy.
Balance of benefits versus disadvantages	☐ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☒ Disadvantages outweigh benefits	The evidence for mortality reduction with routine prophylactic surfactant administration compared to rescue therapy was inconclusive. In settings where CPAP was used to stabilize the infant within the control group and rescue surfactant therapy was given, the evidence showed that routine prophylactic surfactant had no effect on mortality or morbidity. There was also inconclusive evidence of possible increased harm with respect to increased risks of BPD and pulmonary haemorrhage in the intervention group if CPAP was given to the controls. In settings where prophylactic surfactant administration was compared directly with rescue therapy with no CPAP, some evidence of mortality reduction as well as reduction in air leaks was found.
Resource use	☒ Less resource intensive ☐ More resource intensive	The cost of surfactants is relatively high, especially the synthetic ones, and may require additional human resources for administration.
Recommendation direction	☐ In favour of the intervention ☒ Against the intervention	The GDG considered the risks, costs and resource investment in SRT and recommended against its prophylactic use, especially since it has no added benefits when CPAP (a relatively cheaper option) can be administered.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG considered the potential for harm from the intervention and the resource considerations, and thought the recommendation against prophylactic use should be strong.

Recommendation 9.3: In intubated preterm newborns with respiratory distress syndrome, surfactant should be administered early (within the first 2 hours after birth) rather than waiting for the symptoms to worsen before giving rescue therapy.		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the Evidence	☐ High ☐ Moderate ☒ Low ☐ Very low	There was a lack of studies from LMICs and the included studies had methodological limitations. The GDG rated the overall quality of evidence as low.
Values and preferences	☒ No significant variability ☐ Significant variability	The evidence seems to suggest that for preterm neonates with established RDS and with no CPAP, there will be no value in withholding surfactant therapy within the first 2–3 hours after birth only to give it when the symptoms worsen. Mortality impact is seen when the surfactant is administered early, irrespective of the type of surfactant used. With the reduced risk of air leaks and BPD, early intervention will be preferred by many providers.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	The evidence from this review suggests mortality benefits for preterm babies with RDS when they are intubated and surfactant administration is commenced early (within 2–3 hours after birth). There was also conclusive evidence of beneficial effects on morbidities such as BPD and air leaks. The evidence was, however, inconclusive for the reduction in the risk of IVH or sepsis, although for the latter there was some very low-quality and inconclusive evidence of a possible increase in the risk. No conclusive evidence of harm with early surfactant administration compared to delayed therapy for worsening RDS was demonstrated.
Resource use	☒ Less resource intensive ☐ More resource intensive	The cost of surfactants is relatively high, especially the synthetic ones, but there will be no extra costs in administration of the surfactant whether it is given early or late.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG agreed that, under the right conditions, the benefits of early therapy would favour its choice over late rescue therapy.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG placed its emphasis on the added benefits of early SRT within 2 hours of onset of RDS and therefore made a strong recommendation.

Recommendation 10.0: During ventilation of preterm babies born at or before 32 weeks of gestation, it is recommended to start oxygen therapy with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen. **Recommendation 10.1: The use of progressively higher concentrations of oxygen should only be considered for newborns undergoing oxygen therapy if their heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation with 30% oxygen or air.**		
FACTOR	**DECISION**	**EXPLANATION**
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☒ Very low	There was a paucity of evidence from trials specifically addressing this question. Effect estimates could not be directly assessed or were imprecise, and the trials were all conducted in HICs. The GDG rated the overall quality of evidence as very low.
Values and preferences	☒ No significant variability ☐ Significant variability	Notwithstanding the very low quality of the evidence, the mortality benefit observed with using lower oxygen concentration during resuscitation is likely to be valued by health-care providers as well as policy-makers. Moreover, although not able to demonstrate significant differences, the known effect of higher concentrations of oxygen on critical outcomes such as retinopathy of prematurity and the ease of use of air or lower concentrations of oxygen for resuscitation will be preferred by both providers and policy-makers.
Balance of benefits versus disadvantages	☒ Benefits outweigh disadvantages ☐ Benefits and disadvantages are balanced ☐ Disadvantages outweigh benefits	There is very low-quality evidence that initiating resuscitation with lower oxygen concentration (< 50%) would reduce the mortality in preterm neonates requiring positive pressure ventilation at birth, when compared to initiating resuscitation with higher oxygen concentrations (> 50%). The confidence in this result is, however, low as the only study that showed significant reduction in mortality (and contributed to half of the total weightage in the pooled analysis) had significant risk of selection bias. There is very low-quality and inconclusive evidence of lower risk of severe morbidity such as BPD, IVH and need for mechanical ventilation.
Resource use	☒ Less resource intensive ☐ More resource intensive	Use of air requires significantly less resources than 100% oxygen; it can be administered at even the most remote health-care facilities. However, using slightly higher oxygen concentrations – up to 50% – would require use of blenders, which are not easily available in most LMIC settings and therefore require additional resources.
Recommendation direction	☒ In favour of the intervention ☐ Against the intervention	The GDG was unanimous in favour of low (30%) concentration of oxygen or air at the start and then a progressive increase in concentration guided by the newborn's vital signs, including persisting bradycardia.
Overall strength of the recommendation	☒ Strong recommendation ☐ Conditional recommendation	The GDG acknowledged the paucity of evidence, but made a strong recommendation considering that the demonstrated benefits outweigh the harms for an intervention which will be valued in all settings partly because it is also easy to use.

Annex 3. Summary of declarations of interests from Guideline Development Group (GDG) members and how they were managed

Name and expertise contributed to the guideline development	Declared interest(s)	Management of conflict(s) of interest
Professor Carl Bose Expertise: Content expert and end-user	(i) received a grant for development of a maternal and newborn health registry; (ii) received a grant for development of essential newborn care training materials.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation. Nevertheless, Professor Bose did not chair any session during the Technical Consultation.
Dr Wally Carlo Expertise: Content expert and end-user	(i) his institution received large grants for research for which he was a principal investigator.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.
Dr Agustin Conde-Agudelo Expertise: Content expert and end-user	None declared	Not applicable
Professor Caroline Crowther Expertise: Content expert and end-user	None declared	Not applicable
Dr Therese Dowswell Expertise: Methodologist	(i) her institution received grants to support work on systematic reviews.	As one of the methodologists for this guideline, Dr Dowswell did not have voting rights at the Technical Consultation.
Professor Bissallah Ekele Expertise: Content expert and end-user	None declared	Not applicable
Dr Rogelio Gonzalez Expertise: Content expert and end-user	None declared	Not applicable
Professor Malik Goonewardene Expertise: Content expert and end-user	None declared	Not applicable
Ms Gill Gyte Expertise: Consumer representative	None declared	Not applicable
Dr Natasha Hezelgrave Expertise: Methodologist	(i) gave talks on preterm birth and received grant as part of a fellowship in preterm birth.	As one of the methodologists for this guideline, Dr Hezelgrave did not have voting rights at the Technical Consultation.
Professor William J. Keenan Expertise: Content expert and end-user	None declared	Not applicable
Professor Joy Lawn Expertise: Content expert and end-user	None declared	Not applicable
Professor Pisake Lumbiganon Expertise: Content expert and end-user	None declared	Not applicable
Dr Silke Mader Expertise: Content expert and end-user	None declared	Not applicable

Name and expertise contributed to the guideline development	Declared interest(s)	Management of conflict(s) of interest
Dr Silke Mader Expertise: Content expert and end-user	None declared	Not applicable
Professor Elizabeth Molyneux Expertise: Content expert and end-user	(i) received significant grants for implementing interventions relating to topics covered in the guidelines.	The conflict was not considered serious enough to affect GDG membership. Nevertheless, Professor Molyneux did not vote on or chair discussions of those topics during the Technical Consultation.
Dr Rintaro Mori Expertise: Content expert and end-user	None declared	Not applicable
Professor Ashraf Nabhan Expertise: Content expert and end-user	None declared	Not applicable
Professor James Neilson Expertise: Content expert and end-user	None declared	Not applicable
Ms Regina Obeng Expertise: Content expert and end-user	None declared	Not applicable
Professor Vinod Paul Expertise: Content expert and end-user	(i) an academic who takes positions within government and stakeholder decision-making.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.
Professor Zahida Qureshi Expertise: Content expert and end-user	None declared	Not applicable
Dr Larry Rand Expertise: Content expert and end-user	None declared	Not applicable
Dr Jeeva Sankar Expertise: Methodologist	None declared	As one of the methodologists for this guideline, Dr Sankar did not have voting rights at the Technical Consultation.
Professor Ola Didrik Saugstad Expertise: Content expert and end-user	(i) has published research on some of the topics covered by the guidelines.	The conflict was not considered serious. Nevertheless, Professor Saugstad did not vote on or chair discussions of those topics during the Technical Consultation.
Professor Andrew Shennan Expertise: Content expert and end-user	(i) received sponsorship for research; (ii) his institution also received grants from GlaxoSmithKline, etc., for research.	The conflict was not considered serious enough to affect GDG membership. Nevertheless, Professor Shennan did not chair any session during the Technical Consultation.
Dr Jeffrey Smith Expertise: Content expert and implementer	(i) works for Jhpiego, which receives money and donations for research and programmes in preterm birth; (ii) works with the United States Agency for International Development, Laerdal Foundation and the United Nations Commission on Life-Saving Commodities – all entities with active projects relating to preterm birth .	Dr Smith was accepted as a member of the GDG, but was not allowed to chair any session during the Technical Consultation.

Name and expertise contributed to the guideline development	Declared interest(s)	Management of conflict(s) of interest
Professor Roger F. Soll Expertise: Content expert and end-user	(i) received personal sponsorship; (ii) his institution received grants for research.	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation.
Dr João Paulo Souza Expertise: Content expert and end-user	None declared	Not applicable
Professor Alan Tita Expertise: Content expert and end-user	None declared	Not applicable
Dr Khalid Yunis Expertise: Content expert and end-user	None declared	Not applicable

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