

WHO Recommendations on Interventions to Improve Preterm Birth Outcomes

Highlights and Key Messages from the World Health Organization's 2015 Global Recommendations

Key Messages

- Preterm birth is the single largest cause of perinatal and neonatal mortality and morbidity and the leading cause of death in children under the age of 5.
- Infant deaths and long-term disabilities following preterm birth can be reduced when interventions are appropriately provided to the mother at imminent risk of preterm birth and to the preterm infant after birth.
- Interventions are most effective when applied within a continuum that integrates management of women at risk of imminent preterm birth with postnatal care of preterm infants.
- Accurate gestational age dating is essential to guide appropriate care. Careful attention should be paid to dating of pregnancy with the best method available during early visits for antenatal care.

Background

Preterm babies are prone to serious illness or death during the neonatal period. Without appropriate treatment, those who survive often face lifelong disability and poor quality of life. Complications of prematurity are the single largest cause of neonatal death and currently the leading cause of death among children under 5 years. Therefore, global efforts to further reduce child mortality demand urgent actions to address preterm birth.

Infant death and morbidity following preterm birth can be reduced through interventions provided to the mother at imminent risk of preterm birth and to the preterm infant after birth. These interventions target immediate and future morbidities of the preterm infant, e.g. lung immaturity, susceptibility to infection and neurological complications. The guidelines focus on care of pregnant women at imminent risk of preterm birth (birth <37 weeks gestation) and care of preterm babies during the newborn period, with the aim of improving outcomes for preterm infants. The guidelines do not address prevention of preterm birth.

Highlights of recommended and non-recommended practices to improve preterm birth outcomes

	For women with imminent preterm birth (within 7 days)	For preterm infant (early newborn period)
Recommended	<ul style="list-style-type: none"> • Antenatal corticosteroids (ACS) from 24 to 34 weeks in eligible women, provided certain conditions are met • Antibiotics for preterm prelabour rupture of membranes (PPROM) • MgSO₄ for fetus neuroprotection <32 weeks if preterm birth is likely within 24 hours 	<ul style="list-style-type: none"> • Kangaroo mother care when infant weighs 2,000 g or less and clinically stable • Continuous positive airway pressure (CPAP) for preterm infants with respiratory distress syndrome (RDS) • Surfactant for preterm infants with RDS in facilities meeting minimum criteria • Start oxygen therapy with 30% oxygen or air (if blended oxygen is not available) during ventilation of preterm infants born ≤32 weeks • Progressively higher concentrations of oxygen for neonates undergoing oxygen therapy per defined criteria
Not recommended	<ul style="list-style-type: none"> • Tocolysis (acute or maintenance) for purpose of improving neonatal outcomes • Antibiotics for preterm labour with intact membranes • ACS in women with chorioamnionitis likely to deliver preterm 	<ul style="list-style-type: none"> • Prophylactic surfactant before diagnosis of RDS • Start 100% of oxygen during ventilation of preterm infants born ≤32 weeks

Recommended maternal interventions to improve preterm birth outcomes

Interventions to Improve Preterm Birth: Justification and Policy Implications to Incorporate New Guidelines	
WHO Recommendation 2015	Justification and Policy Implications
I. Maternal Interventions	
Recommendation 1: Antenatal corticosteroids to improve newborn outcomes:	
<p>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:</p> <ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • This 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 and that unnecessary treatment of ineligible mothers is avoided. 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 matured babies are exposed to corticosteroid in utero. • Due consideration should be given to local limits of fetus viability in determining the lowest limit of gestational age when antenatal steroids should be administered, including reference to newborn survival and morbidity data. • Appropriate standard of care for the management of women at risk of imminent preterm birth should be provided to the mother as necessary. This is in addition to corticosteroid therapy in a hospital setting where maternal infections can be detected and treated and delivery of the preterm infant be appropriately managed, including provision of emergency obstetric care. • Essential and special care for the management of preterm neonates should be available and provided to the baby to prevent or address any newborn complication, related to prematurity or otherwise.
<p>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.</p>	<ul style="list-style-type: none"> • Establish national service delivery guidelines/protocols for the identification of women at imminent risk of preterm birth.
<p>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.</p>	<ul style="list-style-type: none"> • 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. • Despite the lack of clarity on the benefits of antenatal corticosteroids in women carrying multiple foetuses, this judgement was based 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 pregnancies.
<p>Recommendation 1.3: Antenatal corticosteroid therapy is recommended in women with preterm prelabour rupture of membranes (PPROM) and no clinical signs of infection.</p>	<ul style="list-style-type: none"> • This recommendation cautions against the use of antenatal corticosteroids for women with prolonged rupture of membranes with features of sepsis.
<p>Recommendation 1.4: Antenatal corticosteroid therapy is not recommended in women with chorioamnionitis who are likely to deliver preterm.</p>	<ul style="list-style-type: none"> • Antenatal corticosteroid therapy should not be initiated at the expense of timely delivery of the woman when indicated by maternal or fetus condition. • Antenatal corticosteroids should be avoided in women with evidence of ongoing systemic infection, e.g. septicaemia or tuberculosis.
<p>Recommendation 1.5: Antenatal corticosteroid therapy is not recommended in women undergoing planned caesarean section at late preterm gestations (34–36⁺⁶ weeks).</p>	<ul style="list-style-type: none"> • While there might be some benefits, there is evidence which suggests potential harms of use of antenatal steroids in late preterms. Elective caesarean section should not normally be performed at any gestation <39 weeks.
<p>Recommendation 1.6: Antenatal corticosteroid therapy is recommended in women with hypertensive disorders in pregnancy who are at risk of imminent preterm birth.</p>	<ul style="list-style-type: none"> • 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.
<p>Recommendation 1.7: Antenatal corticosteroid therapy is recommended for women at risk of imminent preterm birth of a growth-restricted foetus.</p>	<ul style="list-style-type: none"> • Despite concern about the effect of antenatal steroids on fetus growth, there is no evidence to suggest that steroids will perform differently in this subgroup compared to the overall preterm population.

Interventions to Improve Preterm Birth: Justification and Policy Implications to Incorporate New Guidelines

WHO Recommendation 2015	Justification and Policy Implications
<p>Recommendation 1.8: Antenatal corticosteroid therapy is recommended in 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.</p>	<ul style="list-style-type: none"> • Clinicians should ensure strict control of maternal blood glucose prior to and/or during pregnancy to reduce the risk of newborn respiratory distress syndrome. • In women with poorly controlled diabetes, the use of corticosteroids should be considered >34 weeks if there is evidence of lung immaturity.
<p>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.</p>	<ul style="list-style-type: none"> • There is no conclusive evidence on the comparative efficacy of dexamethasone and betamethasone that would support a recommendation of one over the other. • Doses and regimens varied slightly across trials comparing dexamethasone and betamethasone but in a majority, a total steroid dose of 24 mg was administered in divided doses 12 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 most commonly used regimens in the studies. Although there were no data on women's satisfaction, women are likely to prefer fewer injections. • Local protocols on the type and dosing regimen of antenatal steroid should be informed by the preparations that are readily available in the setting to encourage uptake and ease of use by providers, and to avoid incorrect dosing and/or wastage of resources.
<p>Recommendation 1.10: A single repeat course of antenatal corticosteroids 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.</p>	<ul style="list-style-type: none"> • A single course in this context refers to a full dose of antenatal corticosteroid as recommended in these guidelines. • This recommendation should be applied only to women between 24 and 34 weeks of gestation.
<p>Recommendation 2: Tocolysis for inhibiting preterm labour:</p>	
<p>Recommendation 2: Tocolytic treatments (acute and maintenance treatments) are not recommended for women at risk of imminent preterm birth for the purpose of improving neonatal outcomes.</p>	<ul style="list-style-type: none"> • Tocolytic treatment compared with no tocolytic treatment does not demonstrate a reduction in adverse perinatal outcomes. Some tocolytic agents may prolong pregnancy for 2–7 days, but this has not been shown to improve critical neonatal outcomes. • 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 fetus 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. A suggested regimen is 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. When tocolysis is considered, a combination of agents should not be used. • The available evidence regarding the potential risks and lack of information on long-term outcomes following tocolysis should be discussed with the woman and her partner to allow for informed decision-making regarding care. • Consideration of use of tocolytics should be individualized and tocolytics should not be used when there is any obstetric or medical contraindication to prolonging the pregnancy, such as preterm prelabour rupture of membranes.
<p>Recommendation 3: Magnesium sulphate for fetus protection against neurological complications:</p>	
<p>Recommendation 3: The use of magnesium sulphate 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.</p>	<ul style="list-style-type: none"> • Magnesium sulphate for neuroprotection should be given only if preterm birth is likely within the next 24 hours. • Three dosing regimens (IV 4 g over 20 minutes, then 1 g/hour until delivery or for 24 hours; IV 4 g over 30 minutes or IV bolus of 4 g as single dose; and, IV 6 g over 20 to 30 minutes, followed by maintenance infusion of 2 g/hour) have been tested in trials which showed a protective effect on outcomes of cerebral palsy and death or cerebral palsy alone. • There is currently insufficient evidence to recommend a specific dosing regimen over others. • This recommendation applies to women carrying either singleton or multiple pregnancies. • There is a need for further research to establish whether repeated treatment with MgSO₄ for neuroprotection is appropriate (in the event that delivery does not occur).

Interventions to Improve Preterm Birth: Justification and Policy Implications to Incorporate New Guidelines	
WHO Recommendation 2015	Justification and Policy Implications
Recommendations 4–5: Antibiotics for preterm labour:	
Recommendation 4: Routine antibiotic administration is not recommended for women in preterm labour with intact amniotic membranes and no clinical signs of infection.	<ul style="list-style-type: none"> It is important that women with any diagnostic or clinical signs of infection be treated accordingly with antibiotics. There is no clear evidence that prophylactic antibiotics prolong pregnancy. Overall, there is no statistically significant evidence that prophylactic antibiotics reduce perinatal deaths, stillbirth or serious infant morbidity.
Recommendation 5: Antibiotic administration is recommended for women with preterm prelabour rupture of membranes.	<ul style="list-style-type: none"> In order to avoid inadvertent antibiotics administration to women with intact amniotic membranes, antibiotics should not be prescribed unless a definite diagnosis of PPRM has been made. Therefore, a policy to prescribe antibiotics for women with PPRM should be accompanied by protocol to reliably diagnose PPRM. Monitor women for signs of clinical chorioamnionitis.
Recommendation 5.1: Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes.	<ul style="list-style-type: none"> For antibiotic prophylaxis in women with PPRM, oral erythromycin 250 mg four times a day for 10 days (or until delivery) should be used. Where erythromycin is not available, penicillin such as amoxicillin can be used.
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.	<ul style="list-style-type: none"> This recommendation was based on the increased risk of necrotizing enterocolitis with co-amoxiclav when compared with placebo and when compared with erythromycin.
Recommendation 6: Optimal mode of delivery:	
Recommendation 6: Routine delivery by caesarean section for the purpose of improving newborn outcomes is not recommended, regardless of cephalic or breech presentation.	<ul style="list-style-type: none"> There is insufficient evidence to support the routine delivery of preterm infants by caesarean section instead of vaginal delivery, regardless of fetus presentation. Caesarean section should be performed for obstetric indications.

Recommended newborn interventions to improve preterm birth outcomes

II. Newborn Interventions	
Recommendation 7: Thermal care for preterm newborns	
Recommendation 7: Kangaroo mother care (KMC) is recommended for the routine care of newborns weighing 2000 g or less at birth, and should be initiated in health facilities as soon as the newborns are clinically stable.	<ul style="list-style-type: none"> The definition of Kangaroo mother care (KMC) is care of a preterm infant 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 breast milk. Health system issues related to Kangaroo mother care 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.
Recommendation 7.1: Newborns weighing 2000 g or less at birth should be provided as close to continuous Kangaroo mother care as possible.	
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.	
Recommendation 7.3: Unstable neonates 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.	<ul style="list-style-type: none"> The selection of a device for creating the thermo-neutral environment, and the strategies for its use, should be carefully assessed in the relevant context. This context will include the patient population including size, maturity and concurrent illnesses; the physical environment; personnel; cost and other resources.
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.	
Recommendation 8: Continuous positive airway pressure (CPAP) for newborns with respiratory distress syndrome:	
Recommendation 8: Continuous positive airway pressure therapy is recommended for the treatment of preterm newborns with respiratory distress syndrome.	<ul style="list-style-type: none"> Technological context of care including the ability to monitor oxygen saturation and cardiorespiratory status must be considered prior to instituting any respiratory intervention (including supplemental

II. Newborn Interventions													
	<p>oxygen 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.</p> <ul style="list-style-type: none"> • This recommendation should be implemented in health facilities that can provide quality supportive care to neonates. • If oxygen therapy is to be delivered with CPAP, it is strongly advised to use low concentrations of blended oxygen and to titrate upwards with the blood oxygen saturation levels. Where blenders are not available, air should be used. The use of 100% oxygen is not recommended because of demonstrable harms. • Respiratory distress syndrome can be diagnosed on the basis of clinical or radiological criteria. 												
Recommendation 8.1: Continuous positive airway pressure therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made.													
Recommendation 9: Surfactant administration for newborns with respiratory distress syndrome:													
Recommendation 9: Surfactant replacement therapy is recommended for intubated and ventilated infants with respiratory distress syndrome (only in health facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available).	<ul style="list-style-type: none"> • Appropriate surfactant use is associated with a significant reduction in neonatal mortality. • 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 may make the surfactant a lower priority. 												
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.													
Recommendation 9.2: Administration of surfactant before the onset of respiratory distress syndrome (prophylactic administration) in preterm newborns is not recommended.	<ul style="list-style-type: none"> • Control groups in older studies showing benefit of prophylactic administration did not include CPAP, which is now part of standard care. Recent studies where CPAP was given to the control group did not show any evidence of benefit for prophylactic surfactant administration. 												
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 (only in health care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available).													
Recommendation 10: Oxygen therapy and concentration for preterm newborns:													
Recommendation 10: During ventilation of preterm babies born at or before 32 weeks gestation, it is recommended to start oxygen therapy with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen.	<ul style="list-style-type: none"> • This recommendation is consistent with the WHO Guidelines on Basic Newborn Resuscitation. 												
Recommendation 10.1: The use of progressively higher concentrations of oxygen should 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.	<ul style="list-style-type: none"> • 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 after 2 minutes of birth. • The following target saturation levels are consistent with the 25% and 75% centiles (IQR) normograms from evidence summary: <table border="1"> <thead> <tr> <th>Time</th> <th>All preterm infants</th> </tr> </thead> <tbody> <tr> <td>At 2 minutes</td> <td>55–75%</td> </tr> <tr> <td>3 minutes</td> <td>65–80%</td> </tr> <tr> <td>4 minutes</td> <td>70–85%</td> </tr> <tr> <td>5 minutes</td> <td>80–90%</td> </tr> <tr> <td>10 minutes</td> <td>85–95%</td> </tr> </tbody> </table>	Time	All preterm infants	At 2 minutes	55–75%	3 minutes	65–80%	4 minutes	70–85%	5 minutes	80–90%	10 minutes	85–95%
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Measures to monitor adherence with guidelines to improve preterm birth outcomes

Table I. Recommended measures to monitor adherence with guidelines

Measures and indicators that can be adapted at regional and country levels to assess adherence to the guideline recommendations	Suggested indicators:
	• The proportion of all babies at risk of being born from 24 to < 34 weeks of gestation who were exposed to antenatal corticosteroids
	• The proportion of all babies at risk of being born at ≥ 34 weeks of gestation who were exposed to antenatal corticosteroids (inappropriate use of ACS)
	• The proportion of all babies born at <32 weeks of gestation and exposed in utero to magnesium sulphate for fetus neuroprotection
	• The proportion of women with preterm prelabour rupture of membranes who received prophylactic antibiotics
• The proportion of neonates weighing ≤2000 g at birth who received Kangaroo mother care	

Policy and program recommendations

The ultimate goal of these guidelines is to improve the quality of care related to preterm birth and outcomes for preterm infants. It is recommended that countries update their policy and programme materials and activities to support implementation of these new guidelines, including the following actions:

- Review/update national clinical guidelines, pre-service educational materials and in-service training materials to ensure that materials reflect current WHO recommendations to improve outcomes for preterm infants.
- Engage national obstetrics, paediatric, general medicine, nursing and midwifery associations to update their members (e.g. at annual meetings, through newsletters, in continuing medical education sessions, etc.) on the new recommendations and the evidence basis for each recommendation.
- Strengthen the skills of health workers to enable them to follow the recommendations, including development of simple training/supervision materials and provider job aids.
- Support activities to improve the quality of care for women with imminent preterm birth within 7 days and for preterm infants, with a focus on overcoming key health system and care barriers and tracking simple process of care and outcome indicators.
- Use existing platforms (e.g. short message service [SMS] for providers, monthly meetings) to remind providers of recommended practices.
- As part of maternal and perinatal death audits in facilities, identify outdated practices that may be harmful and plan for actions to improve adherence to WHO recommendations.
- Strengthen availability and quality of a minimum set of data to support clinical decision-making, programme management and quality improvement efforts aimed at improving preterm birth care and outcomes.
- Increase provider and community awareness of the signs of threatened preterm birth, importance of early care-seeking and referral to appropriate care level.
- Review and update facility and community health worker referral pathways for women at risk of imminent preterm birth.
- To support these recommendations, design and implement programmes with a strong evaluation component, and engage in implementation research, to generate essential programme learning on implementation strategies and approaches in various settings.

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