

Chapter 7



Interventions to Reduce Maternal and Newborn Morbidity and Mortality

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INTRODUCTION

In 2015, an estimated 303,000 women died as a result of pregnancy and childbirth-related complications (WHO 2015a). Most of these deaths occurred in low- and middle-income countries (LMICs). Sub-Saharan Africa had the highest maternal mortality ratio (MMR) in 2015, an estimated 546 maternal deaths per 100,000 live births; the MMR for high-income countries (HICs) was an estimated 17 maternal deaths per 100,000 live births (map 7.1) (WHO 2015a). Although significant progress has been made since 1990 in achieving the Millennium Development Goals (MDGs), with a reduction in the global MMR from 385 to 216 maternal deaths per 100,000 live births, this reduction falls short of the 2015 MDG 5 target of a 75 percent reduction.

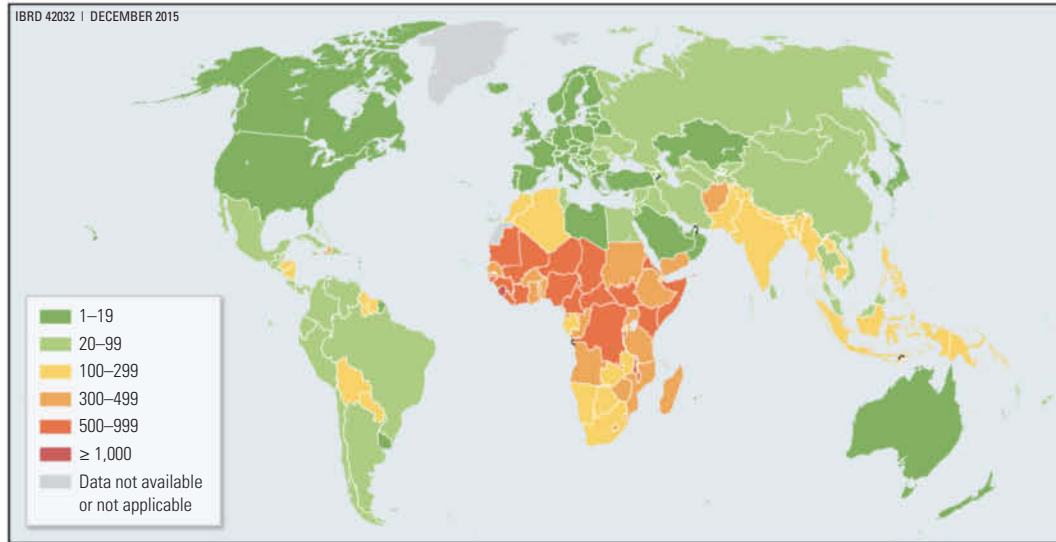
Similarly, mortality for children under age five years (MDG 4) declined by 49 percent, from 12.4 million in 1990 to 5.9 million in 2015, but still substantially short of the 2015 target of a reduction by two-thirds, and the decline is much slower for neonatal deaths (Liu and others 2016). Within countries, when the population is disaggregated by income, education, or place of residence, wide disparities in child mortality can be shown, even in those areas where the overall mortality

seems low. Respiratory infections, diarrhea, and malaria remain important causes of under-five mortality after the first month of life (Liu and others 2016). Neonates account for 45 percent of all deaths under age five years (Liu and others 2016); this share exceeds 50 percent in several regions (Lawn and others 2014). Of all newborn deaths, preterm birth and intrapartum-related complications account for 59 percent (Liu and others 2016), and preterm birth is now the leading direct cause of all deaths under age five years (Lawn and others 2014).

The tracking of progress does not include stillbirths. In 2009, an estimated 2.6 million stillbirths occurred in the last trimester of pregnancy, with more than 45 percent in the intrapartum period (Lawn and others 2011; Lawn and others 2016). The majority of these stillbirths (98 percent) occur in LMICs (Lawn and others 2014).

Significant proportions of these maternal, fetal, and newborn deaths are preventable. A crucial focus of recent initiatives, such as Ending Preventable Maternal Mortality, is quality of care (WHO 2015b). This chapter discusses biomedical interventions for major causes of morbidity and mortality in pregnancy and childbirth in the context of people's right to access good quality, respectful, and timely care—wherever they may live.

Map 7.1 Maternal Mortality Ratio per 100,000 Live Births, 2015



Source: Based on WHO 2015a; map re-created based on WHO 2015a.

INTERVENTIONS TO REDUCE MATERNAL MORTALITY AND MORBIDITY

Major obstetric causes of maternal mortality include hemorrhage (postpartum hemorrhage [PPH], and hemorrhage due to placental abruption, placenta previa, ruptured uterus, and other causes), hypertensive diseases of pregnancy (mainly preeclampsia/eclampsia), and maternal sepsis. In a study conducted across 29 countries in Asia, Latin America and the Caribbean, the Middle East and North Africa, and Sub-Saharan Africa, PPH and preeclampsia/eclampsia each accounted for more than 25 percent of maternal deaths and near-misses; maternal sepsis accounted for approximately 8 percent (Souza and others 2013). The burden of disease due to obstructed labor is difficult to estimate because these data may be coded under sepsis or hemorrhage. However, ruptured uterus, a possible consequence of obstructed labor, accounted for 4.3 percent of maternal deaths and near-miss events in the multicountry study.

Data on indirect causes of maternal deaths—those associated with conditions, such as heart disease, malaria, tuberculosis, and HIV, exacerbated by pregnancy—are also difficult to capture. However, the contribution of indirect causes of maternal deaths is estimated to be about 28 percent and seems to be increasing, particularly in Sub-Saharan Africa (Say and others 2014). In 2015, 2.0 percent of indirect maternal deaths in Sub-Saharan Africa were related to HIV, with the proportion reaching 10 percent or more in five countries (WHO 2015a). This highlights the importance of integrating service delivery during pregnancy and childbirth as recommended by the WHO

Integrated Management in Pregnancy and Childcare (IMPAC) package (WHO 2010a). Interventions to reduce indirect causes of maternal mortality and morbidity are not addressed in this chapter.

Table 7.1 provides an overview of selected medical interventions to reduce poor maternal outcomes for which there is moderate to high-quality evidence.

Postpartum Hemorrhage

Most of the evidence for PPH comes from reviews of studies in both high-income countries (HICs) and LMICs.

Preventing Postpartum Hemorrhage

The most effective intervention for preventing PPH is the use of uterotonics—drugs that contract the uterus—during the third stage of labor before the placenta is delivered. An injectable uterotonic is the drug of choice; however, oral or sublingual misoprostol may be used when injectable uterotonics are not available (table 7.2).

Oxytocin and ergot alkaloids. A Cochrane review assessed the effect of prophylactic oxytocin given during the third stage of labor on PPH (blood loss greater than 500 milliliters) (Westhoff, Cotter, and Tolosa 2013). The review included 20 randomized controlled trials (RCTs) conducted in LMICs and HICs involving 10,806 women. Prophylactic oxytocin, compared with placebo, halved the risk of PPH; when compared with ergot alkaloids, it reduced the risk of PPH by 25 percent. There was no significant difference in the risk of PPH with the combination of oxytocin and ergometrine versus ergot alkaloids alone. Oxytocin was better tolerated than ergot alkaloids.

Table 7.1 Evidence-Based Interventions that Reduce Maternal Morbidity and Mortality

Type of intervention	Main effects	Quality of evidence ^a	Source of evidence
<i>Postpartum hemorrhage (PPH)</i>			
Oxytocin	<ul style="list-style-type: none"> Halves PPH risk when used routinely for prevention Recommended for prevention and treatment 	Moderate	Westhoff, Cotter, and Tolosa 2013; WHO 2012
Misoprostol	<ul style="list-style-type: none"> Reduces PPH risk and the need for blood transfusion Recommended for PPH prevention if oxytocin unavailable 	Moderate	Tunçalp, Hofmeyr, and Gülmezoglu 2012; WHO 2012
<i>Preeclampsia and eclampsia</i>			
Calcium supplementation	<ul style="list-style-type: none"> Halves preeclampsia risk in all women Risk reduction is greatest in high-risk women and those with low dietary calcium intake 	Moderate	Hofmeyr and others 2014; WHO 2013
Aspirin supplementation	<ul style="list-style-type: none"> Reduces the risk of preeclampsia in high-risk women 	Moderate	Duley and others 2007; WHO 2011b
Magnesium sulphate	<ul style="list-style-type: none"> Reduces the risk of first seizure in women with preeclampsia and recurrent seizures in eclampsia, with a trend to reduced maternal mortality 	High	Altman and others 2002; Duley, Gülmezoglu, and others 2010; WHO 2011b
<i>Sepsis</i>			
Prophylactic antibiotics at cesarean section	<ul style="list-style-type: none"> Reduces risk of wound infection, endometritis, and serious maternal infectious morbidity 	Moderate	Smaill and Grivell 2014

Note: This list is not comprehensive. PPH = postpartum hemorrhage.

a. Based on GRADE Working Group grades of evidence (Atkins and others 2004). The GRADE approach considers evidence from randomized trials to be high quality in the first instance, and downgrades the evidence to moderate, low, or very low if there are limitations in trial quality suggesting bias, inconsistency, imprecise or sparse data, uncertainty about directness, or high probability of publication bias. Evidence from observational studies is graded low quality in the first instance and upgraded to moderate (or high) if large effects are yielded in the absence of obvious bias.

Table 7.2 Interventions to Prevent Postpartum Hemorrhage

Evidence-based effective interventions for postpartum hemorrhage prevention
<ul style="list-style-type: none"> Uterotonics used during the third stage of labor: Oxytocin (10 IU IM or IV) is the drug of choice (Westhoff, Cotter, and Tolosa 2013). In settings where oxytocin is unavailable, other injectable uterotonics—ergot alkaloids if appropriate, or the fixed drug combination of oxytocin and ergometrine, or oral misoprostol (600 micrograms)—are recommended (WHO 2012).

Note: IM = intramuscular; IU = international unit; IV = intravenous; µg = microgram.

Misoprostol. A Cochrane review assessed the effect of prophylactic misoprostol compared with uterotonics or no uterotonic given during the third stage of labor to women at risk of PPH (Tunçalp, Hofmeyr, and Gülmezoglu 2012). The review included 72 trials conducted in LMICs and HICs involving 52,678 women. In comparison with oxytocin, oral or sublingual misoprostol was associated with an increased risk of

severe PPH (blood loss greater than 1,000 milliliters). However, misoprostol was significantly more effective than placebo in reducing PPH and blood transfusions. Misoprostol is associated with an increased risk of shivering and fever (temperature of 38°C or higher) compared with oxytocin and placebo. It does not appear to increase or decrease severe maternal morbidity or mortality (Hofmeyr and others 2013).

Misoprostol does not require refrigeration and is inexpensive and easy to administer. In settings in which skilled birth attendants are not present and oxytocin is unavailable, the World Health Organization (WHO) recommends that misoprostol (600 micrograms orally) be given to women in the third stage of labor by community health care workers and lay health workers to prevent PPH (WHO 2012). Continued vigilance for adverse effects is essential. Additional research is needed to further determine the relative effectiveness and the risks of various dosages of misoprostol and to identify the lowest effective dose.

Other Interventions

Uterine massage. Evidence on the efficacy of uterine massage for the prevention of PPH is limited and inconclusive. A Cochrane review evaluated data from two RCTs of 1,491 women that investigated the effects of uterine massage before, after, or both before and after delivery of the placenta (Hofmeyr, Abdel-Aleem, and Abdel-Aleem 2013). No significant difference was observed in uterine blood loss, irrespective of when the massage was initiated, between the intervention and control groups. The WHO does not recommend sustained uterine massage as an intervention to prevent PPH in women who have received prophylactic oxytocin. However, early postpartum identification of uterine atony—failure of the uterus to contract sufficiently—is recommended for all women.

Early versus late cord clamping. A Cochrane review assessed the effects of early cord clamping (less than one minute after birth), compared with late cord clamping after birth, on maternal and neonatal outcomes (McDonald and others 2013). The review included 15 trials conducted in LMICs and HICs involving 3,911 women and infant pairs. There was no significant difference between early versus late cord clamping groups with respect to PPH and severe PPH in the mothers. However, late cord clamping increased early hemoglobin concentrations and iron stores in infants, compared with early cord clamping, and the WHO recommends late cord clamping to improve infant outcomes (WHO 2012).

Controlled cord traction. Two large trials of controlled cord traction (CCT) have been conducted, one of 23,861 women in eight LMICs (Gülmezoglu, Lumbiganon, and others 2012) and the other of 4,013 women in France (Deneux-Tharaux and others 2013). The results of these trials suggest that CCT performed as part of the management of the third stage of labor has no clinically important effect on the incidence of PPH. The WHO weakly recommends CCT by skilled birth attendants (WHO 2012).

Treating Postpartum Hemorrhage

Evidence for the most common interventions for treating PPH due to atony is based on data extrapolated from studies of PPH prevention.

Primary interventions. Emptying the bladder and uterine massage to stimulate contractions are the first steps for the treatment of PPH. Although no high-quality evidence supports these interventions, they allow easier assessment of the uterus and its contractility. Uterine massage is strongly recommended for PPH treatment (WHO 2012). Fluid replacement is a key element in the resuscitation of women with PPH. No RCTs have assessed fluid replacement in this particular condition; the evidence in favor of crystalline fluid replacement is extrapolated from a Cochrane review of fluid replacement in critically ill patients (Perel, Roberts, and Ker 2013).

Drug interventions. The injectable uterotonic drugs oxytocin and ergometrine are both extremely effective in causing uterine contraction. Oxytocin is preferred initially, especially in women with a history of hypertension, because ergometrine can cause hypertension. The intravenous route is recommended for administration of oxytocin. Evidence suggests that administering misoprostol and injectable uterotonics together for PPH treatment does not confer additional benefits (Mousa and others 2014). However, if injectable uterotonics are not available or have been ineffective, misoprostol can be administered. Tranexamic acid may also be given (WHO 2012).

Uterine tamponade. Uterine tamponade, involving a mechanical device to exert pressure from within the uterus, has a reported success rate of between 60 percent and 100 percent (Diemert and others 2012; Georgiou 2009; Majumdar and others 2010; Porreco and Stettler 2010; Sheikh and others 2011; Thapa and others 2010; Yoong and others 2012). This evidence is indirect and comes mainly from case series. The types of devices used for uterine tamponade include urinary catheters (Sengstaken-Blakemore or Foley's), balloon catheters (Bakri and Rusch), and condoms. Although the quality of the evidence is low, the WHO considers the benefits to outweigh the disadvantages and weakly recommends this intervention (WHO 2012).

Artery embolization. Artery embolization is used to treat PPH in facilities with appropriate equipment and expertise. There are no RCTs evaluating this procedure; the evidence from case series and case reports indicates that the success rate ranges between 82 percent and 100 percent (Ganguli and others 2011; Kirby and others 2009; Lee and Shepherd 2010; Touboul and others 2008; Wang and others 2009; Zwart, Dijk, and van Roosmalen 2010). The WHO weakly recommends this intervention (WHO 2012), depending on available resources.

Surgical interventions. Surgical interventions are generally used when other treatments have failed. Surgical interventions include compression sutures (for example, the B-Lynch technique); ligation of the uterine, ovarian, or iliac artery; and total or subtotal hysterectomy. The evidence supporting these procedures is limited because they are emergency, life-saving procedures. The B-Lynch technique has some advantages in that it is relatively simple to perform, preserves fertility, and has good success rates (89 percent to 100 percent) (Price and Lynch 2005). The WHO strongly recommends these life-saving procedures when indicated (WHO 2012).

Nonpneumatic antishock garment. A nonpneumatic antishock garment is a simple low-technology, first-aid device that may help stabilize women with hypovolemic shock, particularly during transport to facilities; however, high-quality research on the garment is lacking. The WHO weakly recommends this intervention, depending on available resources (WHO 2012).

Interventions in the Pipeline

Several lines of active research are underway in PPH prevention and treatment: A large RCT with a sample size of 20,000 is evaluating tranexamic acid compared with placebo in women with PPH (<http://www.thewomantrial.lshtm.ac.uk/>). An inhaled oxytocin development project has been awarded seed funding and is undergoing initial development research in Australia (<http://www.monash.edu.au/pharm/research/iop/>). The WHO is evaluating a room-temperature-stable synthetic oxytocin analogue, carbetocin. In addition, various forms of occlusive gels and foams are in development.

Preeclampsia and Eclampsia

Hypertensive disorders in pregnancy, particularly preeclampsia, complicate 2 percent to 8 percent of all pregnancies, accounting for the majority of the estimated 76,000 annual maternal deaths occurring in LMICs (Duley 2009). A WHO multicountry survey on maternal and newborn health estimates that preeclampsia is associated with more than 25 percent of severe maternal outcomes and is the direct cause of 20 percent of reported maternal deaths (Souza and others 2013). It is associated with 20 percent of infants born prematurely and 25 percent of stillbirths and neonatal deaths (Ngoc and others 2006).

The etiology of preeclampsia is unknown. It is thought to arise from the placenta and is associated with malfunction of the lining of blood vessels. The clinical spectrum of disease in preeclampsia varies, ranging from mild, asymptomatic disease, often occurring close to term, to severe, uncontrolled hypertension typically developing remote from term (less than

34 weeks). Generalized seizures (eclampsia) occur in up to 8 percent of women with preeclampsia in LMICs (Stegers and others 2010), a rate that is 10 times to 30 times more common than in HICs (Duley 2009).

Preventing Preeclampsia

The only interventions that have shown clear benefit in reducing preeclampsia risk in selected populations are low-dose aspirin (Duley and others 2007) and dietary supplementation with calcium (Hofmeyr and others 2014).

Calcium supplementation. A WHO synthesis of evidence from two Cochrane reviews (Buppasiri and others 2011; Hofmeyr and others 2014) involving 15 RCTs conducted in LMICs and HICs and 16,490 women found that calcium supplementation more than halves the incidence of preeclampsia in all women, compared with placebo, with greater reductions in high-risk women and populations with low dietary calcium intake. Calcium supplementation was associated with a 20 percent reduction in the risk of the composite outcome of maternal death or serious morbidity. The WHO strongly recommends that in areas with low dietary calcium intake, calcium supplementation commence in early pregnancy, particularly for women at high risk of preeclampsia, including those with multiple pregnancies, previous preeclampsia, preexisting hypertension, diabetes, renal or autoimmune disease, or obesity (WHO 2011a, 2013).

Low-dose aspirin. In a Cochrane review of 18 trials conducted in LMICs and HICs of prophylactic aspirin in 4,121 pregnant women, low-dose aspirin in women at high risk of preeclampsia was associated with a 25 percent risk reduction (Duley and others 2007). In addition, an 18 percent reduction in the risk of fetal or neonatal death was observed for a subgroup of trials that commenced treatment before 20 weeks' gestation. The WHO recommends low-dose aspirin (75 milligrams a day) to be prescribed and initiated before 20 weeks gestation to those women at high risk of developing preeclampsia (WHO 2011b).

Screening for preeclampsia. Early detection is vital for timely intervention and prevention of progression to severe disease. Monitoring blood pressure and performing urinalysis are the cornerstones of antenatal screening, as are asking about symptoms that may suggest preeclampsia and noting if a fetus is smaller than expected. Detection of preeclampsia should prompt referral for specialist care.

Treating Preeclampsia and Eclampsia

The only definitive cure for preeclampsia is delivery of the baby, by induction of labor or by prelabor cesarean section (CS), to prevent progression of disease and related

morbidity and mortality. The mainstays of treatment are antihypertensive drugs for blood pressure control and magnesium sulphate (MgSO_4) for eclampsia.

Antihypertensive therapy. Antihypertensive therapy in preeclampsia aims to reduce the risk of severe hypertension and stroke, with a steady reduction in blood pressure to safe levels, avoiding sudden drops that may compromise blood supply to the fetus. No evidence is available on the comparative efficacy of commonly used antihypertensive medications, such as labetalol, calcium channel blockers (nifedipine), hydralazine, and methyldopa, for mild to moderate or severe hypertension. All of the agents listed have been used extensively, and the WHO guidelines recognize that they are all reasonable choices for controlling hypertension. The choice of drug should be based on the prescribing clinician's experience with that particular drug, its cost, and local availability (WHO 2011b).

Anticonvulsant prophylaxis and treatment. Substantial evidence exists to demonstrate that MgSO_4 , a low-cost intramuscular or intravenous treatment, is effective in preventing and controlling eclampsia. The Magpie study, a multicountry prospective RCT involving 33 centers and 10,141 women (two-thirds of the participating centers were in LMICs), compared MgSO_4 with placebo in women with preeclampsia. A reduction of more than 50 percent in preeclamptic seizures occurred in the treatment arm, with the number needed to treat of 100 women to prevent 1 case of eclampsia (Altman and others 2002); the number needed to treat fell to 63 for women with severe preeclampsia.

A Cochrane review and meta-analysis of six trials including Magpie confirmed a clinically significant reduction in risk of eclampsia of 59 percent, regardless of the route of administration of MgSO_4 (Duley, Gülmezoglu, and others 2010), with the risk of dying nonsignificantly reduced by 46 percent. Strong evidence indicates that MgSO_4 is also substantially more effective than phenytoin for the treatment of eclampsia (Duley, Henderson-Smart, and Chou 2010). The evidence regarding the effectiveness and safety of a low-dose MgSO_4 regimen is insufficient (Duley, Gülmezoglu, and others 2010); the WHO recommends the administration of the full intravenous or intramuscular regimen involving a loading dose followed by at least 24 hours of maintenance dosing.

Timing of delivery. For mild, moderate, and severe preeclampsia diagnosed at term, the WHO recommends a policy of early delivery by induction of labor, or cesarean section if induction is not appropriate (WHO 2011b). However, limited evidence suggests that induction at more than 36 weeks of gestation reduces poor maternal outcomes in mild preeclampsia (Koopmans and others 2009). For earlier gestations, the decision for delivery

versus expectant management depends on the severity of disease and is influenced by the setting. A Cochrane review finds insufficient evidence for intervention versus expectant management for women with severe preeclampsia between 24 and 34 weeks gestation (Churchill and others 2013); however, the expectant approach is probably associated with less neonatal morbidity. No systematic reviews address the optimal timing of delivery for preeclampsia between 34 and 36 weeks gestation, and significant variation in practice exists. In the absence of robust evidence, the WHO recommends a policy of expectant management for women with severe preeclampsia, both before 34 weeks gestation and between 34 and 36 weeks gestation with a viable fetus, provided that the pregnancy can be monitored for increasing hypertension, maternal organ dysfunction, and fetal distress (WHO 2011b). Clearly, this management requires equitable access to facilities for safe delivery (including CS), skilled attendance at delivery, access to appropriate drugs, and maternal and fetal monitoring.

Technologies and Interventions in the Pipeline

Prevention and treatment. Early calcium supplementation during preconception and early pregnancy, possibly by means of food fortification, is being evaluated by the WHO/PRE-EMPT Calcium in Pre-eclampsia (CAP) study. Funded by the Bill & Melinda Gates Foundation, the trial is being conducted in centers in Argentina, South Africa, and Zimbabwe in populations with known calcium dietary deficiencies. Work is ongoing to assess whether pregnancy and pre-pregnancy supplementation with selenium, which is reduced in preeclampsia (Mistry and others 2008), will affect outcomes from preeclampsia.

The use of statins to treat early-onset preeclampsia has shown initial promise and is under investigation (Ahmed 2011).

Screening. Interest has increased in the development of a blood pressure monitor suitable for settings without medically trained health workers. Such monitors should be automated, validated for accuracy in pregnancy, affordable, and hardwearing, and should have a reliable power supply, for example, solar power or mobile phone charging technology.

Recent evidence from a diagnostic test accuracy study suggests that low plasma levels of placental growth factor can accurately predict delivery within two weeks in women with suspected preeclampsia before 35 weeks' gestation (Chappell and others 2013). In this study, normal levels of placental growth factor accurately predicted which women did not need delivery for preeclampsia within two weeks. This test, which is potentially available as a rapid bedside diagnostic tool, shows

promise as an adjunct to clinical assessment of women with preeclampsia, particularly for its apparent ability to distinguish women who require intensive surveillance and delivery from those who can be managed expectantly as outpatients.

Obstructed Labor

Labor is considered obstructed when the presenting part of the fetus cannot progress through the birth canal despite strong uterine contractions. Obstruction usually occurs at the pelvic brim, but may occur in the cavity or outlet. Causes include cephalopelvic disproportion, shoulder dystocia (fetal shoulders trapped in the pelvis during delivery), and fetal malposition and malpresentation. Obstructed labor accounts for an estimated 4 percent of maternal deaths (Lozano and others 2012), which are caused by ruptured uterus, hemorrhage and puerperal sepsis. Other outcomes, such as obstetric fistulas, lead to considerable long-term maternal morbidity. In LMICs, women with obstructed labor are more likely to have stillbirths, neonatal deaths, and neonatal infections (Harrison and others 2015). Obstructed labor can only be alleviated by means of a CS or other instrumental delivery (forceps, vacuum, symphysiotomy); therefore, referral and appropriate action during labor play a crucial role in reducing the burden of disease.

Preventing Obstructed Labor

A substantial proportion of maternal deaths in LMICs due to obstructed labor occur in community settings, where women are unable to access assisted delivery at health facilities, either because they are disempowered to challenge existing social norms (for example, delivering alone or with traditional birth attendants), or because infrastructure is lacking (for example, roads, transportation, and health facilities). In addition, women may prefer to deliver in the community without skilled assistance because they are afraid of financial costs, low quality of care in health facilities, and disrespectful treatment (Stenberg and others 2013). The first priority for preventing poor outcomes related to obstructed labor is to create the demand for skilled birth assistance and to ensure that this demand can be met.

Maternity waiting homes. A maternity waiting home is a facility that is within easy reach of a hospital or health center that provides antenatal care and emergency obstetric care (van Lonkhuijzen, Stekelenburg, and van Roomalen 2012). Women with high-risk pregnancies or those who live remotely are encouraged to stay at these facilities, if they exist, toward the end of their pregnancies. A Cochrane review conducted in 2012 sought to evaluate the role of maternity waiting homes

on reducing maternal deaths and stillbirths. However, there was insufficient evidence for robust conclusions to be drawn (van Lonkhuijzen, Stekelenburg, and van Roomalen 2012).

External cephalic version. External cephalic version (ECV) is a method of manually encouraging a breech fetus into a cephalic presentation, through the maternal abdomen. Very low quality evidence from a Cochrane review of eight trials conducted in LMICs and HICs involving 1,308 women shows that attempting ECV from 36 weeks gestation may reduce the risk of not achieving a normal vaginal (cephalic) delivery by half, and may reduce the risk of CS by approximately 43 percent (Hofmeyr, Kulier, and West 2015). The WHO currently supports ECV in women with uncomplicated singleton breech presentations at or beyond 36 weeks, but more research is needed.

Treating Obstructed Labor

Cesarean section. CS forms the backbone of the management of obstructed labor and saves many lives. Because of the availability of operative delivery in HICs, maternal deaths there due to obstructed labor are rare; however, CS rates are often disproportionately high in these settings. Overuse of CS has important negative implications for health equity within and across countries (Gibbons and others 2010). A systematic review of ecologic studies finds that maternal, neonatal, and infant mortality decreased with increasing CS rates up to a threshold between 9 percent and 16 percent (Betran and others 2015). Above this threshold, CS rates were not associated with reductions in mortality. Therefore, increasing the availability of CS in countries that show underuse could substantially reduce maternal deaths.

Vacuum and forceps delivery. Operative vaginal delivery may be used to assist women with obstructed labor at the pelvic outlet or low or mid-cavity. Operative vaginal delivery occurs at rates of about 10 percent in HICs, in contrast with the rate of 1.6 percent reported in a large, prospective, population-based study conducted in six LMICs (Harrison and others 2015). Vacuum and forceps procedures are associated with different benefits and risks: forceps are more likely than vacuum to achieve a vaginal delivery but are associated with more vaginal trauma and newborn facial injuries (O'Mahony, Hofmeyr, and Menon 2010). Metal cups may be more effective than soft cups for vacuum delivery, but may be associated with more cephalhematomas in newborns (O'Mahony, Hofmeyr, and Menon 2010). The lack of appropriate and functional equipment, as well as the lack of knowledge, experience, and skills to perform these procedures,

contributes to the low operative vaginal delivery rates in many LMICs. Operator training is vital in all facility settings to maximize benefits and reduce morbidity with vacuum and forceps deliveries.

Symphysiotomy. Symphysiotomy is an operation in which the fibers of the pubic symphysis are partially divided to allow separation of the joint and thus enlargement of the pelvic dimensions during childbirth (Hofmeyr and Shweni 2012). The procedure is performed with local analgesia and does not require an operating theater or advanced surgical skills; it may be a lifesaving procedure for the mother, the baby, or both in clinical situations in which CS is unavailable and there is failure to progress in labor, or in obstructed birth of the aftercoming head of a breech baby.

A Cochrane review found no RCTs evaluating symphysiotomy for fetopelvic disproportion (Hofmeyr and Shweni 2012). Criticism of the procedure because of potential subsequent pelvic instability and because it is considered a second-best option has resulted in its decline or disappearance from use in many countries. Proponents argue that many maternal and neonatal deaths from obstructed labor could be prevented in parts of the world without CS facilities if symphysiotomy was used. Research is needed to provide robust evidence of the relative effectiveness and safety of symphysiotomy compared with no symphysiotomy, or comparisons of alternative symphysiotomy techniques in clinical situations in which CS is not available (Hofmeyr and Shweni 2012).

Maneuvers for shoulder dystocia. A Cochrane review evaluated evidence for maneuvers to relieve shoulder dystocia by manipulating the fetal shoulders (for example, through suprapubic pressure or the corkscrew maneuver), and increasing the functional size of the maternal pelvis by utilizing an exaggerated knee-chest position (Athukorala, Middleton, and Crowther 2006). The evidence from this review of two small trials was insufficient to support or refute any benefits of these maneuvers.

Technologies and Interventions in the Pipeline

The Odon device has been developed to assist vaginal delivery. This technological innovation has the potential to facilitate assisted delivery for prolonged second stage of labor. It consists of a film-like polyethylene sleeve that is applied to the fetal head with the help of an inserter. Because the device is designed to minimize trauma to the mother and baby, it is potentially a safer alternative to forceps and vacuum delivery. A feasibility and safety study is in progress and a comparative trial is planned if it is shown to be safe (WHO Odon Device Research Group 2013).

Maternal Sepsis

Sepsis associated with pregnancy and childbirth is among the leading direct causes of maternal mortality worldwide, accounting for approximately 10 percent of the global burden of maternal deaths (Khan and others 2006). Most of these deaths occur in LMICs; in a prospective study conducted in seven LMICs, 11.6 percent of maternal deaths were due to sepsis (Saleem and others 2014). Although the reported incidence in HICs is relatively low (between 0.1 and 0.6 per 1,000 deliveries), sepsis was reported as the leading direct cause of maternal death in the United Kingdom's Confidential Enquiry into Maternal Death (2006–08 triennium).

Maternal infections occurring before or during the birth of the baby have considerable impact on newborn mortality, and an estimated 1 million newborn deaths associated with maternal infection are recorded each year. Efforts to reduce maternal sepsis have largely focused on avoiding the risk factors, with an emphasis on reducing the frequency of unsafe abortion, intrapartum vaginal examination, and prolonged or obstructed labor; providing antibiotic cover for operative delivery; and using appropriate hospital infection control.

Preventing Maternal Sepsis

The most effective intervention for preventing maternal sepsis is the use of stringent infection control measures to limit the spread of microorganisms, particularly within hospital environments. General measures, such as handwashing with soap or other cleansing agents, are widely acceptable practices for preventing hospital transmissible infections.

Antibiotic prophylaxis in operative vaginal delivery. There is a general assumption that the use of vacuum and forceps–assisted vaginal deliveries increases the incidence of postpartum infections compared with spontaneous vaginal delivery. The evidence from available Cochrane reviews is insufficient to determine whether prophylactic antibiotics given with operative delivery or following third- or fourth-degree perineal tears reduces infectious postpartum morbidities (Buppasiri and others 2010; Liabsuetrakul and others 2004). However, the use of antibiotics among women with a third- or fourth-degree perineal tear is recommended by the WHO for prevention of wound complications (WHO 2014c).

Antibiotic prophylaxis at cesarean delivery. CS is the single most important risk factor for postpartum maternal infection, and routine antibiotic prophylaxis has considerable clinical benefits. In a Cochrane review that includes 95 trials from LMICs and HICs involving more than 15,000 women (Smiall and Grivell 2014), the use of prophylactic antibiotics compared with placebo after CS was associated with substantially

lower risks of endometritis (infection of the lining of the womb) (62 percent reduction), wound infection (60 percent), and serious maternal infectious complications (69 percent reduction). This evidence was considered to be moderate quality.

Preterm and term prelabor rupture of membranes. Rupture of the fetal membranes remote from term carries substantial risk of chorioamnionitis (infection of the fetal membranes) and severe maternal sepsis. Evidence on the benefits of prophylactic antibiotics with preterm rupture of membranes is demonstrated in a Cochrane review of 22 RCTs conducted in LMICs and HICs that involved 6,872 women (Kenyon, Boulvain, and Neilson 2013). Findings reveal that the use of prophylactic antibiotics was associated with a significant reduction in chorioamnionitis (moderate-quality evidence) and markers of neonatal morbidity.

There is no convincing evidence to support the use of prophylactic for prelabor rupture of membranes at term, and this practice should be avoided in its absence (Wojcieszek, Stock, and Flenady 2014).

Vaginal application of antiseptics for vaginal delivery. A Cochrane systematic review of three RCTs involving 3,012 participants assesses the effectiveness and side effects of chlorhexidine vaginal douching during labor (Lumbiganon and others 2004). The review shows no difference in the incidence of chorioamnionitis and postpartum endometritis between women who received chlorhexidine and placebo. No benefits to neonatal infection were observed.

Vaginal application of antiseptics for cesarean delivery. A Cochrane review compares the effect of vaginal cleansing with any antiseptic agent before cesarean delivery to placebo on the risk of maternal infectious morbidities (Haas, Morgan, and Contreras 2013). The review includes five trials involving 1,946 women. The risk of postoperative endometritis was reduced by 61 percent, but no clear difference was detected in postoperative fever or any wound complications. Subgroup analysis suggests that beneficial effects might be greater for women with ruptured membranes.

Treating Maternal Sepsis

Chorioamnionitis and postpartum endometritis. The mainstay of treating maternal sepsis is antibiotics. Although evidence from Cochrane reviews is limited, intrapartum treatment with potent antibiotics is clinically reasonable (Hopkins and Smaill 2002). A Cochrane review of 39 RCTs involving 4,221 women evaluates the comparative efficacy and side effects of different antibiotic regimens for postpartum endometritis (French and Smaill 2004). Wound infection was significantly reduced and treatment was less likely to fail with a combination

of an aminoglycoside (mostly gentamicin) and clindamycin compared with other regimens.

INTERVENTIONS TO REDUCE STILLBIRTHS AND NEWBORN MORTALITY AND MORBIDITY

Addressing stillbirths and neonatal mortality requires interventions across the continuum of care (preconception, antenatal, intrapartum, immediate postnatal period, and after) and interventions across the health system (family and community level, outreach, and clinical care or facility level). Most of these interventions are included in the Lives Saved Tool, developed to model the impact of the interventions at different coverage levels (Walker, Tam, and Friberg 2013), and are part of existing sets of recommended intervention packages for addressing maternal and neonatal outcomes. *The Lancet* Every Newborn Series presents Lives Saved Tool modeling with estimates of lives saved for maternal and neonatal deaths and stillbirths, showing high gains and triple return on investment, with the potential to avert 3 million deaths per year, especially with facility-based care around birth and care of small and sick newborns (Bhutta and others 2014).

RCTs for several well-established interventions that form the cornerstones of newborn care, for example, neonatal resuscitation and thermal care for term newborns, would be impossible for ethical reasons. Important interventions initiated in the antenatal or neonatal period with evidence of health benefits later in childhood, like newborn vaccination or antiretroviral therapy (ART) in babies born to HIV-positive mothers, are not included in this chapter. In addition, we have not covered preconception or adolescent care interventions, such as family planning, for which there is good evidence of a positive impact on perinatal health (Stenberg and others 2013).

Antenatal Interventions

Routine Antenatal Care Visits

A Cochrane review of antenatal care programs reveals that reduced antenatal visits may be associated with an increase in perinatal mortality, compared with standard care (Dowswell and others 2010) (table 7.3). Indirect evidence of the effectiveness of antenatal care in reducing stillbirths is available from further analysis of data from the WHO antenatal care trial, which showed that stillbirth was reduced in the standard care group for participants who received more frequent routine antenatal visits (Vogel and others 2013). This finding is consistent with those of other trials (Hofmeyr and Hodnett 2013).

Table 7.3 Evidence-Based Antenatal Interventions that Reduce Perinatal Morbidity and Mortality

Type of intervention	Main effects	Quality of evidence ^a	Source of evidence
<i>Nutritional</i>			
Folic acid	<ul style="list-style-type: none"> Reduces the risk of neural tube defects when given periconceptually 	High	De-Regil, Fernandez-Gaxiola, and others 2010
<i>Infection prevention and treatment</i>			
Syphilis detection and treatment	<ul style="list-style-type: none"> Reduces stillbirths, neonatal deaths, and preterm birth 	High	Blencowe and others 2011
IPT (malaria-endemic areas)	<ul style="list-style-type: none"> Reduces neonatal mortality and low birthweight Reduces maternal anemia 	High	Radeva-Petrova and others 2014
Insecticide-treated bednets (malaria)	<ul style="list-style-type: none"> Reduces fetal loss and low birthweight 	High	Gamble, Ekwaru, and ter Kuile 2006
Antitetanus vaccine	<ul style="list-style-type: none"> Reduces neonatal mortality from tetanus 	Moderate	Blencowe, Lawn, and others 2010
<i>Intrauterine growth restriction interventions</i>			
Antithrombotic agents in pregnancies identified as high risk	<ul style="list-style-type: none"> Reduces perinatal mortality, preterm birth, and low birthweight 	High	Dodd and others 2013
Doppler velocimetry in high-risk pregnancies	<ul style="list-style-type: none"> Reduces perinatal mortality 	Moderate	Alfirevic, Stampalija, and Gyte 2013
<i>Other interventions</i>			
Labor induction at 41+ weeks for postterm pregnancy	<ul style="list-style-type: none"> Reduces perinatal deaths and meconium aspiration 	High	Gülmezoglu, Crowther, and others 2012
Intensive management of gestational diabetes with optimal glucose control	<ul style="list-style-type: none"> Reduces macrosomia, perinatal morbidity, and mortality 	Moderate	Alwan, Tuffnell, and West 2009; Syed and others 2011

Note: This list is not comprehensive. IPT = intermittent preventive treatment.

a. Based on GRADE Working Group grades of evidence (Atkins and others 2004). The GRADE approach considers evidence from randomized trials to be high quality in the first instance, and downgrades the evidence to moderate, low, or very low if there are limitations in trial quality suggesting bias, inconsistency, imprecise or sparse data, uncertainty about directness, or high probability of publication bias. Evidence from observational studies is graded low quality in the first instance and upgraded to moderate (or high) if large effects are yielded in the absence of obvious bias.

Nutritional Interventions

Folic acid. Several nutritional interventions may be implemented before and during pregnancy. Supplementation of diets with folic acid and fortification of staple commodities periconceptually reduces the risk of neural tube defects that account for a small proportion of stillbirths or neonatal deaths (Blencowe, Cousens, and others 2010; De-Regil and others 2010).

Dietary advice and balanced energy supplementation. Balanced energy and protein supplementation (BES), defined as a diet that provides up to 25 percent of total energy in the form of protein, is an important intervention for the prevention of adverse perinatal outcomes in populations with high rates of food insecurity and maternal undernutrition (Imdad and Bhutta 2012). In a Cochrane review of dietary advice interventions

that includes 15 trials involving 7,410 pregnant women (Ota and others 2012), the risk of stillbirth and small-for-gestational-age babies was reduced by 38 percent for women receiving BES advice, and mean birthweight was increased. Further research on the effectiveness and implementation of BES is necessary.

Maternal calcium supplementation. The WHO synthesized evidence from two systematic reviews on maternal calcium supplementation (Buppasiri and others 2011; Hofmeyr and others 2014) and found moderate-quality evidence that calcium supplementation has no effect on preterm birth overall (WHO 2013). The WHO recommends maternal calcium supplementation from 20 weeks' gestation in populations in which calcium intake is low to reduce the risk of hypertensive disorders in pregnancy (WHO 2013).

Maternal zinc supplementation. Some evidence suggests that zinc supplementation may reduce the risk of preterm birth. A Cochrane review of the intervention includes 20 RCTs involving more than 15,000 women and infants (Mori and others 2012). Zinc supplementation resulted in a small but significant reduction in preterm birth of 14 percent, without any other significant benefits compared with controls. The reviewers conclude that studies of strategies to improve the overall nutrition of populations in impoverished areas, rather than studies of micronutrient supplementation in isolation, should be a priority.

Antenatal Treatment of Maternal Infections

Maternal infections frequently have adverse effects on perinatal outcomes, and striking mortality reductions can be obtained by antenatal interventions related to malaria, HIV, syphilis, and tetanus.

Tetanus. A review of tetanus toxoid immunization concludes that there is clear evidence of the high impact of two or more doses of tetanus vaccine in pregnancy on reducing neonatal tetanus mortality (Blencowe, Lawn, and others 2010). Immunizing pregnant women or women of childbearing age with at least two doses of tetanus toxoid was estimated to reduce mortality from neonatal tetanus by 94 percent.

Syphilis. Pregnant women with untreated syphilis have a 21 percent increased risk of stillbirths (Gomez and others 2013). Evidence of the effect of antenatal syphilis detection combined with treatment with penicillin suggests a significant reduction in stillbirths, preterm births, congenital syphilis, and neonatal mortality (Blencowe and others 2011).

Malaria. Effective prevention strategies for malaria include prophylactic antimalarial drugs through intermittent preventive treatment (IPT) and insecticide-treated bednets (ITNs). IPT has been shown to improve mean birthweight and reduce the incidence of low birthweight and neonatal mortality (Radeva-Petrova and others 2014). ITNs have been shown to reduce fetal loss by 33 percent (Gamble, Ekwaru, and ter Kuile 2006). The WHO recommends the use of long-lasting ITN and IPT with sulfadoxine-pyramethamine to prevent infection during pregnancy in malaria-endemic areas in Africa (WHO 2014b).

HIV. Most children with HIV acquire it from their mothers, and ART is vital in preventing vertical (mother-to-child) transmission. Triple drug regimens commenced antenatally are most effective; however, short ART courses commencing before labor, with treatment extended to newborns during the first week of life, have been shown to significantly reduce mother-to-child HIV transmission (Siegfried and others 2011). The WHO guidelines

recommend that all pregnant women who are eligible for ART (CD4 \leq 350 cells per cubic millimeter or advanced clinical disease) should receive it (WHO 2010b). For ineligible women, combination ART should be provided during pregnancy beginning in the second trimester and should be linked with postpartum prophylaxis (WHO 2010b). Findings from the Kesho-Bora trial, in which early weaning was associated with higher HIV-related infant mortality even with maternal ART prophylaxis during breastfeeding, highlight the importance of breastfeeding in low-resource settings (Cournil and others 2015). ART prophylaxis in these settings should be provided to either the mother or infant for the duration of breastfeeding.

Other infections. There is currently no conclusive evidence of the effects on perinatal outcomes of using viral influenza, pneumococcal, and *Haemophilus influenzae* type b vaccines during pregnancy (Chaithongwongwatthana and others 2012; Salam, Das, and Bhutta 2012).

Treatment of Diabetes Mellitus and Gestational Diabetes

Complications of diabetes range from variations in birthweight to fetal malformations and potentially an excess of perinatal mortality. Any specific treatment for gestational diabetes versus routine antenatal care is associated with a reduction in perinatal mortality (Alwan, Tuffnell, and West 2009). Intensified management including dietary advice, monitoring, or pharmacotherapy for women with gestational diabetes mellitus, when compared with conventional management, resulted in a 54 percent reduction of macrosomic ($>$ 4,000 grams) babies. It was also associated with statistically nonsignificant reductions in other outcomes, including perinatal death, stillbirths, neonatal hypoglycemia, shoulder dystocia, CS, and birthweight (Lassi and Bhutta 2013). Optimal blood glucose control in pregnancy compared with suboptimal control was associated with a 60 percent reduction in the risk of perinatal mortality but a statistically insignificant impact on stillbirths (Syed and others 2011).

Intrauterine Growth Restriction

Risk factors for stillbirths and intrauterine growth restriction (IUGR) largely overlap, and growth-restricted fetuses are at increased risk of mortality and serious morbidity. Improved detection and management of IUGR using maternal body mass index, symphysio-fundal height measurements, and targeted ultrasound could be effective in reducing IUGR-related stillbirths by 20 percent (Imdad and others 2011).

Doppler velocimetry. A Cochrane review of RCTs in HICs shows that the use of Doppler ultrasound of

umbilical and fetal arteries in high-risk pregnancies was associated with a 29 percent reduction in perinatal mortality; however, the specific effect on stillbirths was not significant (Alfirevic, Stampalija, and Gyte 2013).

Antithrombotic agents. Treatment with heparin for pregnant women considered to be at high risk of complications secondary to placental insufficiency leads to a significant reduction in the risk of perinatal mortality, preterm birth, and infant birthweight below the 10th centile for gestational age when compared with no treatment (Dodd and others 2013).

Fetal movement counting. The lack of trials has resulted in insufficient evidence of any benefits of routine fetal movement counting (Mangesi, Hofmeyr, and Smith 2007). However, a reduction in fetal movements may be indicative of fetal compromise; when identified by the mother, awareness could trigger prompt care seeking and further assessment.

Postterm Pregnancy

Elective induction of labor in low-risk pregnancies at or beyond 41 weeks gestation (late term) is recommended in settings with adequate gestational age dating and appropriate facility care. In a Cochrane review of 22 RCTs involving 9,383 women of late-term labor induction, compared with expectant management, the newborns of women who were induced were 69 percent less likely to die perinatally and 50 percent less likely to aspirate meconium (Gülmezoglu, Crowther, and others 2012); there was no significant reduction in stillbirths.

Intrapartum Interventions

Labor surveillance is needed for early detection, clinical management, and referral of women for complications. Basic emergency obstetric care should be available at first-level facilities providing childbirth care. This basic emergency care includes the following:

- The capacity to perform assisted vaginal delivery (including vacuum or forceps assistance for delivery, episiotomy, advanced skills for manual delivery of the infant with shoulder dystocia, and skilled vaginal delivery of the breech infant)
- Availability of parenteral antibiotics, parenteral oxytocin, and parenteral anticonvulsants for preeclampsia or eclampsia
- Skills for manual removal of the placenta and removal of retained products.

Because stillbirths and intrapartum-related neonatal deaths are often associated with difficult and obstructed

labor, assisted vaginal delivery and CS are vital to reduce perinatal morbidity and mortality.

Worldwide, an estimated 40 million births occur at home, most in LMICs and usually in the absence of skilled birth attendants. Limited evidence from two before-and-after studies of community-based skilled birth attendance shows a 23 percent significant reduction in the risk of stillbirth (Yakoob and others 2011). Although there has been an increase in the use of skilled birth attendants globally, much remains to be done for the organization and provision of services; however, this issue is beyond the scope of this chapter. An overview of selected intrapartum interventions can be found in table 7.4.

General Interventions

Hygiene. Poor hygienic conditions and poor delivery practices contribute to the burden of neonatal mortality. Pooled data from 19,754 home births at three sites in South Asia indicate that the use of clean delivery kits or clean delivery practices almost halves the risk of neonatal mortality (Seward and others 2012). The use of a plastic sheet during delivery, a boiled blade to cut the cord, a boiled thread to tie the cord, and antiseptic to clean the umbilicus were each significantly associated with reductions in mortality, independent of kit use.

The partograph. A partograph is usually a preprinted form that provides a pictorial overview of labor progress that can alert health professionals to any problems with the mother or baby (Lavender, Hart, and Smyth 2013). Although the partograph is widely used and accepted to detect abnormal labor, strong evidence to recommend its general use is lacking (Lavender, Hart, and Smyth 2013). Until stronger evidence is available, the WHO supports the use of a partograph with a four-hour action line for monitoring the progress of labor (WHO 2014a).

Fetal monitoring in labor. There is no evidence that the use of electronic fetal heart rate monitoring during labor reduces perinatal mortality. A Cochrane review of 13 RCTs involving more than 37,000 women of continuous cardiotocography compared with intermittent auscultation shows no reduction in perinatal mortality (Alfirevic, Devane, and Gyte 2013). Continuous cardiotocography halved the risk of neonatal seizures without significant reductions in cerebral palsy, infant mortality, or other standard measures of neonatal well-being and was associated with an increased risk of assisted and operative delivery.

Active management of labor. Active management refers to a package of care that includes strict diagnosis of labor, routine amniotomy, oxytocin for slow progress, and one-to-one support (Brown and others 2013). A Cochrane review of seven RCTs involving 5,390 women finds

Table 7.4 Evidence-Based Intrapartum and Neonatal Interventions that Reduce Perinatal Morbidity and Mortality

Type of intervention	Main effects	Quality of evidence ^a	Source of evidence
<i>General</i>			
Clean delivery kits	<ul style="list-style-type: none"> Reduces neonatal mortality 	Moderate	Seward and others 2012
<i>Preterm birth and PPRM</i>			
Antenatal Corticosteroids	<ul style="list-style-type: none"> Reduces neonatal mortality Reduces the risk of RDS and other neonatal morbidities 	Moderate	Roberts and Dalziel 2006
Magnesium sulphate	<ul style="list-style-type: none"> Reduces the risk of cerebral palsy in preterm infants 	Moderate	Doyle and others 2009
Antibiotics (PPROM only)	<ul style="list-style-type: none"> Reduces neonatal infection 	High	Kenyon, Boulvain, and Neilson 2013
Surfactant	<ul style="list-style-type: none"> Reduces RDS-related mortality 	Moderate	Segeer and Soll 2009; Soll and Özek 2010
<i>Neonatal care</i>			
Kangaroo mother care	<ul style="list-style-type: none"> Reduces mortality in low-birthweight infants 	High	Conde-Agudelo, Belizán, and Diaz-Rossello 2014
Cord cleansing (chlorhexidine)	<ul style="list-style-type: none"> Reduces neonatal mortality and omphalitis in community settings 	Low-Moderate	Imdad and others 2013; WHO 2014c
<i>Hypoxic ischemic encephalopathy</i>			
Induced hypothermia	<ul style="list-style-type: none"> Reduces mortality 	High	Jacobs and others 2013
<i>Neonatal sepsis</i>			
Community-administered antibiotics	<ul style="list-style-type: none"> Reduces all-cause neonatal mortality and pneumonia-specific mortality 	Moderate	Zaidi and others 2011

Note: This list is not comprehensive. PPRM = preterm premature rupture of membranes; RDS = respiratory distress syndrome.

a. Based on GRADE Working Group grades of evidence (Atkins and others 2004). The GRADE approach considers evidence from randomized trials to be high quality in the first instance, and downgrades the evidence to moderate, low, or very low if there are limitations in trial quality suggesting bias, inconsistency, imprecise or sparse data, uncertainty about directness, or high probability of publication bias. Evidence from observational studies is graded low quality in the first instance and upgraded to moderate (or high) if large effects are yielded in the absence of obvious bias.

no significant difference in poor neonatal outcomes; however, CS rates were nonsignificantly reduced in the active management group (Brown and others 2013).

Preterm Labor and Preterm Prelabor Rupture of Membranes

Antenatal corticosteroids. The administration of antenatal corticosteroids to women in preterm labor, or in whom preterm delivery is anticipated (for example, in severe preeclampsia), for the prevention of neonatal respiratory distress syndrome (RDS) has been shown to be very effective in preventing poor neonatal outcomes in well-resourced settings. A Cochrane review of 21 RCTs involving 4,269 neonates finds that a single course of steroids administered between 26 weeks and 35 weeks gestation reduced the risk of neonatal death by 31 percent and reduced neonatal morbidity including cerebroventricular hemorrhage, necrotizing enterocolitis, RDS, and systemic infections

(Roberts and Dalziel 2006). However, a large cluster randomized trial (Antenatal Corticosteroids Trial) conducted in LMICs to test provision of antenatal corticosteroids at lower levels of the health system with mainly unskilled workers and limited assessment of gestational age finds no difference in neonatal mortality with the administration of antenatal corticosteroids (Althabe and others 2015). Neonatal mortality in the intervention clusters overall was increased, which may have been due to overtreatment, as were maternal infections. This trial has important implications for the setting, implementation, and scale up of this intervention, notably that antenatal corticosteroids should be used in the context of more accurate assessment of gestational age and assessment for maternal infection; ensuring that maternal and newborn care can be provided should also be a part of this intervention. In the Antenatal Corticosteroids Trial, half of the births were at home (Althabe and others 2015).

Antibiotics. The evidence does not support the routine administration of antibiotics to women in preterm labor with intact membranes in the absence of overt signs of infection (Flenady and others 2013). However, antibiotics for preterm premature rupture of membranes are effective in reducing the risk of a number of early morbidities, including RDS and postnatal infection, without having a significant impact on mortality (Kenyon, Boulvain, and Neilson 2013).

Magnesium sulphate. A Cochrane review of five RCTs involving 6,145 babies found that MgSO₄ given to women considered to be at risk of preterm birth reduced the risk of cerebral palsy by 32 percent and improved long-term outcomes into childhood (Doyle and others 2009). However, evidence is insufficient to determine the existence of neuroprotective benefits for infants of women with high-risk pregnancies at term (Nguyen and others 2013), and more research is needed.

Newborn Resuscitation

Training of birth attendants. Newborn resuscitation is not available for the majority of newborns in LMICs. Limited evidence suggests that training of birth attendants improves initial resuscitation practices and reduces inappropriate and harmful practices (Carlo and others 2010; Opiyo and English 2010) but may not have a significant impact on perinatal mortality. This finding may be because advanced resuscitation, including intubation and drugs, is appropriate only in institutions that provide ventilation. A large cluster RCT of a combined community- and facility-based approach with a package of interventions including community birth attendant training, hospital transport, and facility staff training finds the intervention package to have no detectable impact on perinatal mortality (Pasha and others 2013). This finding suggests that substantially more infrastructure may be necessary, in addition to provider training and community mobilization, to have a meaningful effect on neonatal outcomes.

Essential Newborn Care

The WHO defines essential newborn care as including cleaning, drying, and warming the infant; initiating exclusive breastfeeding; and cord care (WHO 2011a). Ideally, this care should be provided by a skilled attendant; however, most of these tasks can be carried out at home by alternative attendants.

High-quality evidence shows that home visits by community health workers in the first week after birth significantly reduces neonatal mortality and are strongly recommended by the WHO (WHO 2014c).

Neonatal Interventions

The immediate cause of many of the world's 2.8 million annual neonatal deaths is an illness presenting as an emergency, either soon after birth (such as complications of preterm birth and intrapartum hypoxia) or later (due to neonatal tetanus or community-acquired infections). Other important but less prevalent conditions include jaundice and hemorrhagic disease of the newborn. These conditions all have high fatality rates, particularly tetanus and encephalopathy (Lawn and others 2014).

Preventive measures needed to adequately reduce this burden of disease include much of what has already been discussed. Other interventions include routine vitamin K administration in newborns for the prevention of vitamin K deficiency bleeding and early phototherapy for jaundice. Early phototherapy reduces both mortality and chronic disability subsequent to kernicterus and is feasible in facilities (Djik and Hulzebos 2012; Maisels and others 2012).

Postnatal Care

Kangaroo mother care. Kangaroo mother care, which is part of the extra newborn care package for small and low-birthweight infants and includes continuous skin-to-skin contact between mothers and newborns, frequent and exclusive breastfeeding, and early discharge from hospital, has been evaluated in comparison with conventional care in a Cochrane review. The review includes 18 RCTs involving 2,751 infants (Conde-Agudelo, Belizán, and Diaz-Rossello 2014). In low-birthweight infants, kangaroo mother care reduced neonatal mortality by 40 percent, hypothermia by 66 percent, and nosocomial infection by 55 percent.

Exclusive breastfeeding. The WHO recommends exclusive breastfeeding of infants until age six months (WHO 2014c). Infants who are exclusively breastfed for six months experience less gastrointestinal morbidity (Kramer and Kakuma 2012), less respiratory morbidity, and less infection-related neonatal mortality than partially breastfed neonates (WHO 2014c). A meta-analysis shows that breastfeeding education or support (or a combination of education and support) increased exclusive breastfeeding rates (Haroon and others 2013). For small or preterm babies, extra feeding support is needed (WHO 2011a).

Cord cleansing. Pooled data from three community trials involving 54,624 newborns of cord care with chlorhexidine versus dry care show a reduction in omphalitis of 27 percent to 56 percent and in neonatal mortality of 23 percent (Imdad and others 2013). Chlorhexidine cord cleansing did not have these effects when used in hospital settings

(Sinha and others 2015). The WHO recommends daily chlorhexidine application to the umbilical cord stump during the first week of life for newborns who are born at home in settings with high neonatal mortality (WHO 2014c).

Management of Neonatal Encephalopathy

Seizures are common following perinatal hypoxic ischemia. Induced hypothermia (cooling) in newborn infants who are encephalopathic because of intrapartum hypoxia reduces neonatal mortality, major neurodevelopmental disability, and cerebral palsy. This evidence is derived from a Cochrane review of 11 RCTs involving 1,505 term and late preterm infants with moderate or severe hypoxic ischemic encephalopathy (Jacobs and others 2013). Cooling reduced neonatal mortality by 25 percent and the authors conclude that induced hypothermia should be performed in term and late preterm infants with moderate or severe hypoxic ischemic encephalopathy if identified before age six hours (Jacobs and others 2013). However, most of these studies were conducted in HICs and more trials in LMICs are needed before implementing this intervention in these settings. Routine anticonvulsant prophylaxis with barbiturates for the neuroprotection of term infants with perinatal asphyxia is not recommended (Evans, Levene, and Tsakmakis 2007).

Management of Respiratory Distress Syndrome

RDS is the most important cause of mortality in preterm infants. Administration of surfactant in preterm infants significantly decreases the risk of poor neonatal outcomes, but cost is a major factor for LMICs (Seger and Soll 2009; Soll and Özek 2010). Institution of continuous positive airway pressure may bring down the requirement and cost of surfactant therapy (Rojas-Reyes, Morley, and Soll 2012).

Management of Neonatal Sepsis

Antibiotics for treatment. Over 1 million neonatal deaths annually in LMICs are attributable to infectious causes, including neonatal sepsis, meningitis, and pneumonia (Liu and others 2016). Feasible and low-cost interventions to prevent these deaths exist. Oral antibiotics administered in the community reduce all-cause mortality by 25 percent and pneumonia-specific mortality by 42 percent (Zaida and others 2011).

Presumptive antibiotics for group B streptococcus. The risk of serious infection in term newborn infants is increased if group B streptococcus (GBS) is present in the birth canal, if rupture of membranes is prolonged, and if maternal temperature is raised during labor. A Cochrane review of intrapartum antibiotic

prophylaxis (IAP) for mothers colonized with GBS (three trials and 500 women) finds low-quality evidence that early neonatal GBS infection was reduced with IAP compared with no prophylaxis (Ohlsson and Shah 2014). European consensus recommends IAP based on a universal intrapartum GBS screening strategy (Di Renzo and others 2014); however, data on GBS prevalence are not routinely available to inform policies in most LMICs. In the absence of GBS screening and strong evidence to guide clinical practice regarding routine prescription of antibiotics (Ungerer and others 2004), the use of presumptive antibiotic therapy for newborns at risk of GBS and other bacterial infections is recommended (WHO 2011a).

Interventions in the Pipeline

Household air pollution is recognized as a risk factor for several health outcomes, including stillbirth, preterm birth, and low birthweight, but rigorous evidence for the impact of reducing household air pollution on these birth outcomes is lacking (Bruce and others 2013). Interventions to reduce household air pollution may reduce poor perinatal outcomes.

A habitual supine sleeping position has been associated with an increase in stillbirth (Owusu and others 2013). Whether sleeping position can be changed by advice or other interventions, and whether such a change would affect stillbirth rates, remains to be established.

COST-EFFECTIVENESS OF INTERVENTIONS

Increasing the coverage of interventions demonstrated to be effective and cost-effective is essential, but reliable data remain limited (Mangham-Jefferies and others 2014). Chapter 17 of this volume (Horton and Levin 2016) summarizes the findings of a systematic search of the cost-effectiveness literature of reproductive, maternal, newborn, and child health interventions and discusses the difficulties, including methodological gaps, multiple platforms, and outcome measures.

For the 75 high-burden Countdown countries, Bhutta and others (2014) estimate that the additional funding required to scale up effective interventions to reduce preventable maternal and newborn deaths and still births is US\$5.65 billion annually, which they equate to US\$1.15 per person, excluding the initial investment in new facilities. They further estimate that increased coverage and quality of care would reduce maternal and newborn deaths and prevent stillbirths at a cost of US\$1,928 per life saved (or US\$60 per disability adjusted

life-year [DALY] averted); 82 percent of this effect would be from facility-based care.

Costs per DALY averted have been estimated for training initiatives (for example, LeFevre and others 2013), participatory women's groups (for example, Fottrell and others 2013), and safe motherhood initiatives (for example, Erim, Resch, and Goldie 2012), and range from US\$150 to US\$1,000. Cost estimates for CS for obstructed labor have a wider range (US\$200 to US\$4,000 per DALY averted, depending on the country), with a median of slightly more than US\$400 (Alkire and others 2012). Other innovations with lower costs per DALY averted, in the range of US\$20–US\$100—for example, clean delivery kits for home births (Sabin and others 2012)—have a modest impact on DALYs averted.

CONCLUSIONS

Although evidence of effectiveness is not available for several vital interventions, these interventions save the lives of thousands of mothers and newborns every day. For other simple interventions, research has demonstrated convincingly that, if provided in the appropriate time and with the appropriate protocol, many more lives can be saved. However, effective interventions are not consistently used or available in LMICs, and accelerated investments are needed in health system infrastructure, intervention implementation, health worker training, and patient education to improve health outcomes for mothers and newborns.

Even in the poorest settings simple approaches at the family and community levels and through outreach services can save many lives now. Well-known interventions, such as neonatal resuscitation and case management of infections, can be added to existing programs, particularly Safe Motherhood and Integrated Management of Childhood Illness programs, at low marginal cost. Although community-based options are often most feasible, if the commitment to strengthen clinical care systems is lacking, the potential improvements in health outcomes from these options is limited.

Scaling-up of skilled care for pregnancy and childbirth is still required to reach the MDGs in LMICs. However, as increasing numbers of women and babies reach first-level facilities and hospitals, the quality of care challenges in these facilities need to be addressed. A shift in focus to quality of care has the potential to unlock significant returns for every mother and every newborn beyond 2015 to end preventable maternal and newborn deaths and stillbirths by 2030.

NOTE

For consistency and ease of comparison, *DCP3* is using the World Health Organization's Global Health Estimates (GHE) for data on diseases burden, except in cases where a relevant data point is not available from GHE. In those instances, an alternative data source is noted.

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - a) lower-middle-income = US\$1,046 to US\$4,125
 - b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

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