

Chapter 7. Interventions to Reduce Maternal and Child Morbidity and Mortality

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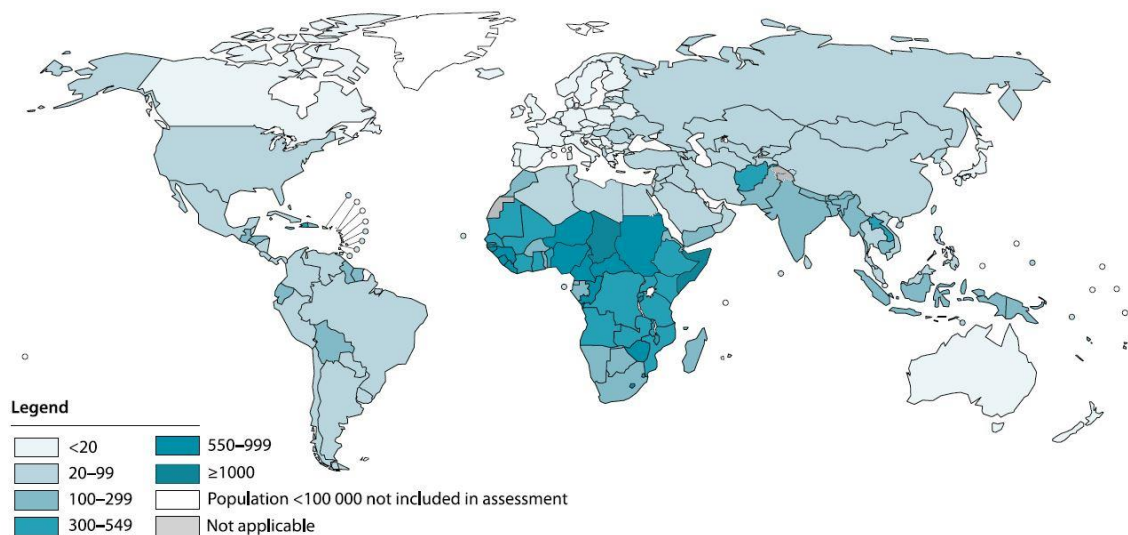
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Introduction

In 2010, an estimated 287,000 women died as a result of pregnancy and childbirth-related complications. Most of these deaths occurred in low-income countries (LICs). Sub-Saharan Africa has the highest maternal mortality ratio (MMR), estimated at 500 maternal deaths per 100,000 live births in 2010; by contrast, the MMR for developed regions was estimated at 16 maternal deaths per 100,000 live births (Souza and others 2013). Although significant progress has been made since 1990 toward achieving the MDGs, with a reduction in the global MMR from 400 to 210 maternal deaths per 100,000 live births, much work remains to be done, as this reduction (almost 50 percent) falls short of the 2015 MDG 5 target of 75 percent.

Figure 1. Map with countries by category according to their maternal mortality ratio (MMR, death per 100 000 live births), 2010



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Similarly, mortality for children under five years (MDG 4) has declined by 47 percent, from nearly 12.4 million in 1990 to 6.6 million in 2012, short of the 2015 target of 67 percent (Souza and others 2013; UNICEF and WHO 2013). Again, the distribution of the global burden of child mortality is disparate. Within countries when the population is disaggregated by income, education, or place of residence, wide disparities can be shown, even in those areas where the overall mortality seems low. Communicable, maternal, neonatal, and nutritional causes account for 25 percent of deaths and remain dominant causes of premature mortality in Sub-Saharan Africa (Hewitt 1988; Ngoc and others 2006). Newborns account for almost half (44 percent) of all under-five deaths, with this percentage reaching 50 percent or higher in several countries (United Nations 2013). Preterm birth and birth asphyxia account for 21% of under-five child mortality in 2008 (Black and others 2010).

The tracking of progress in meeting the MDGs does not include declines in the numbers of stillbirths. In 2009, an estimated 2.64 million stillbirths occurred in the last trimester of pregnancy, with more than 45 percent in the intrapartum period (Cousens and others 2011; Lawn and others 2011). The majority of these stillbirths (98 percent) occur in low- and middle-income countries (LMICs) (Black and others 2010).

Box 1 Millennium Development Goals 4 and 5

MDG 4: Reduce child mortality

Target:

1. Reduce by two thirds, between 1990 and 2015, the under-five mortality rate.

MDG 5: Improve maternal Health

Targets:

1. Reduce by three quarters, between 1990 and 2015, the maternal mortality ratio
2. Achieve, by 2015, universal Access to reproductive health

Significant proportions of these maternal, fetal, and newborn deaths are preventable and underscore the importance of initiatives to meet the Millennium Development Goals (MDG) 4 and 5. This chapter discusses and recommends the implementation of interventions in the context of people's right to access good quality, respectful, and timely care—wherever they may live.

Interventions to Reduce Maternal Mortality and Morbidity

Major obstetric causes of maternal mortality include hemorrhage, hypertensive diseases of pregnancy (mainly preeclampsia/eclampsia), sepsis, and obstructed labor. In a cross-sectional study conducted across 29 countries in Asia, Latin America and the Caribbean, the Middle East and North Africa, and Sub-Saharan Africa, postpartum hemorrhage and preeclampsia/eclampsia accounted for 27 percent and 26 percent, respectively, of severe maternal outcomes (Souza and others 2013). Table 7.1 provides an overview of evidence-based effective interventions to reduce poor maternal outcomes.

The contribution of indirect causes of maternal deaths, such as medical disorders, malaria, tuberculosis, and HIV seem to be increasing, which raises the importance of integrating service delivery during pregnancy and childbirth.

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

Type of intervention	Main effects	Quality of evidence ^a	Source of evidence
<i>Postpartum hemorrhage</i>			
Oxytocin	<ul style="list-style-type: none"> • Halves PPH risk when used routinely • Is well tolerated • Is recommended for prevention and treatment 	High	Westhoff, Cotter, and Tolosa 2013
Misoprostol	<ul style="list-style-type: none"> • Reduces PPH risk and the need for blood transfusion • Side effects of shivering and fever • Recommended for PPH prevention if oxytocin unavailable 	Moderate	Tunçalp, Hofmeyr, and Gülmezoglu 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 	High	Hofmeyr and others 2014
Aspirin supplementation	<ul style="list-style-type: none"> • Reduces the risk of preeclampsia in high-risk women 	High	Duley and others 2007
Magnesium sulphate	<ul style="list-style-type: none"> • Reduces the risk of seizures in women with preeclampsia, with a trend to reduced maternal mortality 	High	Altman and others 2002
Timing of delivery	<ul style="list-style-type: none"> • Induction of labour after 36 weeks' gestation reduces poor maternal outcomes in mild preeclampsia 	High	Koopmans and others 2009
<i>Sepsis</i>			
Prophylactic antibiotics at cesarean section	<ul style="list-style-type: none"> • Reduces risk of febrile morbidity, wound infection, endometritis and serious maternal infectious morbidity 	High	Smaill and Gyte 2010
<i>General interventions</i>			
	<ul style="list-style-type: none"> • 		
Posture in labour	<ul style="list-style-type: none"> • Upright and ambulant postures reduces labor duration and the need for cesarean sections 	High	Lawrence and others 2013

Note: a = Based on GRADE Working Group grades of evidence. (Atkins and others 2004)

Postpartum Hemorrhage

Preventing Postpartum Hemorrhage

The most effective intervention for preventing postpartum hemorrhage is the use of uterotonics—drugs that contract the uterus—during the third stage of labor when 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. Other interventions include uterine massage, cord clamping, and controlled cord traction (table 7.1).

Table 7.2 Interventions to Prevent Postpartum Hemorrhage

Evidence-Based Effective Interventions for PPH 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/ergometrine), or oral misoprostol (600 µg) are recommended. (WHO 2012)
Interventions with No Evidence, or Inconclusive Evidence, for PPH Prevention
<ul style="list-style-type: none">• Uterine massage (Hofmeyr, Abdel-Aleem, and Abdel-Aleem 2013)• Early vs late cord clamping (McDonald and others 2013)• Controlled cord traction (Gülmezoglu and others 2012b; Deneux-Tharaux and others 2013)

Uterotonic Agents. Two uterotonic agents used prophylactically are oxytocin and misoprostol.

[bullet]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 mL) (Westhoff, Cotter, and Tolosa 2013). The review included 20 randomized clinical trials (RCTs) involving 10,806 women. Prophylactic oxytocin, compared with placebo, halved the risk of PPH and, when compared with ergot alkaloids, reduced the risk of PPH by 25 percent.. There was no significant difference in the risk of PPH with the combination of oxytocin/ergometrine versus ergot alkaloids alone. Oxytocin was better tolerated than ergot alkaloids.

[bullet]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 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 mls). 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 where skilled birth attendants are not present and oxytocin is unavailable, the World Health Organization (WHO) recommends that misoprostol (600 µg PO) be given to women in the third stage of labor by community health care workers and lay health workers to prevent PPH (WHO 2012). As for any new medication being used on a large scale, continued vigilance for adverse effects is essential. Additional research is needed to further elucidate the relative effectiveness and the risks of various dosages of misoprostol to identify the lowest effective dose.

***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 and/or 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, postpartum abdominal uterine tonus assessment for early 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 involving a total of 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; late cord clamping increased early hemoglobin concentrations and iron stores in infants, compared with early cord clamping. However, significantly fewer infants in the early cord clamping group required phototherapy for jaundice. Delayed cord clamping is likely to be beneficial to the infant as long as access to treatment for jaundice requiring phototherapy is available.**

***Controlled Cord Traction (CCT).* Two large trials have been conducted, one of 23,861 women in eight LMICs (Gülmezoglu and others 2012b) and the other involving 4,013 women in France (Deneux-Tharaux and others 2013). The results of these trials concur and 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.**

Treating Postpartum Hemorrhage

Evidence for the most common interventions used 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. Fluid replacement is a key element in the resuscitation of women with PPH. No RCTs have assessed fluid replacement in this particular condition; the management 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. 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, as ergometrine can cause hypertension. The intravenous route is the recommended route of administration of oxytocin. Strong evidence suggests that administering misoprostol and injectable uterotonics together for PPH treatment does not confer additional benefits (Mousa and Alfirevic 2007). However, if injectable uterotonics are not available or have been ineffective, misoprostol can be administered.

Other Interventions

[bullet]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 (Sengstaken-Blakemore or Foley's catheters) and balloon catheters (Bakri and Rusch) and condoms.

[bullet]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 rates range 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, Djik and van Roosmalen 2010).

[bullet]Surgical interventions. Surgical interventions are generally used when other treatment modalities have failed. These include compression sutures (for example, the B-Lynch technique); ligation of the uterine, ovarian, or iliac artery; and total or subtotal hysterectomy. The evidence that supports these procedures is limited as 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 B-Lynch 2005).

[bullet]Non-pneumatic antishock garment (NASG). A NASG is a simple low-technology first-aid device that may help to stabilize women with hypovolemic shock, particularly during transport to facilities; however, high quality research on NASG is lacking.

Pipeline Interventions

Several lines of active research are underway in PPH prevention and treatment: A large RCT has passed midway to its final sample size of approximately 15,000 for women who bleed more than usual and who are randomly allocated to tranexamic acid or placebo (<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/>); and the WHO will be evaluating a room temperature stable synthetic oxytocin analogue, carbetocin, in 2014-15. 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, with the majority of the estimated 76,000 annual maternal deaths occurring in LMICs (Duley 2009). A recent WHO multicountry survey on maternal and newborn health estimated that preeclampsia is associated with over 25 percent of severe maternal outcomes and is the direct cause of 20 percent of reported maternal deaths (Souza and others 2013). It is also associated with 20 percent of infants born prematurely and 25 percent of stillbirths and neonatal deaths (Hewitt and Newnham 1988; 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). Severe preeclampsia leads to adverse outcomes, such as stroke, seizures, renal and hepatic injury, clotting disturbances, and hemorrhage (Hewitt and Newnham 1988). Inadequate blood supply to the fetus may lead to growth restriction, fetal death, or prematurity. Generalized seizures (eclampsia) occur in up to 8 percent of women with preeclampsia in developing countries (Steegers and others 2010), a rate that is 10 to 30 times more common than in developed countries (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 Cochrane review of 13 RCTs involving 15,730 women demonstrated 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 (less 900mg a day) (Hofmeyr and others 2014). Calcium supplementation was associated with a modest reduction in the risk of the composite outcome maternal death or serious morbidity. Accordingly, the WHO strongly recommends that in areas with low dietary calcium intake, calcium supplementation commences 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 2011).

Low-dose aspirin. The effect of aspirin is more modest. In a Cochrane review of 18 trials 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 mg 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 a 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.

Frequency of antenatal visits. There is little evidence-based consensus regarding the optimal frequency of antenatal visits. In HICs, antenatal visits are generally based around the United Kingdom Ministry of Health recommendations: visits start at 16 weeks' gestation, followed by visits at 24 and 28 weeks, then fortnightly to 36 weeks, and weekly thereafter (Oakley 1982; WHO 2011a). In LMICs, particularly in rural areas, barriers to regular antenatal care attendance exist. While observational studies suggest a correlation between the number of antenatal visits and improved pregnancy outcomes, increasing attention has been given to fewer, goal-oriented antenatal visits, with the aim of providing the essential components of care rather than increasing the frequency of visits. A Cochrane review including seven trials involving over 60,000 women—three of which were in LMICs) compared standard antenatal regimes of eight to 12 visits with a reduced schedule of usually fewer than five visits). For the group randomized to reduced visits, perinatal mortality was 15 percent higher, particularly in LMICs (Dowswell and others 2010). It is not clear why this effect was observed—improved earlier detection of preeclampsia is only one of the possible mechanisms; in the absence of further evidence, a reduction in antenatal visits cannot be recommended in these settings (WHO 2011b).

Quality of Antenatal Care. Effective antenatal care depends on its quality as well as its availability.

The detection of preeclampsia requires adequately trained staff and functioning equipment. Accurate urinalysis may be unavailable in rural antenatal clinics due to technical or financial limitations, and the cheaper urinary dipsticks have low specificity for significant proteinuria. Furthermore, proteinuria may be a late feature of the disease. Similarly, accurate and frequent BP measurement, together with knowledge about the significance of readings, and a functional referral mechanism for access to specialist care are vital to timely management.

Treating Preeclampsia and Eclampsia

The only definitive cure for preeclampsia is delivery of the baby, by induction of labor or by prelabor caesarean section, to prevent progression of disease and related morbidity and mortality. The mainstays of treatment are antihypertensive drugs for BP control, and magnesium sulphate (MgSO₄) for eclampsia.

- **Antihypertensive therapy:** Antihypertensive therapy in preeclampsia aims to reduce the risk of severe hypertension and stroke, with a steady reduction in BP to safe levels, avoiding sudden drops that may compromise blood supply to the fetus. There is no evidence regarding 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 to control hypertension. Thus, 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 magnesium sulphate (MgSO₄), a low-cost intramuscular or intravenous treatment, is effective in preventing and controlling eclampsia. The MAGPIE study, a multicounty prospective RCT involving 33 centers and 10,141 women (two-thirds of the participating centers were in LMICs), compared MgSO₄ 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 (NNT) of 100 women to prevent one case of eclampsia (Altman and others 2002), reducing to 63 for women with severe preeclampsia. A Cochrane review and metaanalysis of six trials including MAGPIE confirmed a clinically significant reduction in risk of eclampsia of 59 percent, regardless of the route of administration of MgSO₄ (Duley and others 2010a), with the risk of dying nonsignificantly reduced by 46 percent. There is also strong evidence that MgSO₄ is also substantially more effective than phenytoin for the treatment of eclampsia (Duley, Henderson-Smart, and Chou 2010b). There is currently insufficient evidence regarding the effectiveness and safety of low-dose MgSO₄ regimen (Duley and others 2010b), therefore, 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 caesarean section if induction is not appropriate (WHO 2011b). However, high quality evidence indicates that induction at more than 36 weeks of gestation significantly 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 found insufficient evidence for interventionist 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. Therefore, 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 caesarean section), skilled attendance at delivery, access to appropriate drugs, and maternal and fetal monitoring.

Pipeline Technologies and Interventions

Prevention and treatment. Early calcium supplementation (preconception and early pregnancy), possibly by means of food fortification is being evaluated by the WHO/PRE-EMPT Calcium in Pre-eclampsia (CAP) Trial. Funded by the Bill and Melinda Gates Foundation, it 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 BP monitor suitable for settings without medically trained health workers. Such monitors should be automated, validated for accuracy in pregnancy, affordable, and hardwearing, and with a reliable power supply (for example, solar power or using mobile phone charging technology).

Recent evidence from a diagnostic test accuracy study suggests that low plasma levels of placental growth factor (PIGF) 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 PIGF 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 exciting 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.

Community based task-shifting. Task-shifting (the redistribution of clinical tasks among health workforce teams) may help address the barriers to timely diagnose and manage preeclampsia in LMIC settings. Community health volunteers are playing increasing roles in the provision of health care in remote communities and there is potential for them to become involved in screening and referral, as well as in administering MgSO₄ prior to transfer. The Bill and Melinda Gates Foundation-funded study of community level interventions in preeclampsia (CLIP) aims to evaluate a community-based package of care to reduce all-cause maternal morbidity and mortality (Payne and others 2013).

Obstructed Labor

Obstructed labor is an important cause of maternal mortality and morbidity (UNICEF and WHO 2013). Causes include fetopelvic disproportion, shoulder dystocia (fetal shoulders trapped in the pelvis during delivery), and fetal malposition and malpresentation. Appropriate intrapartum care plays a substantial role in reducing the burden of associated poor outcomes. In well-resourced settings, obstructed labor is usually managed by assisted delivery, either instrumental delivery or caesarean section. Assisted instrumental delivery constitutes approximately 10 percent, and caesarean section approximately 26 percent, of all deliveries in the United Kingdom (Health and Social Care Information Centre 2013).

Preventing Obstructed Labor

In LMICs, a substantial proportion of maternal deaths due to obstructed labor occurs 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 there is lack of infrastructure (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). Accordingly, in LMICs, 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 (MWH) 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 Roosmalen 2012). Where MWHs exist, women with high-risk pregnancies or those who live remotely are encouraged to stay at these facilities toward the end of their pregnancy. A Cochrane review conducted in 2012 sought to evaluate the role of MWHs on reducing maternal deaths and stillbirths. However, there was insufficient evidence for robust conclusions to be drawn (van Lonkhuijzen, Stekelenburg and van Roosmalen 2012).

Postural Interventions.

A Cochrane review of 25 RCTs involving 5,218 women found clear evidence that assuming walking and upright positions in the first stage of labor reduces the duration of labor and the risk of operative delivery (Lawrence and others 2013). Another Cochrane review assessed the effects of adopting an “on hands and knees” maternal posture in women with occipito-lateral and occipito-posterior fetal head positions (Hunter, Hofmeyr, and Kulier 2007). Three trials involving 2,794 women were included. There was no significant reduction in operative delivery when the intervention was adopted in late pregnancy, for 10 minute periods, or labor compared with no intervention; however, the latter evidence was limited to one small study, and more research is needed.

Treating Obstructed Labor

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.

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, hence, it may be a lifesaving procedure for the mother and/or the baby in clinical situations where cesarean section is unavailable and there is failure to progress in labor, or in obstructed birth of the after-coming 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 cesarean section 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 cesarean section is not available (Hofmeyr and Shweni 2012).

Fundal Pressure

Fundal pressure involves the application of manual pressure by the birth attendant to the uppermost part of a woman's uterus, directed toward the birth canal during labor in an attempt to assist spontaneous vaginal delivery (Verheijen, Raven, and Hofmeyr 2009). Limited evidence suggests that fundal pressure is used in formal and informal childbirth practice in both developed and less developed countries. However, there is no good evidence available to conclude whether this practice has beneficial or harmful effects (Verheijen, Raven, and Hofmeyr 2009).

Pipeline Technologies and Interventions.

[bullet]*The Odon device.* The Odon device has recently been invented to assist vaginal delivery. This is a low-cost, easy to use, technological innovation to facilitate assisted delivery for prolonged second stage of labor or other reasons. It consists of a film-like polyethylene sleeve that is applied to the fetal head with the help of an inserter. As the device is designed to minimize trauma to the mother and baby, it is potentially a safer alternative to forceps and ventouse delivery. A feasibility and safety study is currently in progress (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 one-tenth of global burden of maternal deaths (Khan and others 2006). Most of the estimated 75,000 sepsis-related maternal deaths occurring worldwide annually are recorded in LICs. Although the reported incidence in HICs is relatively low (between 0.1 and 0.6 per 1000 deliveries), it is nonetheless an important direct cause of maternal mortality. Sepsis was reported as the leading direct cause of maternal death in the United Kingdom's Confidential Enquiry into Maternal Death (2006-08 triennium). Infections occurring before or during the birth of the baby also have considerable impact on newborn mortality, and an estimated one 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 emphasis on reducing the frequency of unsafe abortion, intrapartum vaginal examination, prolonged/obstructed labor, operative delivery, and appropriate hospital infection control.

Preventing Maternal Sepsis

The most effective interventions for preventing maternal sepsis are the use of antiseptics and observation 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 to prevent hospital transmissible infections. Although there are no systematic reviews evaluating the effect of handwashing on maternal mortality from sepsis, the work of Semmelweis in the mid-19th century shed light on the epidemiological basis of puerperal sepsis and confirmed the impact of this simple and inexpensive measure on reducing maternal and morbidity (Noakes and others 2008).

Vaginal application of antiseptics for vaginal delivery. Since the 1980s, vaginal disinfection during labor has been proposed as a strategy to reduce bacterial colonization of the lower genital tract during childbirth. A Cochrane systematic review of three RCTs involving 3,012 participants assessed the effectiveness and side effects of chlorhexidine vaginal douching during labor (Lumbiganon and others 2004). The review showed no difference in the incidence of chorioamnionitis (infection of the fetal membranes) and postpartum endometritis (infection of the lining of the womb) between women who received chlorhexidine and placebo. No benefits were observed in terms of neonatal infections.

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

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. There is insufficient evidence from available Cochrane reviews to determine whether prophylactic antibiotics given with operative delivery or following third- or fourth-degree perineal tears reduces infectious postpartum morbidities (Liabsuetrakul and others 2004; Buppasiri and others 2005).

Antibiotic prophylaxis at cesarean delivery. Cesarean section is the single most important risk factor for postpartum maternal infection, and routine antibiotic prophylaxis has considerable clinical benefits. In a Cochrane review, which included 86 trials involving more than 13,000 women (Smaill and Gyte 2010), the use of prophylactic antibiotics after cesarean was associated with substantially lower risks of febrile morbidity (55 percent reduction), endometritis (62 percent reduction), wound infection, and serious maternal infectious complications (69 percent reduction). Another Cochrane review showed no difference among classes of antibiotics with respect to maternal sepsis, febrile morbidity, endometritis, wound infection, and measures of adverse outcomes (Alfirevic, Gyte and Dou 2010).

Preterm and term prelabor rupture of membranes. Rupture of the fetal membranes remote from term carries substantial risk of chorioamnionitis and severe maternal sepsis. Evidence on the benefits of prophylactic antibiotics preterm PROM was demonstrated in a Cochrane review of 22 RCTs that involved 6,872 women (Kenyon, Boulvain and Neilson 2013), which revealed that the use of prophylactic antibiotics was associated with a significant reduction in chorioamnionitis and markers of neonatal morbidity. More studies are needed to examine the overall benefit of prophylactic antibiotics for term prelabor rupture of membranes (Flenady and King 2002).

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 evaluated the comparative efficacy and side effects of different antibiotic regimen 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 to other regimen.

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/facility level). Most of these

interventions are included in the Lives Saved Tool, developed to model their impact at different coverage levels (USAID 2010), and are already part of existing sets of recommended intervention packages for addressing maternal and neonatal outcomes. Although thorough evaluation of evidence is vital, evidence is not available for some well-established interventions; for example, a RCT of neonatal resuscitation is impossible for ethical reasons, yet neonatal resuscitation is the cornerstone of neonatal care in HICs. Important interventions initiated in the antenatal or neonatal period with evidence of health benefits later in childhood, like newborn vaccination or antiretroviral therapy in babies born to HIV infected 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 regarding antenatal care programs revealed that reduced antenatal visits may be associated with an increase in perinatal mortality compared to standard care (Dowswell and others 2010). Indirect evidence of the effectiveness of antenatal care to reduce stillbirths is available from a re-analysis of data from the WHO antenatal care trial, which showed that stillbirth was reduced in the standard care group who received more frequent routine antenatal visits (Vogel and others 2013). This finding is consistent with the findings of other trials (Hofmeyr and Hodnett 2013).

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

Type of intervention	Main effects	Quality of evidence*	Source of evidence
<i>Nutritional</i>			
Folic acid	<ul style="list-style-type: none"> Reduces the risk of neural tube defects when given periconceptually 	Moderate	Blencowe and others 2010b
Calcium supplementation	<ul style="list-style-type: none"> Reduces preterm birth 	Moderate	Hofmeyr and others 2013
Balanced Energy and protein Supplementation	<ul style="list-style-type: none"> Reduces stillbirth and small for gestational age babies Increases mean birthweight 	Low	Ota and others 2012
<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)	<ul style="list-style-type: none"> Reduces neonatal mortality and low birthweight 	High	Garner and Gülmezoglu 2006
Insecticide bed nets (malaria)	<ul style="list-style-type: none"> Reduces fetal loss and low birthweight 	High	Gamble, Ekwaru, and ter Kuile 2006
Anti-tetanus vaccine	<ul style="list-style-type: none"> Reduces neonatal mortality from tetanus 	Moderate	Blencowe and others 2010a
<i>Intrauterine Growth Restriction (IUGR)</i>			
Antithrombotic	<ul style="list-style-type: none"> Reduces perinatal mortality, 	High	Dodd and others

agents in pregnancies identified as high-risk	preterm birth, and low birthweight		2013
Doppler velocimetry	<ul style="list-style-type: none"> Reduces perinatal mortality in high-risk pregnancies 	Moderate	Alfirevic, Stampalija, and Gyte and others 2010
<i>Other interventions</i>			
Antenatal visits	<ul style="list-style-type: none"> Reducing antenatal visits in LMICs increases the risk of perinatal death 	Moderate	Dowswell and others 2010
Labor induction at 41+ weeks for post-term pregnancy	<ul style="list-style-type: none"> Reduces perinatal deaths and meconium aspiration 	High	Gülmezoglu 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: *Based on GRADE Working Group grades of evidence. (Atkins and others 2004)

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

Type of intervention	Main effects	Quality of evidence*	Source of evidence
<i>General</i>			
Clean delivery kits	<ul style="list-style-type: none"> Reduces neonatal mortality 	High	Seward and others 2012
Skilled birth attendance	<ul style="list-style-type: none"> Reduces stillbirths 	Moderate	Yakoob and others 2011
<i>Preterm labor and PPROM</i>			
Corticosteroids	<ul style="list-style-type: none"> Reduces neonatal mortality Reduces the risk of respiratory distress syndrome (RDS) and other neonatal morbidities 	High	Roberts and Dalziel 2006
MgSO₄	<ul style="list-style-type: none"> Reduces the risk of cerebral palsy 	High	Doyle and others 2009
Antibiotics (PPROM only)	<ul style="list-style-type: none"> Reduces neonatal RDS and 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>			
Newborn	<ul style="list-style-type: none"> Improves initial resuscitation 	Low	Carlo and others

resuscitation training	practices but not perinatal mortality rates		2010; Opiyo and English 2010
Kangaroo mother care	<ul style="list-style-type: none"> Reduces mortality in low birthweight infants 	High	Conde-Agudelo, Belizán and Diaz-Rossello 2011
Cord cleansing (chlorhexidine)	<ul style="list-style-type: none"> Reduces neonatal mortality in community settings 	High	Imdad and others 2013
<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 	High	Zaida and others 2011
Presumptive antibiotics for Group B Streptococcus	<ul style="list-style-type: none"> Is recommended for rupture of membranes more than one day before delivery to reduce neonatal sepsis 	Very low	Ungerer and others 2004

Note: *Based on GRADE Working Group grades of evidence. (Atkins and others 2004)

Nutritional Interventions

Folic Acid. Several nutritional interventions may be implemented before and during pregnancy. Folic acid supplementation or fortification of staple commodities periconceptually reduces the risk of neural tube defects, which account for a small proportion of stillbirths or neonatal deaths (Blencowe and others 2010b).

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 including 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. However, further research on the effectiveness and implementation of BES is necessary.

Maternal Calcium Supplementation. A Cochrane metaanalysis of 11 trials involving 15,275 women found that calcium supplementation to prevent preeclampsia reduced the risk of preterm birth by 24 percent (Hofmeyr and others 2014). Another Cochrane review assessed the effects of routine calcium supplementation during pregnancy (Buppasiri and others 2011) and found no evidence of any additional benefits.

Maternal Zinc Supplementation. Some evidence suggests that zinc supplementation may reduce the risk of preterm birth. A Cochrane review of the intervention included 20 RCTs involving over 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 to controls. The reviewers concluded 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, syphilis, and tetanus.

Tetanus. A review of tetanus toxoid immunization concluded that there was clear evidence of the high impact of two or more doses of tetanus vaccine in pregnancy on reducing neonatal tetanus mortality (Blencowe and others 2010a). The evidence was downgraded to moderate due to the quality of the studies.

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 stillbirth, 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. IPT has been shown to improve mean birthweight and reduce the incidence of low birthweight and neonatal mortality; it may also reduce stillbirth and preterm birth (Garner and Gülmezoglu 2006). Insecticide-treated bed nets (ITN) have been shown to reduce fetal loss by 33 percent (Gamble, Ekwaru, and ter Kuile 2006).**

Other Infections. There is no conclusive evidence on the effects 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 Mellitus

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 to conventional management, resulted in a 54 percent reduction of macrosomic (>4000 grams) babies. It was also associated with statistically nonsignificant reductions on other outcomes including perinatal death, stillbirths, neonatal hypoglycemia, shoulder dystocia, cesarean section, 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 nonsignificant 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. Expert opinion suggests that improved detection and management of IUGR using maternal body mass index (BMI), symphysial-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 developed countries showed that the use of Doppler ultrasound for Doppler velocimetry 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 and others 2010).

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 and Hofmeyr 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 (postterm) 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 postterm 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 and others 2012), but there was no significant reduction in stillbirths.

Intrapartum Interventions

Labor surveillance is needed for early detection, clinical management, and referral 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.

As perinatal asphyxia and stillbirths are often caused by obstructed or prolonged labor, assisted vaginal delivery and cesarean section are vital to reduce perinatal morbidity and mortality.

In LMICs, a significant proportion of women give birth at home, usually in the absence of a skilled birth attendant. A metaanalysis of two before-and-after studies of community-based skilled birth attendance showed a 23% significant reduction in the risk of stillbirth (Yakoob and others 2011).

General Interventions

Comprehensive emergency obstetric care. This care is the standard full package of obstetric care, including the availability of cesarean section and blood transfusion, that is essential for many obstetrics emergencies, for example, placental abruption, where a live fetus needs to be delivered immediately by cesarean section (Neilson 2003). In LMICs, strategies to provide emergency transport could improve fetal outcomes by enabling access to emergency care.

Hygiene. Poor hygienic conditions and poor delivery practices contribute to the burden of neonatal mortality. Pooled data from the control arms of cluster RCTs conducted in 19,754 home births at three sites in 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. Handwashing is important at all levels of care.

The partogram. A partogram is usually a preprinted form to provide a pictorial overview of labor progress and to alert health professionals to any problems with the mother or baby (Lavender, Hart, and Smyth 2013). Although the partogram is widely used and accepted to detect abnormal labor, there is a lack of strong evidence to recommend its general use (Lavender, Hart, and Smyth 2013). Until stronger evidence is available, partogram use should be locally determined.

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 over 37,000 women of continuous cardiotocography (CTG) compared with intermittent auscultation showed no reduction in perinatal mortality (Alfirevic, Devane and Gyte 2013). Continuous CTG 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, including 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 found no significant difference in poor neonatal outcomes; however, cesarean section rates were nonsignificantly reduced in the active management group (Brown and others 2013).

Preterm Labor and Preterm Pre-Labor Rupture of Membranes (PPROM)

Antenatal corticosteroids. It is well established that 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) is very effective in preventing poor neonatal outcomes. A Cochrane review of 21 RCTs involving 4,269 neonates found that a single course of steroids reduced the risk of neonatal death by 31 percent. Neonatal morbidity including cerebroventricular hemorrhage, necrotizing enterocolitis, respiratory distress syndrome, and systemic infections were all significantly reduced with antenatal steroids (Roberts and Dalziel 2006).

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 PPRM are effective in reducing the risk of a number of early morbidities, including respiratory distress syndrome 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, there is insufficient evidence to determine whether there are 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 who are born in LICs. 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 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 found 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 care of the newborn at birth, including cleaning, drying, and warming the infant, initiating exclusive breastfeeding, and cord care (WHO 2011a). Ideally, this should be provided by a skilled attendant; however, most of these tasks can be carried out at home by alternative attendants. The WHO's essential newborn care package includes resuscitation, but the skill level required for resuscitation is more complex (WHO 2011a).

Kangaroo Mother Care. Kangaroo mother care (KMC), which is part of the extra newborn care package for small and low birthweight infants, includes skin-to-skin contact between mothers and newborns, frequent and exclusive breastfeeding, and early discharge from hospital, has been evaluated in comparison to conventional care in a Cochrane review. Sixteen RCTs involving 2,518 infants were included (Conde-Agudelo, Belizán and Diaz-Rossello 2011). In low birthweight infants, kangaroo mother care, reduced neonatal mortality by 40 percent, hypothermia by 77 percent, and nosocomial infection by 58 percent.

Exclusive Breastfeeding. The WHO recommends initiation of breastfeeding within one hour of birth, exclusive breastfeeding of infants until six months of age, and continued breastfeeding until two years of age or longer (WHO 2001). Infants who are exclusively breastfed for six months experience less gastrointestinal morbidity (Kramer and Kakuma 2012). A metaanalysis showed that breastfeeding education and/or support increased exclusive breastfeeding rates (Haroon and others 2013). For small or preterm babies, extra feeding support is needed (WHO 2011a).

Cord Cleansing. A Cochrane review of 34 studies involving 69,338 newborns assessed the effect of cord cleansing with antiseptics to prevent cord infection (omphalitis) and neonatal death. Pooled data from three community trials involving 54,624 newborns, of cord care with chlorhexidine, showed a reduction in omphalitis of 27 percent to 56 percent, and in neonatal mortality of 23 percent (Imdad and others 2013).

Neonatal Interventions

For many of the world's four million neonatal deaths annually, the immediate cause is an illness presenting as an emergency, either soon after birth (such as complications of preterm birth and asphyxia) or later (due to neonatal tetanus or community-acquired infections). Other important but less prevalent

conditions include jaundice and hemorrhagic disease of the newborn. All these conditions have high fatality rates, particularly tetanus and encephalopathy.

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)..

Birth Asphyxia

Seizures are common following perinatal asphyxia. Induced hypothermia in encephalopathic asphyxiated newborn infants 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 (HIE) (Jacobs and others 2013). Cooling reduced neonatal mortality by 25 percent. Induced hypothermia should be performed in term and late preterm infants with moderate or severe HIE if identified before six hours of age (Jacobs and others 2013). Routine anticonvulsant prophylaxis with barbiturates for the neuroprotection of term infants with perinatal asphyxia is not recommended (Evans, Levene, and Tsakmakis 2007).

Respiratory Distress Syndrome

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 significant factor for LMICs (Seger and Soll 2009; Soll and Özek 2010). Institution of continuous positive airway pressure (CPAP) may bring down the requirement and cost of surfactant therapy (Rojas-Reyes, Morley, and Soll 2012).

Neonatal Sepsis

Antibiotics for treatment. Almost one million neonatal deaths annually in LMICs are attributable to infectious causes, including neonatal sepsis, meningitis, and pneumonia. Feasible and low-cost interventions to avert 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 (GBS). 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) found low quality evidence that early neonatal GBS infection was reduced with IAP compared with no prophylaxis (Ohlsson and Shah 2014). Recent European consensus recommends IAP based on a universal intrapartum GBS screening strategy (Di Renzo and others 2014); however, intrapartum GBS screening is not routinely available 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 WHO recommends the use of presumptive antibiotic therapy for newborns at risk of GBS and other bacterial infections (WHO 2011a).

Pipeline Interventions

Household air pollution is recognized as a risk factor for several health outcomes, including stillbirth, preterm birth, and low birthweight, but there is a lack of rigorous evidence for the impact of reducing household air pollution on these birth outcomes (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 2013). Whether sleeping position can be changed by advice or other interventions, and whether such a change would impact stillbirth rates, remains to be established.

Cost-effectiveness

Bhutta and others (2014) estimate that the additional funding required to scale up effective interventions in the 75 high-burden Countdown countries is \$5.65bn annually, which they equate to \$1.15 per person in the population (not including the initial investment in new facilities). They estimate that increased coverage and quality of care would reduce maternal and neonatal deaths and prevent stillbirths at a cost of \$1928 per life saved (or roughly \$60/DALY), with 82% of this effect from facility-based care.

Estimated cost per DALY for training initiatives (e.g. LeFevre and others 2013), participatory women's groups (e.g. Fottrell and others, 2013) and safe motherhood initiatives (e.g. Erim, Resch and Goldie, 2012) ranges from \$150-\$1000 approximately. Caesarian sections for obstructed labour have a wider range (\$200-\$4000/DALY, depending on the country), with a median of just over \$400 (Alkire and others, 2012). Other innovations with lower costs per DALY in the range of \$20-\$100, e.g. clean delivery kits for home births (Sabin and others, 2012), have a modest impact on DALYs saved.

Conclusions

Despite existing evidence-based interventions that prevent and treat major causes of poor maternal, fetal, and newborn outcomes, the delivery and distribution of these interventions remains compromised. Accelerated investments in infrastructure, training, and patient education are needed to bring health benefits to women and children in LICs (Prost and others 2013).

Even in the poorest settings, simple approaches at 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 (IMCI) programs, at low marginal cost. Yet scaling up of skilled care is required to reach the MDGs. Outreach and family care options are more feasible, but if the commitment to strengthen clinical care systems is lacking, the potential reduction in stillbirths and neonatal deaths from those options is limited.

As increasing numbers of women and babies reach primary care facilities and hospitals, the quality of care challenges in those facilities need to be addressed. Research has demonstrated convincingly that simple interventions can save lives if they are provided in the appropriate time and protocol; however, supportive elements are essential if they are to reduce death and severe morbidity.

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