Improving survival of preterm babies in low- to middle-income countries – what can we do?

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Surviving prematurity poses the greatest challenge in neonatal care in low- to middle-income countries (LMICs). South Africa has not made much progress in improving the survival of preterm babies. Neonatal survival of preterm infants has become a national priority since the serious failure to reach the Millennium Development Goal targets in 2015. High rates of prevention are particularly relevant in LMICs, where the neonatal mortality rate is at its highest owing to a lack of simple and effective measures. Preventing prematurity and related complications begins with a healthy pregnancy. Antenatal care and maternal corticosteroids are antenatal interventions that could improve the survival of preterm babies. Postnatal interventions include: the management of neonatal sepsis, meningitis and pneumonia; prevention of hypothermia after delivery, for example, the plastic bag/wrap and cap, which has been extensively researched and is found to be an effective, low-cost method for reducing hypothermia in preterm infants; the use of continuous positive airway pressure (CPAP), including the low-cost CPAP device, which is a cost-effective strategy for providing respiratory support for premature neonates with respiratory distress syndrome; exogenous surfactant; early feeding with breastmilk; and kangaroo mother care. The use of cost-effective, evidence-based interventions can be implemented in LMICs to reduce neonatal mortality.

S Afr J Child Health 2018;12(3):117-120. DOI:10.7196/SAJCH.2018.v12i3.1503

Surviving prematurity, defined as birth before 37 weeks' gestational age, poses the greatest challenge in neonatal care in low- to middle-income countries (LMICs). Premature birth is more common, and prematurity is the most important cause of neonatal death, in these countries. In 2016 it was estimated that sub-Saharan Africa had one of the world's highest neonatal mortality rates (28/1 000 live births), which is 32% higher than the global neonatal mortality rate (19/1 000 live births), with prematurity (35%) accounting for the leading cause of neonatal deaths.[1] South Africa (SA), a middle-income country, had a neonatal mortality rate of 15/1 000 live births in 2015.[2,3]

According to the World Health Organization, 62 out of 65 countries have shown an increase in preterm deliveries over the last 20 years. This increase can be attributed to better documentation and record-keeping, increased maternal age with maternal health conditions – for example, hypertension and diabetes, increased use of infertility treatments and increased induction of labour and caesarean sections before term.[4] Two comparative studies done in Johannesburg, SA, found an 18.5% increase in admissions of very low birth-weight infants (<1 500 g at birth) between 2006 and 2013. Except in the weight category of 750 - 900 g, data from these two studies have shown no significant improvement in mortality in this group of infants, which implies that SA has not made any progress in improving the survival of preterm babies in the past 4 years. However, there was a 32% increase in survival of babies weighing 750 - 900 g, possibly due to the more widespread use of continuous positive airway pressure (CPAP) and surfactant.[5]

Neonatal survival of preterm infants has become a national priority, as the neonatal mortality rate (NMR) has been 30% slower in improving than maternal and child mortality, with the slowest NMR reduction in the countries with the highest burden, such as those in Africa. New NMR targets of ≤10 deaths per 1 000 live births have been set by the Every Newborn Action Plan, and are hoped to be achieved by 2035. If, globally, we continue at the current trajectory, this target will not be achieved, and there will be an additional 18 million neonatal deaths due to prematurity by 2035.[6]

Approximately 2 million deaths per year could be prevented by utilising evidence-based interventions already at our disposal. Such high rates of prevention are particularly relevant in LMICs, where the NMR is at its highest owing to the lack of use of simple and effective measures. Newborn- and child-health communities acknowledge that if women have access to family planning and contraceptives, the health and survival rate of their children will improve. These services will enable women to prevent unplanned pregnancy, space births and achieve their intended family size. In these circumstances, the risk of prematurity is reduced, the mother's health improves and the economic wellbeing of the family is more stable.[7,8]

Specific interventions for improving preterm survival

Preventing prematurity and related complications begins with a healthy pregnancy.[4] Lassi *et al.*[9] undertook an extensive overview of systematic reviews of experimental and observation studies on antenatal, labour-related, delivery-related and postnatal evidence-based interventions aimed at preventing perinatal mortality. The results were summarised into three categories: effective interventions (high-quality evidence that works), promising interventions (moderate-quality evidence that might work) and those providing insufficient evidence to make a judgement (low- or very low-quality evidence).[9] The antenatal and postnatal interventions discussed in the present article are labelled according to these categories.

Antenatal interventions

Maternal antenatal corticosteroid administration is the only effective antenatal intervention, according to Lassi *et al.*[9] An additional four promising interventions during the antenatal period include attendance of antenatal care, tetanus immunisation during pregnancy, administering prophylactic antimalarials during pregnancy and induction of labour for prolonged pregnancy.[9] As the present article focuses on preterm infant survival, only antenatal care and maternal corticosteroids are discussed here.

Attendance of antenatal care (promising intervention)

Data in 2008 from a developed country indicated that preterm delivery and low birth-weight were three and five times, respectively, more likely in women unbooked for antenatal care compared with booked women of similar parity and ethnic background. Previous studies demonstrate that at least four antenatal visits are necessary to decrease the risk of low birth-weight infants and neonatal admissions.[10] Similar findings were demonstrated in a study in 2008/2009 carried out in Limpopo Province, SA, where unbooked mothers were more likely to have a preterm baby, and therefore more likely to face the significant risk of perinatal morbidity and mortality.[11] Although premature birth limits the number of probable antenatal clinic visits, it is still possible to avoid late booking (after 20 weeks' gestation) in an effort to reduce some premature births.[12]

Lassi *et al.*[9] reported that a decreased number of antenatal care visits (between 4 and 9) was associated with a 14% higher risk of perinatal mortality, when compared with the standard number of antenatal care visits (between 12 and 14). The suggestion is that fewer antenatal care visits than the standard may exacerbate neonatal morbidity and mortality.[9]

Antenatal care therefore plays a vital role in ensuring improved pregnancy outcomes and reduced perinatal mortality.[10]

Maternal antenatal corticosteroids (effective intervention)

Respiratory distress syndrome (RDS) is one of the most common causes of mortality in preterm infants. Roberts *et al.*[13] reported that administration of a single course of maternal antenatal corticosteroids (CSs) is associated with a reduction in RDS of 34% (risk ratio (RR) 0.66; 95% confidence interval (CI) 0.56 - 0.77). Additionally, neonatal deaths are reduced by 31% (RR 0.69; 95% CI 0.59 - 0.81), moderate to severe respiratory distress by 41% (RR 0.59; 95% CI 0.38 - 0.91), intraventricular haemorrhage by 45% (RR 0.55; 95% CI 0.40 - 0.76), necrotising enterocolitis (NEC) by 50% (RR 0.50; 95% CI 0.32 - 0.78), the need for mechanical ventilation by 32% (RR 0.68; 95% CI 0.56 - 0.84) and systemic infections in the first 48 hours of life by 40% (RR 0.60; 95% CI 0.41 - 0.88) with use of maternal antenatal CSs. However, the review investigated only 4 middle-income countries out of 21 studies in total. The other 17 studies were conducted in high-income countries. A study at Charlotte Maxeke Johannesburg Academic Hospital in SA showed antenatal CS coverage of 44%, with increased survival, decreased patent ductus arteriosus and decreased intraventricular haemorrhage in neonates weighing >1 500 g. In the same study, it was found that vaginal deliveries were associated with decreased antenatal CS coverage. Possible reasons for this association are mothers presenting in advanced labour, which results in a lessened opportunity to administer antenatal CSs. Sometimes delays occur in transporting mothers from the local clinic to the hospital.[14] Therefore, administration of antenatal CSs to women at risk of imminent preterm delivery in local clinics should be one of the key interventions to decrease neonatal mortality.[9]

Maternal antenatal CSs should be administered between 26w0d and 33w6d. Antenatal CSs are most effective after 24 hours and up to 7 days after the administration of the second dose. However, antenatal CSs can still reduce neonatal death within the first 24 hours of administration, and should therefore be given even if delivery is imminent. Multiple courses of antenatal CSs are not advised until more studies have been conducted on possible adverse neurological or cognitive effects. Caution needs to be exercised when administering antenatal CSs to some women, for example, those with systemic infection such as tuberculosis, and those with diabetes mellitus.[15]

Postnatal interventions

Postnatal interventions to improve survival include the management of neonatal sepsis, meningitis and pneumonia, prevention of hypothermia after delivery, the use of continuous positive airway pressure (CPAP) and exogenous surfactant, early feeding with breastmilk and kangaroo mother care (KMC).

Management of neonatal sepsis, meningitis and pneumonia

Approximately 1 000 000 neonatal deaths occur annually as a result of sepsis, with prematurity increasing the risk of neonatal sepsis.[16,17] Factors responsible for this predisposition include impaired innate immunity, transplacental passage of antibodies peaks during the third trimester, reduced cytotoxic T-cell activity and multiple skin punctures and invasive procedures.[18] Management of neonatal sepsis includes prevention of disease. These measures include good hand-washing practices, sterile techniques during invasive procedures and good antibiotic stewardship.[16] It is vital to timeously identify and start antibiotics in all babies at risk of sepsis, to reduce the burden of neonatal mortality due to sepsis. A systematic review by Zaidi *et al.*[17] in 2011 reported a 25% reduction in neonatal mortality with the use of oral antibiotics (not recommended in a hospital setting) and a 44% reduction in mortality with the use of neonatal care packages that included injectable antibiotics. A Delphi consensus (very low-quality evidence) in the same review reported an 80% reduction in neonatal mortality. These interventions can substantially reduce neonatal mortality and increase preterm survival in district and regional facilities.[17]

Preventing hypothermia

Hypothermia continues to be a major problem for preterm infants, and is directly linked to neonatal morbidity and mortality. Mechanisms of heat loss are through radiation (for example, a cold wall close to the baby), conduction (for example, skin touches a cold surface such as a cold blanket), convection (for example, delivery in a cold room) and evaporation (for example, by losing heat through wet skin). Normal body temperature is defined as 36.5 - 37.5°C. Hypothermia is defined as mild (36 - 36.4°C), moderate (32 - 35.9°C) and severe (<32°C).[19] Admission temperature is inversely related to mortality, with a 28% (odds ratio (OR) 1.28; CI 1.16 - 1.41) increase in mortality for every 1°C decrease in temperature. Additionally, hypothermia on admission results in an 11% (OR 1.11; CI 1.02 - 1.20) increase in sepsis for every 1°C decrease in temperature. Higher odds of intraventricular haemorrhage (OR 1.3; 95% CI 1.1 - 1.6) and death (OR 1.5; 95% CI 1.1 - 1.6) were associated with moderate hypothermia.[20]

The plastic bag/wrap and cap has been extensively researched and found to be an effective, low-cost method for reducing hypothermia in preterm infants. The bag/wrap is applied while the infant is still wet with amniotic fluid. Other measures to prevent hypothermia are keeping the delivery room temperature at 25 - 26°C, placing the infant on pre-warmed surfaces, and using a pre-warmed incubator during transport.[19]

A systematic review conducted in 2015 showed a reduction in hypothermia by 21 - 46% in preterm infants by using plastic bags. This study also looked at the use of plastic bags on term neonates. A 24 - 58% reduction was found with the use of plastic bags. One-third of the studies examined in this systematic review were from LMICs. All the studies used a plastic bag immediately after delivery without drying the infant initially. Five studies in this systematic review used cost-effective materials such as food packaging film or non-sterile grocery store bags. All five studies found a reduction in hypothermia. These are methods that can be used in LMICs to decrease the incidence of hypothermia and, as a result, reduce neonatal morbidity.[21]

Continuous positive airway pressure (promising intervention)

CPAP is an easy-to-use, non-invasive method used in the prevention and treatment of RDS. CPAP provides positive end expiratory pressure (PEEP) that keeps the alveoli open, and therefore recruits more surface area for ventilation.[22] A 35% reduction in mortality occurs (RR 0.65; 95% CI 0.52 - 0.81) with the use of CPAP in premature infants.[23] CPAP provided to infants <32 weeks' gestation or <1 500 g soon after birth reduces the need for intubation and invasive ventilation by 50% (RR 0.50; 95% CI 0.42 - 0.59).[23] It is recommended that CPAP be started during stabilisation in the delivery room. During stabilisation a T-piece is used (which can deliver PEEP), which is therefore a better choice than the self-inflating bag (which cannot deliver PEEP), especially in low-resource countries where CPAP devices are not available in the delivery room.[24] CPAP has also become available in many SA district hospitals, since it has been demonstrated that chances of survival improve if the infant does not need to be transported to a higher level of care for respiratory support. Five-year data from a district hospital in the Western Cape Province, SA, found that the use of CPAP was safe and simple; it reduced the need for intubation and ventilation and reduced the transfer rate of low birth-weight infants to higher levels of care.[25] A study in Malawi also demonstrated that a low-cost CPAP device is a highly cost-effective strategy for providing respiratory support for premature neonates with RDS.[26] Neonates with a very low birth-weight, RDS and sepsis benefited the most. The study showed a 27% improvement in survival, which demonstrates that the implementation of a low-cost CPAP device in LMICs could reduce mortality.[26]

Exogenous surfactant (promising intervention)

Respiratory failure due to insufficient surfactant is a major cause of morbidity and mortality in premature babies. Since the 1990s, the use of exogenous surfactant replacement therapy has been an effective and safe method for treating infants with RDS.[27] Although Lassi *et al.*[9] categorise surfactant therapy as a promising intervention, it is safe to say that surfactant was a neonatology game-changer, making a significant impact on morbidity and mortality.[27] Bahadue *et al.*[28] demonstrated that early rescue surfactant within 2 hours of birth is recommended for infants with established RDS, with a significant reduction in neonatal mortality (RR 0.84; 95% CI 0.74 - 0.95) and chronic lung disease (RR 0.69; 95% CI 0.55 - 0.86). The European RDS Consensus Guideline recommends that neonates >26 weeks' gestation receive surfactant therapy if the FiO_2 requirement is >40%, but that neonates ≤26 weeks' gestation receive surfactant therapy if the FiO_2 requirement is >30%.[24] It has been recommended that surfactant therapy be available in district hospitals that have introduced CPAP, to optimise the management of premature babies with RDS in district hospitals.[25]

Early initiation of breast-milk feeding (effective intervention)

Owing to the nutritional and health benefits of human milk, it should be promoted, supported and protected as the normal and ideal method of feeding preterm babies, particularly in LMICs with poor hygienic conditions. Mothers should receive education and support regarding expressing of milk and establishing and maintaining breast-milk supply. Human milk contributes to the development of the preterm neonate's immature host defence mechanisms, decreasing the risk of NEC and sepsis, and thereby reducing neonatal morbidity and mortality.[29]

The benefits of breastfeeding for infant, mother and public health have been well documented. The short-term benefits to the infant are reduced risk of gastroenteritis, NEC, ear infections, pain following minor procedures, hospital readmissions, respiratory infections, sudden infant death syndrome and urinary tract infections. Long-term benefits of breastfeeding for the infant are a reduced risk of asthma, atopic dermatitis, cardiovascular disease, celiac disease, diabetes, childhood inflammatory disease and obesity. A longer duration of breastfeeding is associated with improved cognition and neurodevelopment.[29]

Kangaroo mother care (effective intervention):

Kangaroo mother care (KMC) is the practice of placing the preterm infant skin-to-skin in the upright position on the parent's chest (usually the mother). The advantages for the infant are improved growth and development, higher weight gain, length and head circumference, improved maintenance of oxygen saturation with fewer episodes of apnoea, more stable heart rate, improved maintenance of body temperature and earlier discharge from hospital compared with infants who do not receive KMC. The risk of nosocomial sepsis is also reduced, by colonisation of the infant with the mother's commensal organisms. Parental (maternal) advantages of practising KMC are improved bonding, increased awareness of the needs of the infant, promotion of breastfeeding, decreased parental stress and depression, a sense of satisfaction in their parenting role and a more confident and competent parent.

The use of KMC has reduced neonatal mortality by 33 - 50%.[9] This type of care is especially useful in LMICs, where there are fewer resources (under-staffing, lack of incubators, overcrowding) available.[30]

The EPICE project

The Effective Perinatal Intensive Care in Europe (EPICE)[31] project evaluated the outcome of infants born between 24w0d and 31w6d gestation in 2011/2012. The main outcome measure was the combined use of four evidence-based practices: administration of maternal antenatal corticosteroids, delivery in a labour ward with the appropriate level of neonatal care, prevention of hypothermia and the use of exogenous surfactant within 2 hours of birth, or early nasal CPAP. The in-hospital mortality and morbidity was 18% lower for infants who received all four interventions. Despite these interventions being widely accessible, only 58.3% of preterm infants received all four interventions in this study. This study showed that these four practices combined could result in increased preterm survival without severe morbidity.[31] The EPICE study shows that basic interventions can impact neonatal mortality, and these 4 interventions can easily be implemented in SA, even in low-resource communities, in an effort to decrease the neonatal mortality rate further.

Conclusion

Neonatal morbidity and mortality continue to be a challenge globally. Prematurity is the leading cause of death in children <5 years of age. There are a few cost-effective, evidence-based interventions that can be implemented in LMICs to reduce neonatal mortality. These include the administration of corticosteroids, prevention of hypothermia, early initiation of breastfeeding, stabilisation on CPAP for all babies at risk of RDS and early rescue surfactant. With perseverance, we **can** reach the Every Newborn target, and prevent further neonatal morbidity and mortality.

Acknowledgements. The authors thank Prof. de Witt, Dr Coetzee and Barbara English for their time and contribution to the article.

Author contributions. HN was responsible for writing and editing the article. TWdW, MC and Barbara English were responsible for editing the article.

Funding. None.

Conflicts of interest. None.

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Accepted 20 April 2018.