**REVIEW ARTICLE**

# The role of the placenta in perinatal asphyxia, neonatal encephalopathy, and neurodevelopmental outcome: A review

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## Abstract

Perinatal asphyxia contributes significantly to neonatal deaths globally. This may occur due to the effects of various phenomena like uterine rupture, infections, maternal hemodynamic compromise (amniotic fluid embolus), placenta, and umbilical cord (umbilical cord knot, placental abruption, or compression). Perinatal asphyxia is the term used for interrupted blood flow or the exchange of gases in the fetus during the prenatal period. The reduced oxygenation induces a cascade of brain injuries, resulting in long-term damage to the infant's brain. Some infants exposed to perinatal hypoxia-ischemia will make an immediate recovery and have normal survival, while others may suffer from an evolving clinical encephalopathy. This review article focuses on the relationship between the placenta, neonatal encephalopathy, and neurodevelopmental outcome. It also aims to identify possible interventions and drive the focus of policymakers towards issues that evolve around perinatal asphyxia, neonatal encephalopathy, and neonatal care and that have a high impact on infant morbidity in sub-Saharan Africa. *(Afr J Reprod Health 2023; 27 [1]: 107-118).*

**Keywords:** Perinatal asphyxia, neonatal encephalopathy, neurodevelopmental outcome, placenta, infant morbidity

## Résumé

L'asphyxie périnatale contribue de manière significative aux décès néonatals dans le monde. Cela peut se produire en raison des effets de divers phénomènes tels que la rupture utérine, les infections, le compromis hémodynamique maternel (embolie de liquide amniotique), le placenta et le cordon ombilical (nœud du cordon ombilical, décollement placentaire ou compression). L'asphyxie périnatale est le terme utilisé pour désigner l'interruption du flux sanguin ou l'échange de gaz chez le fœtus pendant la période prénatale. L'oxygénation réduite induit une cascade de lésions cérébrales, entraînant des dommages à long terme au cerveau du nourrisson. Certains nourrissons exposés à l'hypoxie-ischémie périnatale se rétablissent immédiatement et ont une survie normale, tandis que d'autres peuvent souffrir d'une encéphalopathie clinique évolutive. Cet article de synthèse se concentre sur la relation entre le placenta, l'encéphalopathie néonatale et les résultats neurodéveloppementaux. Il vise également à identifier les interventions possibles et à attirer l'attention des décideurs sur les problèmes qui évoluent autour de l'asphyxie périnatale, de l'encéphalopathie néonatale et des soins néonatals et qui ont un impact élevé sur la morbidité infantile en Afrique subsaharienne. *(Afr J Reprod Health 2023; 27 [1]: 107-118).*

**Mots-clés:** Asphyxie périnatale, encéphalopathie néonatale, évolution neurodéveloppementale, placenta, morbidité infantile

## Introduction

Every year, it is estimated that around 20 million infants are born with low birth weight, i.e., <2.5 kg, and about 14.9 million infants are born preterm[1]. Preterm birth (PTB), which is eventually the direct cause of more than one million deaths every year, may be the leading cause of mortalities among children under the age of five[2]. Among all other risk factors for newborns, perinatal asphyxia is the third leading cause of neonatal death, trailing only premature birth and infections[3]. Perinatal asphyxia is the process by which blood flow or placental or pulmonary exchange of gases is interrupted during the perinatal period. If perinatal asphyxia is severe, it can lead to a series of brain injuries, eventually resulting in long-term damage to the infant's brain. There is a potential that infants exposed to perinatal hypoxic-ischemia will recover quickly and have a normal life, but a small number will develop clinical encephalopathy (NE). A wide range of complications due to hypoxic-ischaemic

encephalopathy (HIE) or NE may have an impact on the sensory, motor, behavioral and cognitive development of the child[4].

As per the World Health Organization (WHO), birth asphyxia is defined as a condition in which the infant fails to initiate and sustain breathing in a new-born at the time of birth. This is a temporary disruption of the availability of oxygen that indicates a risky metabolic challenge, even in the case where such an absence doesn't lead to fatal consequences. Hypoxemia (abnormally low oxygen concentration in the fetal blood) from causes due to asphyxia, may lead to the accumulation of carbon dioxide known as hypercapnia. Various biochemical changes take place inside the body of an infant due to the combined effect of decreased oxygen supply (hypoxia) and blood supply (ischemia), the impact of which is neuronal cell death and brain damage. If asphyxia remains untreated, it may cause dysfunction in multiple organ systems. In low-income countries, perinatal asphyxia may account for 25% of all neonatal deaths[5].

The most common cause of perinatal death in infants weighing <1000g in South Africa is unexplained intrauterine death (IUD). Placental histology may lead to defining the reason behind perinatal death and the harmful effects. Evidence from the investigation of the placenta consequent to an adverse perinatal outcome is often underutilized[6]. Placental abruption also has been associated with a higher risk of maternal and perinatal complications including disseminated intravascular coagulation (DIC), severe birth asphyxia, couvelaire uterus and perinatal death. These complications can be associated with poor perinatal outcomes. It is thus vital to be aware of placental abruption with these clinical characteristics, and ensure speedy delivery in tertiary care centers that have sufficient intensive care facilities for best maternal-neonatal care[7]. In South Africa, there is a continuous rise in neonatal deaths. We need to question if the deaths are due to the limited accessibility of neonatal intensive care unit beds in the country, insufficient provisions and difficult transport systems, lack of proper health care and attention to antenatal and postnatal care. Simple preventative measures may be undertaken to decrease the perinatal mortality rate, in addition to neonatal resuscitation and other programs like breastfeeding and KMC training for health care providers[8].

## *Placenta pathophysiology and its clinical significance*

The placenta facilitates the transfer of nutrients and oxygen to the fetus for healthy fetal growth[9]. Hence, the placenta is the most important but the least understood organ of the body. During the developmental phases, it executes various functions that are later performed by individual organs such as the gut, lungs, kidneys, endocrine glands, and the liver. The placenta is anatomically adapted to primarily supply oxygen and nutrients to the fetal brain by having a large surface area for this exchange; it also has a thin interhaemal membrane that separates the maternal and fetal circulations. Additionally, to facilitate the transfer, it implements other key strategies such as restructuring of the maternal uterine arteries that supply the placenta to guarantee maximum perfusion. Furthermore, maternal metabolism is profoundly affected by hormones produced in the placenta. These hormones primarily build up energy reserves for the mother and later release energy from these reserves to support fetal growth in later phases of pregnancy and post-natal lactation[10]. Moreover, the pathways required to be involved in placental vascularization and maternal immune activation are equivalent to those necessary for typical fetal development, particularly neurovascular development. Thus, disruption of angiogenic pathways at the materno-fetal interface mediated by the immune system may also have enduring neurological issues for the infant[11].

The placenta predominantly affects maternal-fetal physiology. Since it plays numerous functions and has several responsibilities, any irregularities in the placenta's functioning may cause adverse effects on pregnancy outcomes. Maternal, fetal, and placental causes can lead to a state in which the fetal growth is restricted to below the tenth percentile of the estimated weight for gestational age, called intrauterine growth restriction (IUGR). IUGR may be associated with fetal morbidity and mortality[11]. The growth of the fetus begins early in pregnancy due to cell division and subsequent cell hyperplasia, which is followed by augmented cell size or cell hypertrophy. Later,

the cell hyperplasia ends and the cellular hypertrophy remains contributing to fetal growth. Placental growth and development are analogous to the fetal sequence of cell hyperplasia and hypertrophy throughout pregnancy trimesters. Meanwhile, the nutrient delivery system is maintained between the placenta and the fetus. Fetal growth abnormalities can be caused by any insult occurring during the fetal growth period[12].

Maternal infections may also commonly occur during pregnancy and have considerable impact on infant physiology. These infections are associated with developmental delays *in utero* and even fetal death[13]. Low- and middle-income countries also bear a high burden of communicable diseases during pregnancy (such as malaria, human immune deficiency virus, sexually transmitted infections, etc.), and it is also evident that these widespread infections play a role in poor birth outcomes through inflammation-supported disruption of the development of the placenta and its function[14–17]. Malaria parasitaemia also affects blood flow in the uterine and umbilical arteries during early stages of pregnancy. This may be due to modifications in placentation and angiogenesis, respectively. Malaria parasitaemia also increases the likelihood of IUGR[18].

### *Neonatal encephalopathy*

Assessment of placental abnormalities can update our understanding of the etiology and improve our control of neonatal encephalopathy (NNE)[19]. Globally, NNE is the leading cause of childhood mortality and morbidity, followed by perinatal hypoxic-ischemic insults. We can observe improvements in the ability to study, diagnose, observe, and enhance the care of the newborn with developments in techniques such as neuroimaging in the monitoring of the biomarkers, brain, and tissue. However, the major challenge is the availability of these imaging facilities in low-income regions like Tanzania[20]. Perinatal insult causes perinatal asphyxia, which results in suffocation, anoxia, and increased levels of carbon dioxide. Fetal ischemia or hypoxia increases the risk of encephalopathy in infants, which can result in permanent motor loss, mental impairment, and neonatal death. Neonatal death accounts for nearly 40% of all deaths in children under the age of five[21].

Acute reduction in fetal blood flow and oxygenation from sentinel events during birth such as a ruptured uterus, placental abruption, or umbilical cord prolapse may be a major cause of NNE. Other causes of NNE include inflammation, infections, metabolic diseases, toxins, stroke, genetic disorders, and placental disease. Abnormal fetal growth and congenital defects are also linked with NNE[22]. The global incidence of NNE is estimated to be three per 1,000 live childbirths and adverse long-term consequences include learning difficulties, cerebral palsy (CP), epilepsy, and cognitive impairment[23,24]. The major symptoms of NNE are altered level of consciousness, seizures, loss of tone, interrupted or obstruction in respiration ability, and multi-organ dysfunction[23].

### *NNE and its impact*

The absence of blood flow or gas exchange to and from the fetus approximately before, during, or after birth is known as perinatal asphyxia. Due to decreased blood flow, it may cause profound systemic and neurologic sequelae. Perinatal asphyxia can occur as a result of a variety of conditions, including uterine conditions (e.g., uterine rupture), maternal hemodynamic compromise (amniotic fluid embolus), placenta and umbilical cord (also known as placental abruption, umbilical cord knot or compression), and infections[25]. Birth asphyxia contributes around 20–25% to the neonatal mortality rate worldwide. The most common cause of brain injury in the fetus is inadequate oxygenation, which leads to brain injury. Excessive free radicals form within the fetal brain due to the neonatal brain's high metabolic demands, free ions' high concentration, and fatty acids, which also generate other toxic compounds like peroxynitrite[23]. Table 1 summarizes the possible outcomes of perinatal asphyxia and HIE. The heterogeneous phenomenon of NE is characterized by disturbed neurological function during the early days of life until after birth in an infant born at or beyond the gestational period of 35 weeks[4]. NNE, which is a clinical term with no specific etiology, can be caused by a variety of factors[24].

In about 20% of cases of NNE, HI starts before birth. Another 30% of cases begin during delivery, while 35% occur during the birth process.

**Table 1:** A summary table of reported outcomes in perinatal asphyxia and HIE[4]

| | |
|---|---|
| Short-term complications | Death; HIE; Seizures |
| Long-term complications | Visual impairment; Motor impairment; Cerebral palsy; Hearing loss<br>Attention; Lower test scores<br>Educational: Increased support requirements; Irritability<br>Neuropsychiatric: Psychotic symptoms<br>Cognitive: Episodic and working memory<br>Behavioral: Attention<br>Explosiveness<br>Neurodevelopmental: Autistic spectrum |

HIE, hypoxic-ischemic encephalopathy

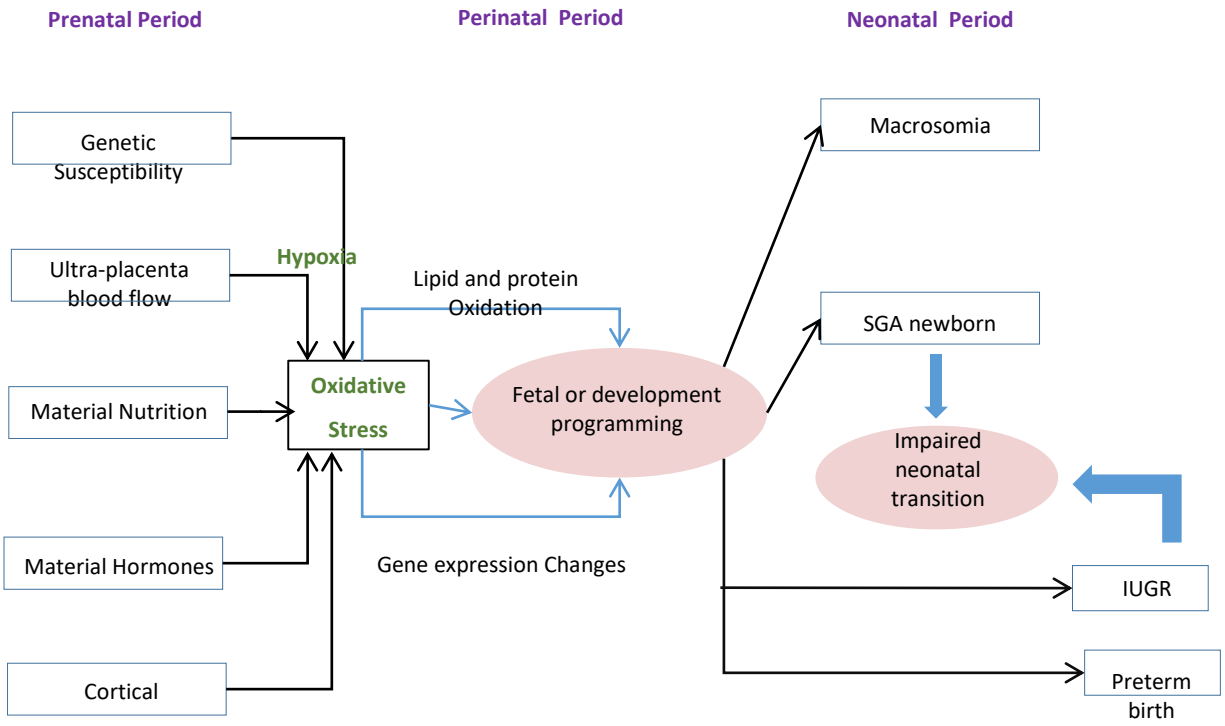


**Figure 2:** Various events during the prenatal, perinatal, and neonatal periods[4]

There are only 10% of cases where hypoxic-ischemia develops after birth. In most cases, there is an acute hypoxic-ischemic insult that affects the deeper brain structures like the brain stem, basal ganglia, and thalamus, while subacute hypoxic-ischemia, may cause the watershed damage. However, HI insults resulting in injuries are comparatively rare, since most cases result in intrapartum death and the infants do not need go for a magnetic resonance imaging (MRI) evaluation to establish the brain injuries. A two-fold brain damage process occurs due to perinatal hypoxic-ischemia. Prior to birth, HI produces excitatory neurotransmitters that lower cellular pH, resulting in neural cell death, as well as toxic compounds and free radicals accumulation. When oxygenation after birth begins and recovery of perfusion starts, the metabolism of these toxins begins and can set up destructive molecular pathways that cause secondary energy failure within the first hour post-birth. The delay or impairment in cerebral oxidative energy, which is evident within 6 to 8 hours after birth, can last for a maximum of 72 hours after birth. This adds up to necrosis and apoptosis, which can cause major brain damage to neuronal cells. This postnatal cell death process can

last up to weeks[23]. Figure 1 shown below demonstrates a variety of events that impact neonatal health during the prenatal, perinatal, and neonatal periods.

The following are the diagnostic criteria for neonatal HIE[25]:

- Metabolic acidosis with a pH <7.0
- Base deficit -12
- At 10 minutes, the APGAR score is 5, indicating that resuscitation is still required.
- Presence of multiple organ system failures
- Hypotonia, irregular pupillary movements, weak or absent sucking, apnea, clinical seizures, or hyperpnea, are all signs of encephalopathy.
- There are no other possible explanations for the neurologic results (congenital neurologic disorder, metabolic mistake that is present at birth, medication effect, genetic disorder).

### *Intrapartum cardiotocograph monitoring and perinatal outcomes*

The intrapartum cardiotocograph (CTG) was first introduced in 1970s[26]. The CTG monitors the fetal heart rate and uterine tone throughout time, allowing clinicians and researchers to investigate the association between uterine activity and heart rate. Fetal heart rate patterns are thought to convey physiological information about the fetus' oxygenation[27]. During labour, uterine contractions cause a reduction in placental blood flow[28]. The fetus may be at risk of inadequate oxygenation as a result of this decline[29]. Hypoxia is thought to be responsible for a portion of perinatal fatalities and the occurrence of CP[30,31].

Intrapartum CTG monitoring is designed with the goal of lowering perinatal mortality and CP. CTG monitoring has no advantage over intermittent auscultation (IA) for women who are considered to be at low risk for a poor perinatal outcome[32]. As a result, most professional guidelines for intrapartum fetal monitoring believe IA to be appropriate for low-risk women. Professional guidelines advocate continuous intrapartum CTG monitoring for women who are at higher risk[33–35]. The use of CTG monitoring has increased over the last two decades, with compelling evidence that it correlates with an increase in caesarean section rates[36]. Maternal mortality and major maternal morbidity appear to be on the rise in some high-income nations, and this is linked to an increase in the number of caesarean sections performed[37,38]. A review by Small *et al.*[39] found that CTG monitoring during preterm labor was associated with a higher incidence of CP.

### *Role of placenta in maternally-derived bioactive substances*

Preterm birth (PTB) can have significant neurodevelopmental problems. Variations in the placental role have been studied in conjunction with many antenatal situations that are risk factors for poor neurodevelopment, fetal growth restriction, PTB and inflammation *in utero*. Figure 2 depicts some placental factors that may be useful in identifying various biomarkers, and understanding the underlying mechanisms that lead to poor neurodevelopmental outcomes in children[4].

The placenta protects fetal brain development from maternally derived bioactive substances such as cortisol. It also serves as a source of neurotropins and neuroactive steroids, which play important roles in axonal growth, apoptosis control, neuronal proliferation, and myelination. The new placental biomarkers were found to be effective in the pathogenesis and early detection of poor neurodevelopmental outcomes in both preterm and full-term newborns. The genetic variants and epigenetic biomarkers were assessed, and the data has been collected. Key tissues controlling the fetal environment, along with the placenta, may improve the ability to predict future infant health by combining observable changes in placental function with genetic and epigenetic variants. Eventually, this may facilitate and improve lifelong neurodevelopmental capability by directing health resources to developing countries.

NNE is established by a reduced level of consciousness or seizures, associated with difficulty breathing, and by reduced tone and reflexes. High mortality rates in infants and newborns may be associated with NNE. Predisposing factors for NNE may be antenatal, perinatal, or a combination of both[4]. Figure 2 may be helpful to clearly determine factors and conditions causing cognitive impairment in infants.

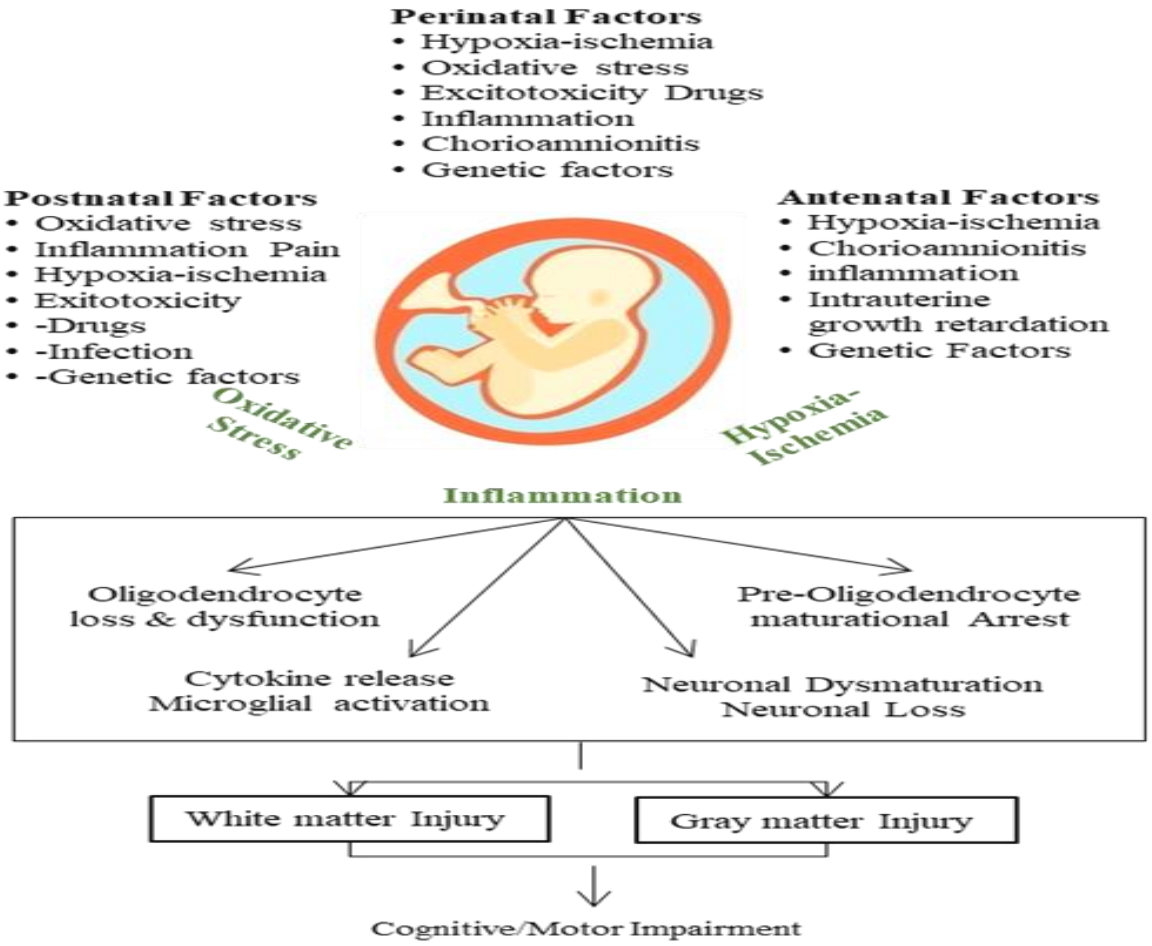


**Figure 2:** Factors and conditions causing cognitive impairment[40]

### *Available treatments and an action plan to prevent neonatal mortality*

Regardless of the cause of NNE, therapeutic hypothermia (HT) is the only therapy option. Identifying the NNE's etiology can also help investigators focus their efforts on things like sepsis and metabolic workups to ensure optimal management. This could pave the way for additional targeted medicines linked to the underlying process, as well as improvements in prevention methods[4]. Until neuroprotection medications became available, newborns with HIE could only receive intensive care that focused on comfort rather than cure. These measures included resuscitation in the delivery room, correction of metabolic abnormalities (glucose, calcium, magnesium, and electrolytes), treatment of seizures, and monitoring for multiorgan failure (including blood pressure, metabolic acidosis, cardiac dysfunction, and hypoventilation)[3]. About 0.5–3/1000 live births are affected by moderate or severe There is a higher risk of mortality or disability, including CP, among children in developing countries. Congenital anomalies and abnormal fetal growth are linked with NE, pointing to its role in developmental problems. With the advent of research and the development of new tools for differential diagnosis, these can be applied for individualized treatment, prevention, and prediction of NNE[22].

While death or disability after NNE may be reduced by therapeutic HT in high-income countries, the efficacy and safety of the same in low- and middle-income countries remain doubtable. In Southern Asia, therapeutic HT

combined with an optimal supportive intensive care unit reduced mortality and moderate-to-severe disability[41]. In South Africa, high mortality and perinatal death due to intrapartum-associated delivery asphyxia are common, like in other developing and underdeveloped countries. The rural areas of these countries are the most afflicted and have the most inadequacies. These deaths can be avoided, and mortality rates reduced, with better provisions for mothers' waiting amenities in rural areas, partogram-based labour-management, advances in fetal monitoring, and the recruitment of midwife staff for South African Maternity units[42].

### *The scenario of infant mortality in South Africa*

In South Africa, approximately 7000 newborns die every day. As per current trends, the decline of neonatal mortality is slower in comparison to mortality among children aged 1–59 months. As a result, the ratio of neonatal deaths among all deaths in children under the age of five has increased dramatically, from 40% in 1990 to 47% in 2018. Hence, the reduction of infant mortality is gaining global importance not only due to the rise in the percentage of neonatal deaths among under-five deaths but also to shift the focus of health interventions and research to identify and address major reasons behind infant deaths. Since the causes of neonatal deaths are largely different from those of other under-five deaths, they demand separate intervention and research plans. It is observed that among children who pass away within the first four weeks after birth, the majority, about 99%, are reported to be from poor regions of the world, particularly South Asia and sub-Saharan Africa. According to data from 2018 studies, the neonatal mortality rate in Sub-Saharan Africa was 28 deaths per 1000 live births. Although, by 2030, the WHO target for South Africa is <12 newborn deaths per 1000 live births, a lot of work still needs to be done to meet the challenges of handling and reducing preterm births (Table 2). To comprehend and investigate trends in neonatal mortality in two sub-Saharan countries[43].

### *Improvement in encephalopathy prognosis with the advent of neuroprotective treatment*

Because multiple pathways are involved in understanding the complex process of brain injury in newborns, determining the timing of the injury and identifying infants at risk in the early stages of NNE may be a little complicated. Mostly, multiple injuries occur in infants before birth. Normal fetal development may be disrupted due to abnormal perinatal brain injury up to a critical point in the intrauterine period, which may be the determining factor behind permanent changes in phenotype, developing the foundation for fatal embryonic diseases. Furthermore, a newborn's susceptibility to perinatal injuries may be due to brain development and structure[44].

With the growth and development of neuroprotective treatment by therapeutic HT for infants with mild and severe encephalopathy, the prognosis for encephalopathy has improved. Most importantly, because HT is a time-sensitive intervention with a very narrow therapeutic window, the outcome prediction in these infants has changed. Blood biochemistry, clinical examination, and electrophysiology are currently the only known markers. Emerging technologies that use physical and biological markers have the potential to improve the selection of infants who will benefit more from therapeutic interventions. Based on outcomes in proteomics, transcriptomics, and metabolomics and physiological markers like the variability of heart rate, EEG analysis, and MRI in combination with neuroprotective measures, possibilities exist to improve outcomes in HIE or NE[4].

Therapeutic HT is the only treatment available with maximum advantage if given within the initial six hours of life[24]. Thus, only moderate HT has been observed to have a proven positive impact, on perinatal asphyxia-driven brain damage. Currently, a huge number of pharmaceuticals are under study as add-on therapy for HT. These medications are supposed to stop the adverse consequences of prenatal hypoxic-ischemia-induced damage to molecular pathways. The most effective treatment for birth asphyxia may be a combination of HT and subsequent fetal pharmaceutical treatments. One or more destructive pathways will be interrupted by this combination treatment. High anticipation remains for this treatment because of its role in the restoration of the developing brain, and it is furthermore expected to play a progressively important role in the years to come[23]. Further research is desirable to understand and estimate the

**Table 2:** Causes and percentage share of these causes in mortality in Kenya and South Africa[43]

| Causes | Kenya | South Africa |
|---|---|---|
| Preterm Birth Complications | 36% | 28% |
| Intrapartum Related events | 20% | 29% |
| Sepsis or tetanus | 14% | 16% |
| Congenital abnormalities | 10% | 13% |
| Diarrhea | 0 | 0 |
| Pneumonia | 5% | 7% |
| Other conditions | 15% | 8% |

efficiency of combined therapeutic strategies with HT therapy to achieve the maximal neuroprotective effect[45].

In low-income countries, HIE is common. Due to the lack of therapeutic HT facilities, the risk of morbidity rises, and the chances of survival decrease. Several trials conducted in newborn infants with HIE show the use of erythropoietin (EPO) to help reduce morbidity and improve neurodevelopmental outcomes. This positive result was also observed in infants that were deprived of therapeutic HT. Previous research hasn't found any significant side effects from using the medicine. The latest studies concluded that EPO improves neurodevelopmental outcomes and that is quite safe in neonates with HIE[46].

## *Current markers for prediction of outcome*

Various clinical presentations and different neurodevelopmental outcomes are linked to patterns of brain injury in the term called NE. Prenatal risk factor measurement may not determine or predict the pattern of neonatal brain injury[47]. Currently, the universal focus remains on biomarkers as the standard to support perinatal asphyxia diagnosis. The placental examination may reveal markers for fetal processes within the mother or the intrauterine fetus. Expert evaluation of placental pathology can provide specific data, whereas MRI may help to clarify the mechanism of asphyxia and its timing when used in conjunction with clinical examination of infants with NE. To recognize the hypoxic-ischemic insult, evidence of multi-organ failure can be beneficial in babies with severe encephalopathy and can be used as a supplemental diagnostic criterion. Similarly, multiple tissue biomarkers have been identified that suggest brain injuries in infants with NE, but these biomarkers are yet to be validated in clinical practice[5]. Table 3 shows various markers that help in the prediction of outcomes.

## *Future interventions and policy guidelines*

NE may be caused by multiple factors, such as HIE, abnormalities in the placenta, perinatal infections, neonatal vascular stroke, coagulopathies, and metabolic disorders. However, the cause of NE is unknown in more than half of the cases[24]. A considerable ratio of neonatal deaths occurs in the neonatal units of hospitals. Asphyxia, low birth weight, prematurity, and neonatal infections are the principal causes of neonatal hospitalization and morbidity. There are several simple initiatives that can be used to reduce neonatal hospital admissions and deaths in South Africa[48]. A high percentage of morbidity in newborns is preventable with improved quality of care. It can also minimize long-term morbidity in survivors after birth. Improving the quality of post-resuscitation care and filling gaps in the health-care system for affected newborns may contribute to the gains by global efforts to improve neonatal care[49]. Existing and upcoming policies to advance outcomes in this population include prevention of PTB and prenatal, perinatal, and postnatal methods to guard the developing brain[49]. Along with the introduction of neuroprotective therapies, distinct attention must be paid to the further enhancement of antenatal and perinatal care[3]. The studies and reports on relative intrapartum aspects must support increased observation in these clinical conditions and emphasize the importance of vigilant management to optimize new born outcomes[50]. Initiatives like a comprehensive research endeavour and program, the United States Agency for International Development-funded Neonatal Health Research Initiative in India and the International Clinical Epidemiology Network to conduct a detailed study of various aspects of neonatal health, have gained high importance[4].

Further, there is limited access to trained birth attendants and emergency obstetric intervention in sub-Saharan Africa; thus, the probability of the influence of peripartum hypoxic events on NE is very high. Though the burden of NE in sub-Saharan Africa is quite high, the roles of infectious comorbidities, such as chorioamnionitis and neonatal bacteremia, and the influence of other aspects putting infants at risk for the etiology of NE have been barely defined[51]. It's critical to recognize that the statistical data presented thus far has primarily focused on high-income countries, where

**Table 3:** Various markers associated with predictors of outcome

| Predictors of outcome Standard | Advantages | Disadvantages |
|---|---|---|
| Acid-base balance | A widely available test that can be measured early using scalp and cord sampling | Testing with invasive methods is unable to distinguish the severity of the injury |
| pH | early response to HI | The abnormal outcome with low PPV |
| Lactate | A more accurate representation of the metabolic pathway | No gain over pH |
| Apgar score | A non-invasive, rapid assessment of the newborn condition upon birth. | Because of the substantial inter-observer variation, the long-term outcome cannot be properly analyzed. |
| Clinical examination | Non-invasive, useful for observing changes in clinical status as the injury progresses, and predictive at discharge | Clinical experience is required, which is influenced by intubation, medicines, and HT, and is a poor predictor of long-term success |
| EEG/aEEG | "Gold standard," early predictive value if the condition is normal, importance of subclinical seizure detection, non-invasive | Resources, equipment, and clinical experience are required to apply and interpret |
| **Novel** | | |
| HRV | HIE severity is differentiated, and it is non-invasive. | It necessitates the use of specialized equipment |
| MRI/MRS | Explicit injury patterns improve prognosis, and early changes are extremely obvious | It necessitates the use of specialized equipment, the transport of a sick child to an MRI machine or department, and the neonates' ability to remain still for long periods of time |
| Biomarkers | Pilot tests have shown a lot of promise | Not recommended for medical usage. |
| Serum | Reflects the metabolic status of the entire system | Invasive testing, mixed indicators from cerebral and other organ problems, and only modest volumes are available |
| Cord blood | Large volumes are possible, and they are available early. | Blood from both the fetus and the placenta |
| CSF | Signs in the brain are reflected | Very tough to sample |
| Urine | Comparatively easy to sample | If you have severe renal disease, you're going to be affected |
| Proteomics | Easy to test and relatively steady | Specialized equipment is necessary, and injury responses are delayed |
| Metabolomics | Responsive to metabolic changes in a timely manner | Specialized equipment is required, and environmental considerations must be taken into account |
| Transcriptomics | Very stable, involved in essential cell cycle and cell death events | It takes specialized equipment, and most markers are completely new and difficult to find. They may also control several pathways |

MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; CSF, cerebrospinal fluid; HRV, heart rate variability; EEG, electroencephalogram; aEEG, amplitude-integrated electroencephalogram; PPV, positive predictive value; HIE, hypoxic-ischaemic encephalopathy

more research is undertaken each year. However, middle-income countries bear the majority of the burden of neonatal[4]. For the medical staff working in areas lacking sophisticated technology, simple yet effective systems will be useful for the assessment of infants with HIE and for prognosis of the neurodevelopmental outcome[52]. Simple yet effective systems will be useful for the assessment of infants with HIE and the prognosis of their neurodevelopmental outcomes for medical staff working in areas lacking sophisticated technology[48,53]. Documentation of associated intrapartum factors should increase vigilance in these medical conditions and emphasize the importance of careful management to optimize newborn outcomes[40]. The burden of neonatal mortality in South Africa and other regions of the developing world represents high annual neonatal deaths. The evidence review led to this recommendation for increased funding for newborn research and health programs[54].

## Conclusion

It is evident that the underdeveloped and developing countries need to be supported by the

high-income countries to overcome the high infant morbidity rates due to birth asphyxia and related issues. The assistance may include the provision of equipment or the transfer of technology for the treatment and diagnosis of affected infants. We aimed to discuss the current situation of neonatal care of term infants with alleged birth-related issues, as well as limitations in available treatment and diagnosis of affected infants globally and in the South African population, in this review. The aim of the study is to explore feasible interventions to improve acute and neonatal care in low-income countries. The current need is to find dependable, effective, and low-cost ways to enable early documentation of newborns who are at risk of long-term harm. We need to advocate for policy changes that may eventually lead to significant, and enduring improvements in the quality of life for these children, their communities, and their parents.

## Conflict of interest

The authors declare no conflicts of interest.

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