REVIEW

Does perinatal asphyxia impair cognitive function without cerebral palsy?

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Some studies on neurodevelopmental outcomes after neonatal encephalopathy have suggested that cognitive deficits do not occur in the absence of cerebral palsy. It is increasingly apparent that childhood survivors of overt neonatal encephalopathy may have cognitive impairments, even in the absence of functional motor deficits. The risk of cognitive deficits is related to the severity of neonatal encephalopathy and the pattern of brain injury on neuroimaging, particularly the watershed pattern of injury. A better understanding of the risk factors for cognitive abnormalities after neonatal encephalopathy will ultimately lead to interventions to prevent these deficits. Identifying the full spectrum of neurodevelopmental outcomes after neonatal encephalopathy will also allow care givers to identify children requiring early intervention to maximise their potential for independent function throughout development.

of “perinatal asphyxia” in recognition of the variable timing of injury resulting in this syndrome.

The American College of Obstetricians and Gynecologists task force on neonatal encephalopathy and cerebral palsy concluded that an acute intrapartum event could only result in cerebral palsy of the spastic tetraplegic type and could not result in isolated cognitive deficits, such as mental retardation.⁹ Earlier studies on neurodevelopmental outcomes after fetal hypoxia and other presumed causes of asphyxia did not identify infants with isolated cognitive deficits,¹⁰ yet few population-based studies exist.^{5 6 11 12} Nevertheless, in examining the long-term outcomes of children with neonatal encephalopathy or risk factors for hypoxia-ischaemia, some studies have shown that isolated cognitive deficits may occur in the absence of functional motor deficits.^{11–18} In this era of potential treatments for neonatal brain injury, including hypothermia, we need a better understanding of the motor and cognitive outcomes of survivors of neonatal encephalopathy. Furthermore, understanding the spectrum of neurodevelopmental outcomes after neonatal encephalopathy will allow clinicians and researchers to identify children requiring early intervention and continued follow-up to maximise their potential for independent function throughout development.

This review will consider whether long-term cognitive deficits can occur in the absence of functional motor deficits after neonatal encephalopathy. We will examine evidence from animal models and human studies and consider the role of newer imaging techniques, such as MRI.

ANIMAL STUDIES

A variety of animal models have been used to examine the long-term effects of perinatal hypoxic-ischaemic brain injury, including rodent, sheep, guinea pig and monkey. A distinction exists between the injury that occurs in the mature and immature brain, which may be explained by differences in free-radical generation and management, glutamate receptor expression or programmed cell death.¹⁹ The strength of these studies is that uniform models can be applied to assess the timing, pattern and size of injury. The difficulty in extrapolating these results to human brain injury is the use of relatively simple models to study a complex

Neonatal encephalopathy occurs in 1–6 of every 1000 live full-term births and is a major cause of neurodevelopmental disability¹: 15–20% of affected infants will die during the postnatal period, and an additional 25% will sustain permanent clinical deficits.^{2 3} The deficits of greatest concern include functional motor and cognitive deficits. Functional motor deficits are often described as cerebral palsy, a non-progressive motor or postural disorder originating in early life. Cognitive deficits include mental retardation or subnormal intellectual function resulting in impaired language skills, learning, executive functions or social ability.

Hypoxic-ischaemic encephalopathy certainly accounts for a substantial fraction of neonatal encephalopathy, yet many newborns with this condition have no documented hypoxic-ischaemic insult.⁴ There is continuing controversy as to whether neonatal encephalopathy is primarily related to insults sustained in the antepartum or intrapartum period.^{5–7} Although many risk factors, such as maternal hypothyroidism, pre-eclampsia, preterm premature rupture of the membranes and chorioamnionitis, are clearly prenatal,⁶ recent evidence from prospective cohorts of neonatal encephalopathy using magnetic resonance imaging (MRI) shows that most brain injury actually happens at or near the time of birth.^{7 8} For the purpose of this review, the term “neonatal encephalopathy” is used instead

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disease process, the causes of which are not fully understood. Nevertheless, we can use these studies as a bridge to understanding the progression of early brain injury and link to neurodevelopmental outcomes.

Antenatal insult models

Rats subjected to antenatal hypoxia by placing the pregnant dam in a hypoxic environment, although not different from normal rats in physical or reflex development, show delayed development in learning ability and orientation.²⁰ These differences in cognition seem to change throughout the animal's lifetime. Whereas juvenile rats have diminished spatial orientation and marked hyperactivity that normalises during adulthood, differences become more pronounced in relation to the complexity of the task in late adulthood.

Perinatal or postnatal insult models

Rats subjected to 15–25 min of postnatal anoxia in early life have no behavioural or motor deficits at early time points, but are impaired in spatial learning, complex discrimination learning and spatial memory in adulthood.^{21–23} The Rice–Vannucci model of postnatal ischaemia followed by hypoxia also causes hyperactive spontaneous activity in juvenile rats, which resolves during adulthood.^{24–25} However, not all models of postnatal hypoxia-ischaemia result in deficits in cognition. Studies by Hoeger *et al*^{26–27} in which rats and guinea pigs underwent postnatal asphyxia for up to 20 min showed neurodegeneration and neuronal loss in the CA1 hippocampus, cerebellum and hypothalamus, but no difference in cognitive or motor development.

In an attempt to more accurately reproduce presumed perinatal causes of hypoxia-ischaemia in rats, antenatal removal of the uterus at term gestation and exposure to 0% fractional inspired oxygen for 10–20 min before delivery causes no long-term motor deficits, but impaired relearning during adulthood.^{28–29} In a primate model, rhesus monkeys that undergo 12–17 min of asphyxia immediately after birth have memory deficits with a specific visual delayed response problem at 8–10 years of age, but normal visual and motor function.³⁰ Histologically, these different models show damage primarily to the hippocampus, usually in the CA1 and also in the CA2/3 regions, as well as the striatum and parasagittal cortex.^{31–33}

In summary, animal studies show the selective vulnerability of the developing brain to hypoxia-ischaemia, with predominant injury in the hippocampus, striatum and parasagittal cortex. The resulting hypoxic-ischaemic injury often causes impairments in memory, learning and spatial orientation, often in the absence of gross motor deficits.

HUMAN STUDIES

Defining perinatal or birth asphyxia is difficult because of the multitude of potential causes, as well as the limited association between risk factors and neurodevelopmental outcomes. Given the variety of methods used to identify perinatal asphyxia in different observational studies, including Apgar scores, umbilical cord gases, fetal heart tracings and presence of meconium, the specific effects on future intellectual and cognitive function are not entirely clear. Given the non-specific nature of these markers, others have used the clinical signs of neonatal encephalopathy as a valuable indicator of brain injury to identify those newborns at increased risk for long-term neurodevelopmental deficits. Thus, to more clearly evaluate outcomes, studies can be divided into those that enrol newborns on the basis of these non-specific markers of asphyxia and those that enrol newborns with encephalopathy.

Markers of “asphyxia”

Outcomes after “perinatal asphyxia” defined using these non-specific markers are difficult to study for several reasons: the lack of well-defined populations using consensus definitions, the need for long-term follow-up and the absence of brain imaging to confirm the type, pattern and severity of brain injury in the individual newborn.³⁴

Many studies that use markers of asphyxia conclude that below-normal intelligence does not occur as a consequence of perinatal brain injury in the absence of cerebral palsy.^{35–37} However, the results of studies using these markers are conflicting. In a large prospective study, antenatal, but not peripartum, risk factors for asphyxia were associated with differences in IQ at the age of 7 years³⁸ (table 1). Whereas one study found that the level of initial arterial acidosis was inversely related to IQ at early school age,³⁹ another study did not find an association between umbilical artery acidosis and IQ.⁴⁰ Other studies have not shown an association of cognitive development with abnormalities of fetal heart rate patterns, pre-eclampsia or other presumed causes or indicators of fetal hypoxia.^{35–36–41–42}

In many infants identified by these non-specific markers of asphyxia, isolated cognitive deficits have been observed despite seemingly normal intellect and motor function. In a study of newborns with Apgar scores of 0 or 1 at 1 min of life, one third of children had delayed language development or speech deficits at the age of 5 years.⁴³ In addition, long-term neuropsychological sequelae (eg, memory, executive function) were found in adolescent survivors, with two or more of these markers of perinatal asphyxia (eg, low Apgar score, acidosis, intrapartum bradycardia, meconium, abnormal neurological examination).¹³

Neonatal encephalopathy

The presence of an abnormal neurological examination early in life is the single most useful indicator that a brain insult has occurred and allows categorisation of newborns into groups of low, moderate and high risk for abnormal neurodevelopmental outcomes^{1–5–44} (table 2). Clearly, newborns with mild encephalopathy do not have an increased risk of overt or subtle motor and cognitive deficits.^{14–15–45} By contrast, infants with severe encephalopathy do have an increased risk of cerebral palsy and mental retardation.^{11–12–45} Neonates with moderate encephalopathy are the most difficult group in whom to accurately predict long-term motor and cognitive function.^{11–14–34} Increasing evidence suggests that children with moderate neonatal encephalopathy have cognitive deficits, such as memory impairments, visual-motor or visual-perceptive dysfunction, or increased hyperactivity, even in the absence of functional motor problems.^{11–17} Although these cognitive deficits are not limited to “mental retardation”, they often result in delayed school-readiness and a need for additional school-age interventions.

Robertson *et al*⁴⁵ prospectively followed a large cohort of neonates with evidence of hypoxic-ischaemic encephalopathy, defined as an early abnormal neurological examination and one or more markers of “asphyxia”. At 5.5 years of age, non-disabled survivors (children without cerebral palsy, seizures, blindness, hearing loss or IQ >3 standard deviations (SDs) below mean) with moderate neonatal encephalopathy had an increased risk of delayed school-readiness compared with normative data and a matched control group. In particular, they had lower scores for quantitative language, auditory memory, letter recognition and lower IQ and visual-motor integration (VMI) scores. At the 8-year follow-up, with 75% of the original cohort remaining, *non-disabled* survivors of moderate neonatal encephalopathy were similar to controls in receptive vocabulary and perceptual-motor skills, but had

Table 1 Studies examining long-term cognitive outcomes after neonatal encephalopathy or perinatal asphyxia (discussed in the text)

Study	Ref no	Type	Inclusion criteria	No of cases	Age at f/u (years)	Neurodevelopmental tests carried out
Studies that include functional motor deficits						
Dixon <i>et al</i> , 2002	11	PB CC	Moderate or severe NE	195	1–2	Griffiths Mental Developmental Scale
Marlow <i>et al</i> , 2005	12	C	Moderate or severe NE	65	7	BAS-II, NEPSY, Behaviour Questionnaire
Barnett <i>et al</i> , 2002	14	C	Apgar ≤ 5 at 5 min and NE	53	5–6	Touwen, Movement ABC, WPPSI-R
Miller <i>et al</i> , 2004	18	C	NE or UA pH < 7.1 , UA BD > 10 or 5 min Apgar ≤ 5	68	2.5	BSID-II MDI
Naeye and Peters, 1987	38	C	Fetal, intrapartum or neonatal hypoxia	19 117	7	WISC
D'Souza <i>et al</i> , 1981	43	C	Apgar ≤ 1 at 1 min	26	2.5	Hearing, RDLS, EAT
Robertson <i>et al</i> , 1989	15	CC	Mild, moderate or severe NE	145	8	WISC, PPVT, VMI, MSRI, ESAT, KDAT
Studies that exclude functional motor deficits						
Maneru <i>et al</i> , 2001	13	CC	Apgar ≤ 6 , UA pH ≤ 7.15 , meconium, bradycardia, respiratory distress, abnormal neuro exam	28	Teen	RAVLT, WISC, COWAT
Moster <i>et al</i> , 2001	17	PB CC	NE or low Apgars	727	8–13	Questionnaire
Stevens <i>et al</i> , 1999	39	C	Initial arterial pH 7.1–7.3	48	4–7	WPPSI-R
Handley-Derry <i>et al</i> , 1997	40	CC	UA BD > 12 mmol/l, no or minor NE	48	4–8	Motor, cognitive development; memory, behaviour

ABC, Assessment Battery for Children; Apgar, adaptability, partnership, growth, affection, resolve; BAS-II, British Ability Scales school age battery; BD, base deficit; BSID-II MDI, Mental Development Index of Bayley's Scale of Infant Development; C, cohort; CC, case-control; COWAT, Controlled Oral Word Association Test; EAT, Edinburgh Articulation Test; ESAP, Edmonton Spelling Abilities Test; f/u, follow up; KDAT, Keymath Diagnostic Arithmetic Test; MSRI, McCracken Standard Reading Inventory; NE, neonatal encephalopathy; NEPSY, Neuropsychological Assessment Scale; PB CC, population-based case-control; PPVT, Peabody Picture Vocabulary Test; RAVLT, Rey's Auditory Verbal Learning Test; RDLS, Reynell Developmental Language Scales; UA, umbilical artery; VMI, Developmental Test of Visual-Motor Integration; WISC, Wechsler Intelligence Scale Test for Children; WPPSI-R, Wechsler Pre-School and Primary Scale of Intelligence—Revised.

marked delays in reading, spelling and arithmetic.¹⁵ These children were more likely to be at least one grade level behind controls or those with mild encephalopathy.

Other population-based studies of neonatal encephalopathy also document isolated cognitive impairments. In a large Western Australian cohort study, children with moderate or severe neonatal encephalopathy had considerable delays in the general quotient of the Griffiths Mental Development Scales at 1–2 years of age, even after excluding those with cerebral palsy or other potentially contributory medical conditions.¹¹ Consistent with these findings, children in the UK with moderate encephalopathy and without motor disability at 7 years of age were similar to controls in general cognitive ability, but lower in the language and sensorimotor scales, as well as narrative memory and sensory repetition.¹²

Moderate encephalopathy was defined as seizures or two or more of the following: abnormal consciousness, abnormal tone, abnormal reflexes, respiratory difficulty or feeding difficulty of central origin. In addition, children without disability after severe encephalopathy (those comatose or stuporous, requiring ventilation for > 24 h, or on convulsive treatment) were lower in all subsets and worse than the moderate group in attention and memory domains. In Norway, survivors of neonatal encephalopathy without major neurological abnormalities were more likely to have minor motor impairments, late development of skills and attention deficit-hyperactivity disorder, with a need for extra educational resources.¹⁷ In particular, those with encephalopathy and an Apgar score of 0–3 at 5 min of age had a 13-fold increase in minor motor impairment, a 14-fold increase in

Table 2 Components and grading of encephalopathy in term newborns

Clinical Encephalopathy Score (range: 0–6)*			
Encephalopathy sign	Score = 0	Score = 1, if abnormal	
Alertness	Alert	Irritable, limited responsiveness or coma	
Tone	Normal	Hypotonia or hypertonia	
Reflexes	Normal	Hyperreflexia or hyporeflexia	
Respiratory status	Normal	Respiratory distress or support needed	
Feeding	Normal	Gavage feeds or gastrostomy tube	
Seizures	None	Clinical seizure	
Three clinical stages of encephalopathy†			
Feature	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control	Normal	Mild hypotonia	Flaccid
Complex reflexes	Weak	Weak or absent	Absent
Autonomic function	Sympathetic	Parasympathetic	Both depressed
Seizures	None	Common	Uncommon

*Adapted from Miller *et al*.⁴⁴

†Adapted from Sarnat and Sarnat.⁴⁶

attention deficit hyperactivity disorder and a sevenfold increase in epilepsy compared with controls. In the absence of encephalopathy, an Apgar score of 0–3 was not associated with increased risk.

More recently, randomised clinical trials of hypothermia have used strict entry criteria to define more homogeneous populations of term neonatal encephalopathy. Both recent trials report an excess of cognitive abnormalities relative to motor abnormalities. In the selective head cooling trial, newborns with moderate or severe encephalopathy based on markers for perinatal depression, clinical criteria and amplitude-integrated electroencephalogram recordings were randomly assigned to either head cooling with mild systemic hypothermia or conventional care.⁴⁷ At 18 months of age, 13% of cooled infants and 12% of control infants with moderate encephalopathy had Bayley Mental Development Indices (MDI) 2 SD below the normal mean (scores <70) without severe neuromotor disability. Likewise, in the whole-body hypothermia study, 6% of the hypothermia group and 9% of the control group had Bayley MDI 2 SD below the normal mean in the absence of cerebral palsy.⁴⁸

Together, these studies raise the concern that a sizable group of children with neonatal encephalopathy may ultimately require interventions for cognitive or behavioural deficits at school age, even in the absence of functional motor deficits such as cerebral palsy.

BRAIN IMAGING

Timing of brain injury in neonatal encephalopathy

Given the absence of definitive laboratory or clinical markers consistent with asphyxia in many neonates who develop encephalopathy, it is commonly presumed that brain injury results predominantly from antenatal events.^{4 6 35 49} In an effort to better understand the acute patterns of neonatal brain injury, multiple cohorts have been imaged with MRI in the initial days of life. Newborns with encephalopathy show an evolving injury pattern on MRI consistent with more acute perinatal events, rather than remote antenatal brain injury.^{7 8} In a prospective cohort of neonatal encephalopathy, >90% of affected newborns had evidence of perinatally acquired insults on MRI, with a very low rate of established antenatal brain injury.⁷ These findings include brain swelling, loss of grey–white matter differentiation, abnormal signal intensities in the deep grey nuclei or posterior limb of the internal capsule or an acutely developing region of infarction. The use of diffusion-weighted MRI has also greatly improved our ability to time the onset of brain lesions. The reduction in apparent diffusion coefficients on diffusion-weighted imaging that occurs with brain injury in the term newborn evolves over the initial days of life and normalises over the second week. Diffusion MRI provides a dynamic window on evolving neonatal brain injury and further implicates the perinatal period as the most common time at which the brain is actually injured.^{50 51} Taken together, antenatal factors may lead to greater susceptibility to perinatal problems in some, whereas in others an acute sentinel is documented as a single perinatal event.

Patterns of brain injury

MRI can also be applied to better understand the heterogeneity of brain injury associated with neonatal encephalopathy. In particular, the pattern of brain injury in neonatal encephalopathy can distinguish associated risk factors and clinical presentation and can identify those newborns at greatest risk of abnormal motor and cognitive outcome.⁵² In a primate model of term neonatal brain injury, the specific regional distribution of injury was associated with different durations and severities of ischaemia: partial asphyxia caused injury to the cerebral white matter, and acute and profound

asphyxia caused injury to deep grey nuclei (basal ganglia and thalamus).^{53 54} A comparable regional vulnerability is observed in the term newborn, resulting in two major patterns of injury detectable by MRI: (1) a watershed predominant pattern involving the white matter, particularly in the vascular watershed, extending to cortical grey matter when severe (fig 1) and (2) a basal ganglia–thalamus predominant pattern involving the deep grey nuclei and perirhinal cortex, extending to the total cortex when severe.^{8 55} As expected from the primate models, newborns with basal ganglia–thalamus patterns of injury have the most intensive need for resuscitation and the most severe clinical encephalopathy.

Advanced brain imaging is emerging as a powerful tool to correlate the location and severity of these lesions with neurodevelopmental outcomes. Although it is accepted that the risk of an abnormal neurodevelopmental outcome increases with the severity of the injury, the pattern of injury also conveys important prognostic information. In particular, the basal ganglia–thalamus and watershed patterns of injury are associated with impairments in different developmental domains. The basal ganglia–thalamus predominant pattern or abnormal signal intensity in the posterior limb of the internal capsule on MRI is associated with severely impaired motor and cognitive outcomes.^{8 56–58} Given the frequent occurrence of cerebral watershed injury⁸ and cerebellar injury^{59 60} with the basal ganglia–thalamus predominant pattern, cognitive deficits may result from damage to areas outside the deep grey nuclei themselves. By contrast, newborns with the watershed pattern have predominantly cognitive impairments that often occur without functional motor deficits.^{8 61}

The recognition of cognitive deficits in the absence of functional motor deficits may be delayed beyond the first year of life. Survivors of neonatal encephalopathy with abnormal MRI are more likely to have minor perceptual–motor difficulties or neurological impairments at 5–6 years of age, in the absence of gross motor deficits or differences in IQ.¹⁴ In another cohort, cognitive deficits associated with the watershed pattern of injury were detected at 30 months, but were largely overlooked at 12 months of age.¹⁸ Some children

Figure 1 Watershed pattern of injury. Magnetic resonance imaging acquired on the second day of life: axial T2-weighted spin echo (TR 3000 ms, TE 120 ms, 4 mm slice thickness) image showing the characteristic T2 hyperintensity of the cortex and white matter in the posterior intervascular boundary regions (arrowheads). Axial average diffusivity maps (TR 7000 ms, TE 99.5 ms, 3 mm slice thickness, no gap, three repetitions per image, 18×36 cm field of view, 128×256 acquisition matrix, with 1.4×1.4 mm² in-plane resolution) show reduced diffusivity isolated to the frontal and parieto-occipital intervascular boundary zones (arrows), with sparing of the deep grey nuclei.

with neonatal encephalopathy and normal outcomes at 2 years of age show persistent white matter changes on follow-up imaging.⁶² It is possible that frontal white matter injury may manifest as impaired cognition with preserved motor function, but possibly not until later time points. In addition, the presence of abnormal cognitive outcomes at later time points may also depend on the child's postnatal environment, socioeconomic conditions and access to rehabilitative services.¹⁸

Advanced quantitative brain imaging techniques, such as volumetrics and morphometry, magnetic resonance spectroscopy and diffusion tensor imaging, can now be applied to measure subtle brain injuries, such as white matter injuries, and determine their association with long-term cognitive deficits.^{18–63} For example, in a recent case series, five patients with delayed recall, in the setting of intact semantic memory and motor function between 8 and 14 years, were found to have bilateral hippocampal atrophy on MRI.¹⁶

Together, these studies suggest that brain imaging, particularly in those with the watershed pattern of injury, has the potential to identify those newborns at highest risk of long-term cognitive deficits, even in the absence of overt motor signs.

CONCLUSIONS

The concept that neonatal brain injury is almost always secondary to acquired insults such as "perinatal asphyxia" is being modified by careful epidemiological studies. These studies are beginning to elucidate the genetic, antenatal, perinatal and postnatal factors that underlie the vulnerability of the newborn brain, as well as the mechanisms that contribute to potential resilience and recovery. Although MRI, in particular diffusion tensor imaging and magnetic resonance spectroscopy, has improved our ability to determine the timing of neonatal brain injury, the resolution of these techniques is limited to days rather than hours. A full understanding of why newborns with similar risk factors may have different neurodevelopmental outcomes is still lacking.

In this era of increasing medical litigation, these data should not be used as evidence of inappropriate or inadequate prenatal or perinatal care. The studies described in this review are primarily about cohorts of critically ill children with overt encephalopathy, rather than children identified later in life on the basis of isolated cognitive impairments. Furthermore, in an individual newborn, the specific cause of the encephalopathy is often not apparent. The assumption in many of these studies is that once other causes of encephalopathy are excluded, such as genetic syndromes or congenital infections, the remaining cases are primarily related to hypoxia-ischaemia. Recent imaging studies support this assumption in showing acute changes with patterns of injury that are most consistent with hypoxia-ischaemia injury. These imaging changes correlate well with both acute and long-term neurological findings.

As the limitations of studies of neonatal encephalopathy are recognised, it is increasingly clear that childhood survivors of neonatal encephalopathy are at risk of cognitive deficits, even in the absence of functional motor deficits. With sophisticated and detailed measures of cognition, there seems to be an association between specific cognitive deficits, such as language and memory deficits, with the severity of neonatal encephalopathy and the pattern of brain injury, even in those without functional motor deficits. These differences are apparent in survivors of moderate and severe overt neonatal encephalopathy, particularly with the watershed predominant pattern of brain injury. This recognition allows doctors and care givers an opportunity to optimally care for infants after neonatal encephalopathy by

What is already known on this topic

- Neonatal encephalopathy is a heterogeneous condition that often leads to functional motor and cognitive deficits
- In survivors of neonatal encephalopathy, the risk of adverse motor and cognitive outcomes is associated with the severity of the encephalopathy, as well as the pattern and severity of abnormalities on brain imaging.

What this study adds

- Survivors of overt neonatal encephalopathy are at risk for developing cognitive deficits, even in the absence of functional motor deficits.
- These cognitive deficits are apparent in survivors of moderate and severe neonatal encephalopathy, particularly with the watershed predominant pattern of brain injury.

identifying those who may benefit most from rehabilitative services and early intervention, to maximise educational and social function. A better understanding of the risk factors for cognitive abnormalities after neonatal encephalopathy will ultimately lead to interventions to prevent these deficits and improve the outcome of affected newborns.

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