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The neonatal period: A missed opportunity for the prevention of iron deficiency and associated neurological consequences?

E K McCarthy and M E Kiely

Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences, University College Cork and INFANT Research Centre, Ireland.

Running title Iron deficiency in the neonatal period

Correspondence Dr Elaine McCarthy, Postdoctoral Researcher, School of Food and Nutritional Sciences, Room 105, Food Science Building, University College Cork, Cork, Ireland. Email: elaine.mccarthy@ucc.ie

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ABSTRACT

Iron deficiency is the most common micronutrient deficiency worldwide. Iron is essential for the development of multiple organ systems, most especially the developing brain. Iron deficiency, particularly during sensitive periods of brain development, such as in early childhood, is associated with long lasting adverse consequences for cognition, motor function and behaviour. Little consideration has been given to iron deficiency in newborn infants and its potential health consequences. Fetal iron accretion is compromised by pregnancy complications such as preterm birth and gestational diabetes mellitus, and our work has identified an increased risk of low iron stores at birth from maternal lifestyle factors such as smoking and obesity. Early-life events, including Caesarean section delivery, further add to the cumulative risk of neonatal iron deficiency, which can persist throughout infancy into early childhood. While investigations into the long-term neurological consequences of neonatal iron deficiency are limited, there is evidence of poorer memory, motor function and language ability in children born iron deficient. Recently, we also identified significant behavioural consequences of neonatal deficiency persisting from 2 to 5 years of age, with effects particularly apparent in 'high-risk' children born to obese or smoking mothers or delivered by Caesarean section. Interventions targeting the fetal/neonatal period could, therefore, represent a key opportunity for the prevention of iron deficiency and its associated long-term health consequences. A dual approach is required, comprising public health strategies targeting prevention, to improve health in women of reproductive age, and the development of screening strategies for the early detection of iron deficiency in newborn infants.

KEYWORDS

Iron; iron deficiency; neonatal period; neurological development; newborn infant; maternal health.

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INTRODUCTION

Iron deficiency, characterised by a reduction or depletion of the body's iron stores, is the most common micronutrient deficiency in the world, affecting almost 2 billion people (McLean *et al.* 2009). Women of reproductive age and young children are especially vulnerable, given the increased demands for iron during these periods of rapid growth and development (McLean *et al.* 2009; Domellof *et al.* 2014). Iron is critical to the development of multiple organ systems, but most especially the developing brain. Iron deficiency, particularly during periods of rapid brain development, such as in early childhood, can have catastrophic consequences, with long lasting adverse effects on cognition, motor function and behaviour widely reported (Lozoff *et al.* 2006; Georgieff 2011).

The late fetal and neonatal period is characterised by rapid and critical brain development; however, despite this, little consideration has been given to iron deficiency in newborn infants and its potential health consequences. Newborn infants are at an increased risk of iron deficiency, as iron transfer to the growing fetus in utero is compromised by a number of maternal and pregnancy-related factors (Rao and Georgieff 2007). Furthermore, low iron stores and iron deficiency at birth have been shown to predispose infants to iron deficiency later in infancy and early childhood (Georgieff *et al.* 2002; Hay *et al.* 2007; Akkermans *et al.* 2016).

Here we provide an in-depth review of iron deficiency in the neonatal period, outlining the importance of iron to the developing brain, the acknowledged and unacknowledged risks for iron deficiency in newborn infants and, importantly, potential strategies for the prevention of neonatal iron deficiency and its associated long-term health consequences.

IRON AND THE DEVELOPING BRAIN

Iron is essential for the developing brain, given the key role it plays in fundamental neuronal processes, including neurotransmitter and energy metabolism and myelination (Lozoff and Georgieff 2006; Lynch *et al.* 2018). Iron deficiency, particularly during sensitive periods of brain development, can disrupt these fundamental processes, as summarised in **Table 1**, resulting in adverse neurological consequences that often remain even after correction of the deficiency (Unger *et al.* 2012; Lynch *et al.* 2018). Brain

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development during the fetal and neonatal period is one such period of sensitivity, making newborn infants especially vulnerable to the neurological consequences of iron deficiency. In-depth, extensive reviews of the underlying neurobiological effects of neonatal iron deficiency are available elsewhere (Lozoff and Georgieff 2006; Beard 2008; Georgieff 2011; Lynch *et al.* 2018).

Neurological consequences of neonatal iron deficiency

Despite the critical role of iron in the developing brain, investigations into the neurological consequences of iron deficiency in newborn human infants have been limited, often constrained by inadequate sample sizes and short-term neurological follow-up. To date, abnormalities in the auditory neural pathway after birth were reported in term and preterm infants with cord ferritin concentrations <76 µg/L (Amin *et al.* 2010; Amin *et al.* 2013; Choudhury *et al.* 2015; ElAlfy *et al.* 2018), while reduced haemoglobin at birth, reflective of anaemia, the end-stage of iron deficiency, was associated with altered neonatal temperament in the first week of life (Wachs *et al.* 2005). Infants born to mothers with gestational and pre-gestational diabetes with cord ferritin ≤34 µg/L, a threshold the authors calculated to reflect brain iron depletion, also had poorer recognition memory at ~15 days old (Siddappa *et al.* 2004). Furthermore, iron deficiency at birth that persisted into infancy was associated with poorer emotional reactivity and motor development at 9 months (Armony-Sivan *et al.* 2016; Santos *et al.* 2018).

In the first study with long-term follow-up, Tamura *et al.* (2002) observed poorer language ability, fine motor skills and tractability (ability to obey rules/behaviour) in 5-year-olds born with cord ferritin in the lowest quartile, corresponding to ferritin concentrations <76 µg/L. Infants with low iron stores at birth born to mothers with diabetes also had long-term impairments in recall memory and psychomotor development into early childhood (Siddappa *et al.* 2004; DeBoer *et al.* 2005; Riggins *et al.* 2009). Contrastingly, iron status at birth was not associated with cognitive outcomes at 1 year of age in a prospective cohort in Benin (Mireku *et al.* 2016). Recently, in our large maternal-infant birth cohort in Ireland, we identified significant behavioural consequences, measured using the Child Behaviour Checklist, of neonatal iron deficiency persisting from 2 to 5 years of age, with effects particularly

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apparent in 'high-risk' children born to obese or smoking mothers or delivered by Caesarean section (observations under review).

RISK FACTORS FOR NEONATAL IRON DEFICIENCY

The total body iron content of term-born infants is ~75 mg/kg bodyweight, with the majority of this (70-80%) in red blood cells as haemoglobin. The remainder of the iron is incorporated into iron-containing proteins, such as myoglobin and cytochromes, or kept as storage iron, in the form of ferritin and hemosiderin (Widdowson 1974; Dallman *et al.* 1980). However, this body iron content is highly variable as both modifiable and non-modifiable risk factors can affect fetal iron accretion, predisposing newborn infants to iron deficiency at birth and later in infancy (Hay *et al.* 2007; Rao and Georgieff 2007). These factors range from the widely acknowledged risks of maternal iron deficiency and prematurity, to the more unacknowledged and recently emerged risks of maternal obesity and delivery by Caesarean section. Given that many of these risk factors often occur concurrently, the potential cumulative effect on neonatal iron status is considerable.

Maternal iron status

Pregnant women are especially vulnerable to iron deficiency and anaemia, as ~1000 mg of iron must be acquired during pregnancy to support feto-placental development and preserve maternal iron balance (McLean *et al.* 2009; Fisher and Nemeth 2017). Sufficiently large iron stores at the onset of pregnancy, in addition to a diet abundant in bioavailable iron, are required to meet these increased requirements and avoid the development of iron deficiency (Lynch *et al.* 2018). However, this is challenging: maternal iron deficiency affects 10-33% of pregnancies in Europe, with the highest rates observed in women during the third trimester (Milman *et al.* 2017). Worryingly, recent data also suggests that poor maternal iron status, particularly in the third trimester, may be associated with adverse offspring neurological development (Janbek *et al.* 2019).

Infants born to mothers with iron deficiency during pregnancy have reduced cord ferritin concentrations at birth, with maternal ferritin concentrations of 12-13.6 µg/L suggested as thresholds below which fetal iron accretion is affected (Gaspar *et al.* 1993; Hokama *et al.* 1996; Sweet *et al.* 2001; Jaime-Perez *et al.*

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2005; Shao *et al.* 2012; Lee *et al.* 2016). Infants born to mothers with mild/moderate iron deficiency anaemia (haemoglobin <110 g/L) during pregnancy have reduced iron stores at birth (Hokama *et al.* 1996; Emamghorashi and Heidari 2004), while severe maternal iron deficiency anaemia (haemoglobin <70 g/L) results in reduced cord haemoglobin concentrations, in addition to reduced iron stores (El-Farrash *et al.* 2012; Basu *et al.* 2016). Furthermore, infants born to anaemic mothers, but with adequate neonatal iron stores at birth, have an increased risk of iron deficiency and iron deficiency anaemia later in infancy (Colomer *et al.* 1990; Kilbride *et al.* 1999).

Prematurity and low birth weight

Two-thirds of an infant's total body iron is accreted during the third trimester of pregnancy. Infants born premature are deprived of this significant iron accretion, with preterm birth also often coupled with other pregnancy complications that further compromise neonatal iron status (Singla *et al.* 1985; Rao and Georgieff 2001). Total body iron content, haemoglobin and ferritin concentrations are lower in preterm infants (Halliday *et al.* 1984; Singla *et al.* 1985; Lackmann *et al.* 1998), even in late-preterm infants born ≥34 weeks' gestational age (Ozdemir *et al.* 2013; Yamada and Leone 2014). Between 20% and 50% of preterm infants are either born iron deficient or will become deficient in early infancy (Amin *et al.* 2010; Berglund *et al.* 2010; Amin *et al.* 2012; Uijterschout *et al.* 2015; Akkermans *et al.* 2016), with rates of 80-85% reported in preterm infants exclusively breastfed or receiving inappropriate iron supplementation (Iwai *et al.* 1986; Hall *et al.* 1993).

Apart from the considerable impact of preterm birth itself, postnatal factors can also alter the baseline iron status of preterm infants, leading to an increased risk of iron deficiency. Postnatal iron requirements are increased in preterm infants to facilitate their high rate of postnatal 'catch-up' growth, doubling their birth weight in 1-2 months, and the earlier onset of erythropoiesis, occurring 1-3 months earlier than in term infants (Lundstrom *et al.* 1977; Rao and Georgieff 2001). Phlebotomy blood losses, routine for infants admitted to the Neonatal Unit, can result in a substantial loss of iron, especially if uncompensated (Obladen *et al.* 1988; Domellof and Georgieff 2015; Akkermans *et al.* 2016), while

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delayed or inappropriate iron supplementation is another significant risk for iron deficiency (Agostoni *et al.* 2010).

Low birth weight infants, including term, preterm or small-for-gestational age infants with a birth weight <2500 g, are typically born with lower iron stores and have an even more rapid relative growth rate (Mukhopadhyay *et al.* 2012; Domellof *et al.* 2014). Infants born with an extremely low birth weight of <1000 g are at the highest risk, as without an appropriate external iron source they may be in negative iron balance within the first month of life (Shaw 1982).

Pregnancy complications

Pregnancy complications characterised by uteroplacental vascular insufficiency and/or chronic hypoxia, such as that caused by gestational diabetes mellitus, hypertension and preeclampsia, can also impact neonatal iron status. In response to hypoxia, iron is drawn from hepatic storage pools to support increased erythropoiesis, resulting in reduced ferritin concentrations and increased transferrin and transferrin receptor concentrations in infants born to mothers with such conditions (Chockalingam *et al.* 1987; Murata *et al.* 1989; Verner *et al.* 2007). The iron status of infants born to mothers with gestational diabetes mellitus is further compounded if the infant is born macrosomic (Georgieff *et al.* 1990; McLimore *et al.* 2013). Worryingly, these conditions can also result in reduced iron content of the liver, heart and brain, with neonatal liver and brain tissue iron reduced by 60% and 40%, respectively in post-mortem studies of newborn infants born to mothers with uteroplacental insufficiency (Petry *et al.* 1992; Georgieff *et al.* 1995).

Maternal smoking

Maternal smoking during pregnancy can result in fetal hypoxia, due to increased vascular resistance and thus poorer blood flow in the umbilical and uterine arteries, caused mainly by carbon monoxide. In such hypoxic conditions, erythropoiesis is stimulated, resulting in increased haematocrit and haemoglobin concentrations in infants (Meberg *et al.* 1979; Varvarigou *et al.* 1994; Wojtyla *et al.* 2012). Reduced iron stores at birth have also been reported in infants born to smoking mothers (Sweet *et al.* 2001; Chelchowska and Laskowska-Klita 2002; Hay *et al.* 2007). In our maternal-infant birth cohort,

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maternal smoking was identified as an independent risk factor for neonatal iron deficiency: 17% of infants born to smoking mothers had cord ferritin <76 µg/L compared to 7% of infants born to non-smokers (McCarthy *et al.* 2017).

Maternal obesity

The highest rates of obesity in women of reproductive age in Europe are seen in the UK and Ireland; almost 1 in 5 women of reproductive age have a body mass index (BMI) >30 kg/m^2 (Devlieger *et al.* 2016). This is concerning as obesity in women who enter pregnancy is associated with an increased risk of adverse pregnancy outcomes, including preeclampsia, gestational diabetes mellitus and delivery of macrosomic infants, with long-term consequences for both the mother and child (Poston *et al.* 2016). Maternal obesity is now also emerging as a risk factor for neonatal iron deficiency.

A positive correlation between early pregnancy maternal BMI and cord serum transferrin receptors was first reported in a Norwegian cohort (Hay *et al.* 2007). Subsequently, maternal obesity both pre- and during pregnancy has been associated with reduced transferrin saturation, iron and ferritin concentrations and increased transferrin receptors in newborn infants (Dao *et al.* 2013; Phillips *et al.* 2014; Jones *et al.* 2016; McCarthy *et al.* 2017). While the mechanism of action remains to be fully elucidated, the iron-regulatory hormone, hepcidin, has been suggested to a play a role (Dao *et al.* 2013). In healthy pregnancies, hepcidin is downregulated in the second and third trimester to allow an increased supply of iron into maternal circulation. The low-grade, chronic pro-inflammatory state of obesity results in an overexpression of hepcidin, inhibiting intestinal iron absorption and the release of iron from hepatic stores (Dao *et al.* 2013). Elevated hepcidin and inflammatory marker concentrations have been observed in obese pregnant women in some (Dao *et al.* 2013; Garcia-Valdes *et al.* 2015; Jones *et al.* 2016; Flynn *et al.* 2018), but not all studies (Phillips *et al.* 2014; Cao *et al.* 2016). Moreover, a potential threshold effect of maternal obesity was recently suggested, with poorer maternal and neonatal iron status associated with class 2 maternal obesity (≥35 kg/m^2) only (Dosch *et al.* 2016; Flynn *et al.* 2018).

Mode of delivery

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The obstetric mode of delivery is another often unacknowledged determinant of neonatal iron status. In a meta-analysis by Zhou *et al.* (2014), when compared to vaginal delivery, delivery by Caesarean section was associated with decreased haemoglobin, haematocrit and erythrocyte concentrations in both the peripheral and cord blood of term-born neonates. More recently, we observed an independent adverse effect of delivery by Caesarean section on neonatal iron stores, with infants delivered by Caesarean section twice as likely to have iron deficiency at birth than those delivered vaginally (McCarthy *et al.* 2017). This adverse effect of Caesarean deliveries is likely due to a shorter period of placental transfusion due to immediate cord clamping and a weaker placental transfusion force associated with reduced uterine/vaginal contraction, maternal hypotension and a lack of a gravitational effect (Yao *et al.* 1968; Pisacane 1996). This is concerning, given the reported rise in Caesarean deliveries worldwide, with rates of 26-33% in the UK and Ireland (Boerma *et al.* 2018; Health Service Executive 2018).

STRATEGIES FOR THE PREVENTION OF NEONATAL IRON DEFICIENCY

Interventions targeting the fetal and neonatal period could represent a key opportunity for the prevention of neonatal iron deficiency and its associated consequences for neurological development and iron status later in infancy. As many of the aforementioned risk factors for neonatal iron deficiency are modifiable, strategies aimed at the prevention of iron deficiency should be prioritised; although, screening strategies for early detection should also be considered, especially as prevention may not always be feasible.

1. Improved health and lifestyle of women of reproductive age

Interventions targeting the mother are the best way to prevent iron deficiency in newborn infants. To prevent maternal iron deficiency and anaemia, and thus its associated consequences for neonatal iron status, the World Health Organization recommends an iron intake of 30-60 mg/day during pregnancy, with 60 mg recommended in regions with a high anaemia burden (World Health Organization 2016). Recommended intakes in Ireland and the UK are lower, at 15 and 14.8 mg/day respectively (Food Safety Authority of Ireland 1999; Scientific Advisory Committee on Nutrition 2010). To achieve these intakes,

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iron supplementation is widely used in low- and high-resource settings, with daily supplementation shown to reduce iron deficiency and iron deficiency anaemia in pregnant women at term (Pena-Rosas *et al.* 2015). However, supplementation strategies are not without limitations, as compliance may be poor, particularly in low-resource settings, and care is required to avoid excessive intakes (Wessling-Resnick 2017). Moreover, the direct effect of maternal iron supplementation on neonatal iron status and other neonatal outcomes is yet to be determined (Domellof *et al.* 2014; Pena-Rosas *et al.* 2015).

Public health strategies to improve overall maternal health and lifestyle are also urgently required. For example, the prevention of obesity in women of reproductive age is now recognised as critical to the health of mothers and their offspring. Strategies incorporating a life-course approach, targeting the prevention of obesity prior to conception are recommended (Hanson *et al.* 2017), particularly as recent diet and lifestyle interventions in obese pregnant women did not result in significant improvements in pregnancy outcomes (Dodd *et al.* 2014; Poston *et al.* 2015). Community-based awareness initiatives, combined with government policies, as have been recently implemented in The Netherlands (Denktas *et al.* 2014), appear to be the most promising strategy thus far.

2. Delayed clamping of the umbilical cord

In the first minutes after birth, a newborn infant can receive a substantial blood transfusion from the placenta, with a 32% increase in blood volume observed in infants held below the uterus for 3 minutes after birth (Yao *et al.* 1969). Delayed clamping of the umbilical cord, for 1-3 minutes after birth or after cord pulsations stop, will therefore result in a larger placental transfusion than if the cord was clamped immediately after birth.

A delay in cord clamping is recommended for term neonates, delivered vaginally or by Caesarean section, in the provision of essential neonatal care (National Institute for Health and Care Excellence 2014; World Health Organization 2014; Royal College of Obstetricians & Gynaecologists 2015). Delayed cord clamping results in increased neonatal haemoglobin and ferritin concentrations after birth, without an increased risk of adverse health outcomes in the mother or infant, aside from some reports of an increased risk of polycythaemia (Hutton and Hassan 2007; McDonald *et al.* 2013). These

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improvements in iron status and decreased risk of iron deficiency and anaemia last throughout early infancy (Andersson *et al.* 2011; Mercer *et al.* 2018), even to 8-12 months of age (Gyorkos *et al.* 2012; Kc *et al.* 2017). Furthermore, increased brain myelination at 4 months (Mercer *et al.* 2018) and improved fine motor and social development at 4 years, but not 1 year (Andersson *et al.* 2014, Andersson *et al.* 2015), has been reported in infants randomised to delayed clamping.

Preterm infants, particularly those requiring stabilisation or resuscitation, can sometimes be denied this important placental transfusion at birth. However, delayed cord clamping is recommended for preterm infants, where possible (World Health Organization 2014), with recent efforts being made to better incorporate delayed cord clamping into the stabilisation procedures for preterm infants (Knol *et al.* 2018). Elevated ferritin and haemoglobin concentrations after birth, a reduction in blood transfusion need and a lower risk of intraventricular haemorrhage and necrotising enterocolitis have all been reported in preterm infants delivered with delayed clamping (Rabe *et al.* 2012; Ranjit *et al.* 2015; Kc *et al.* 2017). More recently, umbilical cord milking, a method of actively stripping blood from the cord, has been suggested as an alternative to delayed clamping in preterm infants; however, further research is required, particularly with respect to the long-term effects of this method (Al-Wassia and Shah 2015; Safarulla 2017).

Despite current recommendations and the strong evidence supporting the benefits of delayed clamping, significant variability in this practice remains (Winter *et al.* 2007; Devin and Larkin 2018).

3. Tailored supplementation regimens in high-risk infants

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition have stated that general iron supplementation in breastfed or formula-fed term infants is not required (Domellof *et al.* 2014). In contrast, the American Academy of Pediatrics recommend 1 mg/kg/day of iron supplements for term, breastfed infants from 4 months of age until the introduction of iron-containing complementary foods (Baker and Greer 2010). While this recommendation has since been questioned (Hernell and Lonnerdal 2011), given that it was based on one study (Friel *et al.* 2003), it was devised in response to the significant variability in neonatal iron

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stores, even amongst term infants. This substantive variability should be taken into consideration by clinicians, as preventive iron supplementation may be necessary on an individual basis, particularly in 'high-risk' term infants. Although, the potential risks of iron supplementation, particularly for growth and immune function, must also be carefully considered (Iannotti *et al.* 2006; Cusick *et al.* 2018). The establishment of a screening protocol or tool, identifying the infants most at risk, could aid clinicians in the development of such individualised supplementation regimens.

Iron supplementation is recommended for preterm infants but extreme caution is warranted, as their underdeveloped antioxidant defence system can also place them at an increased risk of iron overload (Wessling-Resnick 2017). To achieve the necessary iron balance, current recommendations for enteral iron intakes in preterm infants are 2-3 mg/kg/day from the age of 2-6 weeks until at least 6-12 months (Agostoni *et al.* 2010; Baker and Greer 2010). While these recommendations, made in 2010, were based on a limited evidence basis, there remains limited appropriate evidence since then to formulate revised recommendations, particularly with respect to optimal supplementation doses and duration (McCarthy *et al.* 2019). Therefore, these recommendations should continue to be implemented in clinical practice, but further consideration must be given to more tailored supplementation regimens for individual patients, informed by monitoring of iron status indices, including ferritin and haemoglobin, both during and after the infant's hospital stay. Although, this monitoring should be incorporated into routine blood tests as part of standard clinical care, where possible, to avoid additional phlebotomy losses in this vulnerable population group.

4. Screening strategies for early detection

As the prevention of neonatal iron deficiency is not always feasible, for example when deficiency is secondary to conditions such as prematurity, screening strategies to facilitate the early detection of iron deficiency in newborn infants are pertinent. Early detection will enable prompt treatment, thus ensuring normal neurological development in at-risk individuals. Currently, screening strategies are either non-existent, target older infants or focus solely on anaemia screening, all of which present significant challenges to achieving early detection.

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Iron status can be considered as a continuum, moving from iron depletion to deficiency to anaemia, with each stage reflected by changes in iron biomarker concentrations (**Table 2**). As anaemia is the end-stage of iron deficiency, screening for anaemia, measuring haemoglobin, will prove ineffective in facilitating the early detection of neonatal iron deficiency and preventing its associated neurological consequences. Furthermore, during periods of increased iron demands, iron will be prioritised to red blood cells, to support erythropoiesis, over all other organs, including the brain (Petry *et al.* 1992; Siddappa *et al.* 2004; Lozoff *et al.* 2008). Therefore, the brain will become iron depleted prior to the appearance of anaemia, resulting in the observed long-term neurological consequences (Georgieff 2017).

Ideally, screening strategies should therefore incorporate biomarkers that more accurately reflect or measure the iron content or iron-dependent processes in the brain. While research is ongoing into potential novel biomarkers that directly assess iron-dependent brain functions (Rao *et al.* 2018), a more feasible approach at this time may be to relate a current early-stage iron biomarker directly to iron-dependent brain function. Ferritin concentrations, reflective of body iron stores, have been suggested, as reduced cord ferritin concentrations at birth are associated with short- and long-term adverse neurological outcomes (Tamura *et al.* 2002; Siddappa *et al.* 2004). However, further research is required to ascertain the most appropriate ferritin threshold for use in infants, as the thresholds used to date were estimated based on population biomarker distributions and calculations, rather than on their direct relation to a functional brain outcome. Reticulocyte haemoglobin content, reflective of functional iron availability, has been recently suggested as another potential biomarker for the early detection of individuals at risk of brain iron deficiency, prior to the emergence of anaemia (Ennis *et al.* 2018). The incorporation of validated biomarkers sensitive to iron-dependent brain dysfunction into a screening protocol or tool as part of standard neonatal care at birth could represent a significant step towards early detection and thus prevention of iron deficiency and its associated long-term neurological consequences.

CONCLUSIONS

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Newborn infants are highly susceptible to iron deficiency, with fetal iron accretion compromised by a number of maternal and pregnancy-related factors. As iron deficiency at birth is associated with long-term consequences for neurological development and subsequent iron status, strategies aimed at reducing the risk of iron deficiency in newborn infants are of the utmost importance. A dual approach, comprising public health and clinical strategies targeting prevention, and screening strategies for the early detection of iron deficiency in newborn infants is required. Public health strategies to improve the overall health and nutritional status of women of reproductive age are becoming increasingly important, although the efficacy and feasibility of such strategies requires further investigation. In clinical practice, delayed cord clamping should be employed for term and preterm births, when possible, while a more tailored, personalised approach towards infant supplementation, informed by iron status monitoring, should be considered, especially in the case of high-risk infants, such as those born premature or with a low birth weight. Moreover, the development of biomarker-based screening strategies for the early detection of iron deficiency in newborn infants could represent an invaluable opportunity to prevent the long-term health consequences of neonatal iron deficiency, especially in high-risk individuals where prevention is often not feasible.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Table 1 Iron and neurotransmitter metabolism, energy metabolism and myelination in the developing brain

Neurotransmitter Metabolism	Energy Metabolism	Myelination
• Most direct effect of iron is thought to be on the synthesis of the monoamine neurotransmitters, dopamine, serotonin and norepinephrine (Lynch *et al.* 2018). Monoamine synthesis begins in mid-gestation, until about 3 years of age. • Altered monoamine metabolism results in disturbed sleep cycles, motor control, memory and social-emotional development (Herlenius and Lagercrantz 2004; Beard 2008).	• Iron deficiency affects neuronal energy metabolic balance, especially in the hippocampus, the region responsible for recognition memory processing and other cognitive functions (Rao *et al.* 2003; Lozoff and Georgieff 2006). • Disrupted energy metabolism results in abnormal arborisation (branching) of dendrites and synapse formation, leading to long-lasting morphological changes (Tran *et al.* 2008).	• Iron deficiency, particularly in the late fetal and early childhood period, results in hypomyelination, a decrease in the production and quality of myelin, the fatty acid sheath surrounding neurons (Beard *et al.* 2003; Ortiz *et al.* 2004). • Hypomyelination impacts all brain regions, but disturbances in the auditory and visual systems of infants have been most closely linked to impaired myelination (Algarin *et al.* 2003; Amin *et al.* 2013).

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Table 2 Relationships between iron biomarkers and iron status, and important considerations for each biomarker

	Iron Depletion	Iron Deficiency	Iron Deficiency Anaemia	Iron Overload	Biomarker Considerations
Storage Iron					
Ferritin	↓	↓	↓	↑	Confounded by inflammation
Transport Iron					
Iron	Normal	↓	↓	↑	Diurnal and prandial variation
Transferrin	Normal	↑	↑	↓	Diurnal and prandial variation
Transferrin saturation	Normal	↓	↓	↑	Diurnal and prandial variation
Soluble transferrin receptor	Normal	↑	↑	Normal	Limited availability, assay issues
Erythrocyte protoporphyrin	Normal	↑	↑	Normal	Lacks specificity for iron
Functional Iron					
Mean corpuscular volume	Normal	Normal	↓	Normal	Lacks specificity for iron
Haemoglobin	Normal	Normal	↓	Normal	Low specificity and sensitivity

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