Iron deficiency during the first 1,000 days of life: are we doing enough to protect the developing brain?

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Abstract

Iron is essential for the functioning of all cells and organs, most critically for the developing brain in the fundamental neuronal processes of myelination, energy and neurotransmitter metabolism. Iron deficiency, especially in the first 1,000 days of life, can result in long-lasting, irreversible deficits in cognition, motor function and behaviour. Pregnant women, infants and young children are most vulnerable to iron deficiency, due to their high requirements to support growth and development, coupled with a frequently inadequate dietary supply. An unrecognised problem is that even if iron intake is adequate, common pregnancy-related and lifestyle factors can affect maternal-fetal iron supply in utero, resulting in an increased risk of deficiency for the mother and her fetus. While preterm birth, gestational diabetes mellitus and intrauterine growth restriction are known risk factors, more recent evidence suggests that maternal obesity and delivery by Caesarean section further increase the risk of iron deficiency in the newborn infant, which can persist into early childhood. Despite the considerable threat that early-life iron deficiency poses to long-term neurological development, life chances and a country's overall social and economic progress, strategies to tackle the issue are non-existent, too limited or totally inappropriate. Prevention strategies, focused on improving the health and nutritional status of women of reproductive age are required. Delayed cord clamping should be considered a priority. Better screening strategies to enable the early detection of iron deficiency during pregnancy and early-life should be prioritised, with intervention strategies needed to protect maternal health and the developing brain.

Introduction

Iron deficiency is the most common micronutrient deficiency in the world and continues to present a major burden to health in both low and high-resource settings[1]. Iron deficiency anaemia, reported in over 1.2 billion people in 2016, is one of the top five leading causes of years lived with disability globally and the leading cause of years lived with disability in low and middle-income countries[2]. Given the critical role of iron in the functioning of all cells and organ systems, reducing the prevalence of iron deficiency and anaemia globally is considered an urgent priority by the World Health Organisation (WHO)[3].

Iron stores become depleted if dietary iron intake and/or absorption is inadequate or physiological losses through blood are uncompensated for. Iron deficiency occurs when iron stores are insufficient to meet the needs of an individual; therefore, individuals with increased iron requirements are at the greatest risk. Iron requirements are at their highest during the first 1,000 days of life. They increase almost 10-fold during pregnancy, increasing from 0.8 mg/day in the first trimester to ~7.5 mg/day in the third trimester[4]. This means close to 1000mg of iron must be acquired during the pregnancy to preserve maternal iron balance and support fetoplacental development[5]. As infancy and early childhood is characterised by rapid growth and development, iron requirements per kilogram of body weight are higher from 6-24 months of age than during any other period of life[6]. Failure to meet these increased requirements predisposes pregnant women, infants and young children to iron deficiency and iron deficiency anaemia.

The aim of this paper is to provide an in-depth review of the current perspectives on iron deficiency in the first 1,000 days of life, with a particular focus on the key determinants of iron status during this period. The lasting consequences for neurological development are discussed, while challenges in defining and diagnosing iron deficiency in pregnant women, infants and young children are identified. Finally, suggestions are made for prevention and screening strategies to help tackle this global public health issue.

Iron deficiency in the first 1,000 days

The first 1,000 days arguably represents the period of life with the greatest risk of iron deficiency. In Europe, the prevalence of iron deficiency during pregnancy ranges from 28 to 85%, with the highest rates reported in women in their third trimester and in those

unsupplemented[7]. Up to a third of pregnant women have iron deficiency anaemia in Europe, with higher rates reported in low and middle-income countries, ethnic minorities and pregnant adolescents[1; 7; 8]. Rates of iron deficiency anaemia are typically <5% amongst 6-24-month-old children, although iron deficiency and depleted iron stores have been reported in up to half of European children in this age group[9; 10].

Dietary determinants of iron status

Inadequate dietary iron intakes and/or poor iron absorption are considered significant risk factors for iron deficiency during pregnancy and early childhood. Current dietary recommendations for the first 1,000 days are presented in **Table 1**, with much variability observed across agencies due to differing assumptions around the efficiency of iron absorption and utilisation in these population groups.

Important physiological adaptations in iron absorption and mobilisation occur during pregnancy, but women must still enter pregnancy with sufficiently large iron stores and consume a diet abundant in bioavailable iron during pregnancy to avoid iron deficiency[11]. However, inadequate dietary iron intakes and poor compliance with dietary guidelines are widely reported amongst pregnant women worldwide[12; 13], with 60-100% of pregnant women in Europe not meeting recommended intakes[14]. To further compound this, many women begin pregnancy with already depleted iron stores as inadequate iron intakes are also common amongst women of reproductive age[7; 15].

The assumption is that healthy term infants are born with sufficient body iron stores to meet their requirements until they have doubled their birth weight, usually around 4-6 months of age[16]. As iron is transferred back from stores to the blood compartment to meet the infant's iron requirements, exclusive breastfeeding during this period, despite its low iron concentration, is sufficient to meet the needs of the infant[6]. It is only after this point that the infant becomes dependent on external dietary iron sources, as evidenced by the considerable increase in recommended intakes from 7 months onwards. Failure to incorporate sufficient iron-rich complementary foods into the diet and the early introduction and/or excessive intake of unmodified cow's milk are significant risk factors for iron deficiency in 6-24-month olds[17-19]. Unfortunately, inadequate iron intakes are widely reported amongst infants and young children in Ireland[18; 20], the UK[21] and across Europe[9].

Non-dietary determinants of iron status

Even if dietary iron supply is adequate, there are several pregnancy-related and lifestyle factors that can compromise maternal-fetal iron supply in utero. Any disruption to maternal-fetal iron supply is especially detrimental to the developing fetus who is entirely dependent on maternal supply to meet its increased iron requirements for growth and development. Iron is actively transported from the mother to the fetus through the placenta[11], with the iron-regulatory hormone, hepcidin, particularly critical at this time in controlling plasma iron concentrations and tissue iron distribution[22]. Maternal hepcidin concentrations are decreased in the second and third trimester of healthy pregnancies to allow for an increased iron supply into maternal circulation to support fetal demand[5; 23].

Disruption in maternal-fetal iron supply generally occurs through three key pathways; compromised maternal iron status, altered fetal iron delivery and/or demand or a reduction in fetal iron accretion. Critically, such disruption in iron supply to the fetus increases the risk of iron deficiency in the newborn infant, with 10-85% iron deficiency reported in infants at birth, depending on the aetiology of the disruption[24]. Infants born deficient are also at an increased risk of iron deficiency later in infancy and early childhood, as low iron stores at birth track into early childhood[25; 26].

Compromised maternal iron status

Despite the earlier assumption that the fetus could accumulate enough iron independent of maternal iron status[23; 27; 28], more recent evidence has emphasised the importance of maternal iron status to fetal and neonatal iron status. Infants born to mothers with iron deficiency with and without anaemia at delivery and/or mid-late gestation have lower umbilical cord ferritin concentrations at birth, indicative of poorer iron stores[29-34]. A maternal ferritin concentration of 12-13.6 µg/L has been suggested by some as the threshold below which fetal iron status is compromised[33; 34]. Maternal anaemia has also been shown to result in reduced neonatal haemoglobin concentrations at birth in some cohorts[35-37]. Worryingly, this effect of maternal anaemia appears long-lasting[38; 39]. Zhang and colleagues in China observed that maternal anaemia in the 2nd trimester was associated with an increased risk of infant anaemia at both 5-7 and 11-13 months of age[40].

Disruption to fetal iron delivery and/or demand

Several pregnancy complications can result in a decrease in fetal iron delivery and/or an increase in fetal iron demand, thereby increasing the risk of iron deficiency in the newborn infant. Maternal hypertension, intrauterine growth restriction (IUGR) and gestational diabetes mellitus are characterised by intrauterine fetal hypoxia, which stimulates erythropoiesis and the production of haemoglobin, thereby increasing fetal iron demand beyond the system's capacity[24]. In pregnancies complicated by IUGR, approximately 10% of all pregnancies, placental iron transport is also decreased due to uteroplacental vascular insufficiency, with reduced liver and brain iron concentrations observed in these infants[41; 42]. Similar findings are observed in infants of diabetic mothers; almost 65% of these infants are born iron deficient with worrying evidence of brain iron depletion reported[43; 44].

In addition to these clinical complications, there are common lifestyle factors that can further disrupt maternal-fetal iron supply. Maternal smoking during pregnancy can induce fetal hypoxia, resulting in reduced cord ferritin concentrations at birth[25; 32; 45; 46]. Though widely acknowledged as a risk to maternal and infant health[47], only recently has maternal obesity both prior to and during pregnancy emerged as a considerable risk factor for iron deficiency. Maternal obesity is associated with poorer iron status, particularly low ferritin concentrations, in both pregnant women[48-51] and their newborn infants[46; 48; 52-54]. While micronutrient deficiencies often coexist with obesity, termed the "double burden" of malnutrition, the effect of maternal obesity on iron status is thought to be due to reduced iron absorption rather than just reduced dietary iron intakes[55; 56]. The low-grade, chronic inflammation associated with obesity is thought to result in an over-expression of hepcidin, inhibiting intestinal iron absorption and iron stores mobilisation, thereby reducing maternal-fetal iron supply[52]. However, further investigation into this mechanism is required, as some[48; 49; 51; 52] but not all studies[50; 57; 58] have observed elevated hepcidin and inflammatory marker concentrations in obese pregnant women. Additionally, a potential BMI threshold above which upregulation of hepcidin is induced has been suggested by some investigators recently[50; 58; 59].

Reduction in iron accretion

The majority of fetal iron accretion occurs in the third trimester of pregnancy, therefore infants born premature miss out on this critical period of accretion[23; 60]. Preterm infants have lower total body iron content, haemoglobin and ferritin concentrations than term infants[61; 62]. Worryingly, this means that up to 50% of preterm infants are either born iron deficient or will develop deficiency very early in infancy[63-66]. In addition to the impact of preterm birth itself, preterm infants have very high iron requirements given their high rate of postnatal growth and an earlier onset of erythropoiesis. They can also experience significant iron loss through uncompensated phlebotomy blood losses[60; 67; 68]. Similarly, low birthweight infants are born with low iron stores[6; 69]. In particular, extremely low birthweight infants of <1000g can be in negative iron balance within the first month of life if an appropriate external iron source isn't provided[70]. Timely, appropriate iron supplementation is therefore of the utmost importance to this vulnerable cohort, although much variability still exists with respect to iron dosing, duration of supplementation and delivery method in practice[71].

Interestingly, although widely unacknowledged, obstetric mode of delivery can have a significant influence on the accretion of iron in the infant. Infants born by Caesarean section have lower haemoglobin, haematocrit and erythrocyte concentrations in peripheral and cord blood when compared to infants delivered vaginally[72]. In our own prospective maternal-infant cohort in Ireland, infants delivered by Caesarean section were twice as likely to be iron deficient at birth in comparison to those delivered vaginally[46]. This effect is thought to be due to a shorter placental transfusion period because of immediate cord clamping and a weaker placental transfusion force, all reducing the transfer of iron to the infant through the umbilical cord at delivery[73; 74]. Rates of deliveries by Caesarean section have increased dramatically worldwide, with rates of 26-33% reported in Ireland and the UK[75; 76].

Neurological consequences of iron deficiency during the first 1,000 days

The rate of growth and development of the brain is among the highest during the first 1,000 days, making this period critical for immediate brain function but also for laying the foundations for later brain function[77]. **Figure 1** illustrates the key milestones and processes that occur in brain development throughout the lifespan, with the importance of the early-life period particularly evident.

Iron deficiency during pregnancy and early-life has many health consequences for both the mother and her child, but the long-lasting neurological consequences are perhaps the most

concerning. Consistent mechanistic evidence has shown that iron plays a key role in the fundamental neuronal processes of myelination and neurotransmitter and energy metabolism[11]. Iron deficiency can therefore disrupt these processes, resulting in adverse neurological consequences that often remain long after correction of the deficiency itself. Excellent reviews of the neurobiological effects of iron deficiency are provided elsewhere[11; 78; 79], with the focus of this review on the observational evidence underpinning the association between iron deficiency and brain development in early life.

The impact of maternal iron status on neonatal iron status has been discussed, but it can also present an immediate threat to fetal brain development. Monk and colleagues observed that low maternal iron intakes in the third trimester were associated with altered neonatal brain structure, particularly of the cortical grey matter[80]. Using health and population register data from Sweden, the offspring of women diagnosed with anaemia in the first and/or second trimester of pregnancy were at an increased risk of developing neurological disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder[81]. The significant variability in study design can make it difficult to interpret studies in this field, but a 2019 systematic review by Janbek *et al.* did conclude that maternal iron status during pregnancy may be associated with offspring cognition, academic achievement and behaviour[82]. Since then, significantly higher scores in working memory and executive function at 7 years of age were observed in children born to mothers that had ferritin concentrations >12µg/L in the first trimester in a large birth cohort in Spain[83].

The long-lasting consequences of postnatal iron deficiency, particularly from 6-24 months of age, are widely reported and acknowledged, with poorer cognition, intelligence, motor function and behaviour commonly observed[79; 84]. To date, little consideration has been given to the consequences of iron deficiency in the neonatal period. Neurophysiological disturbances are observed within 24-48 hours of birth in infants born iron deficient (frequently defined as cord ferritin <70-76µg/L), with abnormalities in the auditory system often reported[85; 86]. Neonatal iron deficiency is also associated with poorer recognition memory at 15 days old[44], poorer motor outcomes at 9 months[87] and poorer language ability, fine motor skills and tractability at 5 years[88]. We recently identified lasting behavioural consequences of iron deficiency at birth in our prospective, low-risk maternal-infant cohort, with this effect most apparent in the children born to mothers with obesity or delivered by Caesarean section[89]. This is concerning as we know early social-emotional development is

considered an important determinant of future educational attainment, career and earning potential and overall quality of life[90].

Challenges in the diagnosis of iron deficiency

In contrast to other nutrients, there is no single biomarker that can truly assess the iron status of an individual or population. Iron status should be considered as a spectrum, moving from the early stage of depleted iron stores to iron deficiency to the final stage of iron deficiency anaemia. A wide range of biomarkers that reflect storage, transport, supply and functional iron are available to assess the different stages of iron status as outlined in **Figure 2**. Additional indicators including hepcidin and reticulocyte haemoglobin content are currently under investigation as potentially useful biomarkers in some populations[11; 91]. However, there are limitations to each biomarker, given that they are frequently confounded by other factors, particularly inflammation or lack specificity and/or sensitivity for iron. Difficulties in standardisation and harmonisation across different labs also present significant challenges to interpretation[92].

The diagnosis of iron deficiency is further complicated in pregnant women, infants and young children, as serious knowledge gaps remain as to the most appropriate biomarkers and thresholds for this stage of life. Haemoglobin, a marker of functional iron is routinely employed in practice, but this is perhaps given the ease with which it can be measured with a point-of-care test. The over-reliance on haemoglobin, particularly in this population is a major concern, as iron is prioritised to the red blood cells for erythropoiesis above all other organs. The liver, heart, skeletal muscle and critically, the brain will all become iron deficient prior to any disturbances in haemoglobin concentrations[43; 93].

Secondly, the thresholds applied to each biomarker are often not specific to this population and are not related to any relevant health outcomes. Currently used thresholds for many biomarkers are either extrapolated from other populations and do not account for the unique physiological adaptations in iron homeostasis that occur during pregnancy and early infancy or are solely based on the distribution of a marker in a given population[94]. This means many thresholds currently used are completely arbitrary and certainly not related to any meaningful health outcomes in this high-risk population. The huge variability and lack of consistency in the current use of thresholds, even amongst international agencies, further complicates matters.

While much debate continues as to the most appropriate biomarkers and thresholds[95-97], health professionals, clinicians and researchers should aim to assess iron status using a battery of biomarkers, but at a very minimum, using both ferritin (with an inflammatory marker as it is an acute phase reactant) and haemoglobin[98]. The WHO recommend ferritin thresholds of 12µg/L for children <5 years and 15µg/L for everybody else, including pregnant women, with thresholds of 110g/L for children <5 years and pregnant women for haemoglobin[98; 99]. Ferritin continues to be considered an important indicator of the earliest stage of iron deficiency, although some investigators have suggested adjustments to the thresholds applied in infants and young children[100; 101]. Research is also ongoing into novel biomarkers that may provide more sensitive indicators of impending brain dysfunction due to iron deficiency in infants and young children[102-104].

Strategies to combat iron deficiency in the first 1,000 days

While the first 1,000 days of life represents the period of greatest risk for iron deficiency, it also represents the period of greatest opportunity to tackle this global public health issue. Many of the risk factors outlined in this paper are modifiable and thus preventable, while the impact of those that aren't preventable could certainly be lessened through early identification. Interventions targeting the fetal and early-life period represent the best opportunity to prevent iron deficiency and its lasting consequences for health. While several intervention targets could be considered, in this review, we've suggested three key targets that we feel are the most achievable and meaningful.

Target 1 - improvements in nutrition and health status of women prior to conception

Many of the risk factors for iron deficiency in the first 1,000 days are maternal or pregnancy-related. Therefore, interventions targeting the mother should be considered as one of the best ways to prevent iron deficiency in infancy and early childhood. As a starting point, poor micronutrient status and obesity are the major challenges that need to be addressed by any such interventions.

To combat the widespread issue of iron deficiency, iron supplementation is commonly used, as daily supplementation has been shown to reduce the prevalence of iron deficiency and iron deficiency anaemia in pregnant women at term[105]. However, the positive effect of

supplementation during pregnancy outside of this, for neonatal iron status or health outcomes remains very much unclear[6; 105]. Moreover, compliance with supplementation strategies is often poor, particularly in low and middle-income countries and untargeted supplementation can be dangerous[106]. Taking all of this into consideration, it's likely that starting supplementation during pregnancy is too late to influence long-term health outcomes in the offspring, so strategies to improve nutrient intakes and status in girls and women prior to conception are more pertinent.

Changes in body mass index require an even earlier intervention than that required to improve the nutritional status of women prior to pregnancy. Lifestyle and behavioural interventions among pregnant women with overweight and obesity have been shown to improve dietary intakes and physical activity levels[107-109]. However, for the most part, such interventions have not resulted in improved clinical outcomes in the mothers or their offspring[109; 110]. A life course approach has been suggested as a better alternative, whereby the prevention of obesity prior to conception is recommended, with a focus on a healthy weight status beginning in adolescence and right through the childbearing years[111; 112]. An integrated approach is required to achieve this, composed of community-based awareness initiatives and education programmes targeting adolescent girls, women of reproductive age, women and couples planning a pregnancy and those not planning but still able to conceive.

Target 2 – consistent, widespread employment of delayed clamping of the umbilical cord

After birth, placental transfusion continues with a net transfer of blood, along with red blood cells, stem cells and plasma from the placenta to the newborn infant[113]. Clamping of the umbilical cord stops this transfer, with varying practices in the timing of cord clamping reported.

Delayed clamping of the umbilical cord, considered by many to be 1-3 minutes after birth or after cord pulsations stop, will allow for a greater placental transfusion than if the cord was clamped immediately. This increased placental transfusion results in increased haemoglobin, haematocrit and ferritin concentrations after birth in both term[114; 115] and preterm infants[116-118]. These benefits are long-lasting with improved iron stores and a decreased risk of iron deficiency observed throughout infancy, up to 8-12 months of age[119-122]. An increased risk of jaundice requiring phototherapy in infants receiving delayed cord clamping has been suggested as a potential risk of this practice[115], but a recent review by Andersson and Mercer

stresses that this conclusion is exaggerated and not evidence based[113]. Furthermore, improved neurological outcomes have been observed following delayed cord clamping, with increased brain myelination at 4 months and improved fine motor and social development at 4 years reported[122; 123].

Delayed cord clamping, albeit with varying definitions around timing, is recommended for all term neonates, regardless of mode of delivery, by multiple professional bodies worldwide[124-126]. The WHO also recommend delayed cord clamping for preterm infants, where possible[124], although this can be difficult given the complicated nature of many preterm deliveries. As preterm infants are especially vulnerable to iron deficiency, efforts are now being made to allow for the incorporation of delayed cord clamping into the stabilisation procedures of these infants in the delivery room[127]. Despite consistent evidence to support the benefits of delayed cord clamping and recommendations from professional bodies, the practice of delayed cord clamping is not widespread or even consistent within countries and regions[128; 129].

Target 3 – development of appropriate screening strategies to enable early detection

When secondary to preterm birth and some pregnancy complications, prevention of iron deficiency may not always be feasible. Therefore, strategies targeting both prevention but also screening are needed to reduce the risk of iron deficiency and its lasting health consequences. Screening during the first 1,000 days will allow for the early detection of iron deficiency, thereby enabling prompt and targeted treatment to prevent its associated neurological consequences.

Current screening strategies to tackle the issue are either non-existent, too limited or totally inappropriate to protect the developing brain. There are currently no screening strategies for the early detection of iron deficiency in pregnant women, infants or young children in Ireland. Some assessment of iron status is undertaken in pregnant women and hospitalised preterm or low birth weight infants, but this frequently relies on haemoglobin concentrations to indicate the need for further investigation and tests. The American Academy of Pediatrics recommend universal screening of infants at 12 months of age using haemoglobin concentrations[130]. In 2015, the US Preventive Services Task Force concluded that there was insufficient evidence to assess the benefits and harms of screening for iron deficiency anaemia in pregnant women and children aged 6-24 months[131; 132]. In contrast, the recent UK

guidelines on the management of iron deficiency in pregnancy outline that haemoglobin should be routinely measured around 28 weeks' gestation and followed up with an assessment of ferritin concentrations, if anaemia detected[133].

Future screening strategies need to be appropriately timed, incorporate the most relevant and meaningful biomarkers and identify those at the highest risk. Many questions remain as to the most appropriate biomarkers for use in this population group, but a move away from relying solely on haemoglobin to screen for risk is warranted. However, this does require further development of other biomarkers and better education as to why the use of haemoglobin for such purposes does not protect the developing brain. Perhaps screening tools that identify individuals as high-risk based on their own and their mother's clinical history and past exposures/risks are a stepping stone towards the development of a much-needed screening programme. Without such a screening programme, iron deficiency and its long-lasting neurological consequences will continue to threaten those most vulnerable.

Conclusions

The first 1,000 days of life represents the period of greatest risk for iron deficiency and its long-lasting neurological consequences. Inadequate dietary intakes prior to and during pregnancy can be compounded by several pregnancy-related and lifestyle factors that disturb maternal-fetal iron supply in utero. Unfortunately, this means that many of the commonly held assumptions during this period, particularly pertaining to women and newborn infants having sufficient iron stores to meet their increased requirements do not always hold true. To further complicate matters, serious questions remain as to the most appropriate biomarkers and thresholds for the diagnosis of deficiency in this population, with re-evaluation of the diagnostic criteria necessary. There continues to be a lack of research into this area, with trimester-specific ferritin thresholds during pregnancy one area that needs urgent attention to enhance our ability to identify the women at most risk.

The lasting neurological consequences of iron deficiency represent a real cost and burden to individuals, but also wider society. Therefore, the earlier we can protect the developing brain from the consequences of suboptimal iron, the better it is for our society's long-term health and prosperity. To do so, a dual approach encompassing both prevention and screening strategies must be adopted. Prevention strategies need to focus on improving the health and nutritional status of young women, prior to ever becoming pregnant, while delayed cord

clamping should be considered a priority in the obstetric field. Better screening strategies, incorporating screening tools and point-of-care tests, are needed, to facilitate the early detection and identification of those at the greatest risk. These targets need to be achieved to protect both maternal health and the developing brain.

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References

1. McLean E, Cogswell M, Egli I *et al.* (2009) Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public Health Nutr* **12**, 444-454.
2. Collaborators GDaIIaP (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **390**, 1211-1259.
3. World Health Organisation (2014) *Global nutrition targets 2025: policy brief series (WHO/NMH/NHD/14.2)*. Geneva: World Health Organisation.
4. Bothwell TH (2000) Iron requirements in pregnancy and strategies to meet them. *Am J Clin Nutr* **72**, 257s-264s.
5. Fisher AL, Nemeth E (2017) Iron homeostasis during pregnancy. *Am J Clin Nutr* **106**, 1567s-1574s.
6. Domellof M, Braegger C, Campoy C *et al.* (2014) Iron requirements of infants and toddlers. *J Pediatr Gastroenterol Nutr* **58**, 119-129.
7. Milman N, Taylor CL, Merkel J *et al.* (2017) Iron status in pregnant women and women of reproductive age in Europe. *Am J Clin Nutr* **106**, 1655s-1662s.
8. Marvin-Dowle K, Burley VJ, Soltani H (2016) Nutrient intakes and nutritional biomarkers in pregnant adolescents: a systematic review of studies in developed countries. *BMC Pregnancy Childbirth* **16**, 268.
9. Eussen S, Alles M, Uijterschout L *et al.* (2015) Iron intake and status of children aged 6-36 months in europe: a systematic review. *Ann Nutr Metab* **66**, 80-92.
10. van der Merwe LF, Eussen SR (2017) Iron status of young children in Europe. *Am J Clin Nutr* **106**, 1663s-1671s.
11. Lynch S, Pfeiffer CM, Georgieff MK *et al.* (2018) Biomarkers of Nutrition for Development (BOND)-Iron Review. *J Nutr* **148**, 1001s-1067s.
12. Harika R, Faber M, Samuel F *et al.* (2017) Micronutrient Status and Dietary Intake of Iron, Vitamin A, Iodine, Folate and Zinc in Women of Reproductive Age and Pregnant Women in Ethiopia, Kenya, Nigeria and South Africa: A Systematic Review of Data from 2005 to 2015. *Nutrients* **9**.
13. Livock M, Anderson PJ, Lewis S *et al.* (2017) Maternal micronutrient consumption periconceptionally and during pregnancy: a prospective cohort study. *Public Health Nutr* **20**, 294-304.
14. Milman NT (2020) Dietary Iron Intake in Pregnant Women in Europe: A Review of 24 Studies from 14 Countries in the Period 1991-2014. *J Nutr Metab* **2020**, 7102190.
15. Milman NT (2019) Dietary Iron Intake in Women of Reproductive Age in Europe: A Review of 49 Studies from 29 Countries in the Period 1993-2015. *J Nutr Metab* **2019**, 7631306.
16. Domellof M (2007) Iron requirements, absorption and metabolism in infancy and childhood. *Curr Opin Clin Nutr Metab Care* **10**, 329-335.
17. Thane CW, Walmsley CM, Bates CJ *et al.* (2000) Risk factors for poor iron status in British toddlers: further analysis of data from the National Diet and Nutrition Survey of children aged 1.5-4.5 years. *Public Health Nutr* **3**, 433-440.
18. McCarthy EK, ní Chaoimh C, Hourihane JOB *et al.* (2017) Iron intakes and status of 2-year-old children in the Cork BASELINE Birth Cohort Study. *Mat Child Nutr* **13**, e12320-n/a.
19. Agostoni C, Decsi T, Fewtrell M *et al.* (2008) Complementary Feeding: A Commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* **46**, 99-110.

20. Irish Universities Nutrition Alliance (2012) National Pre-School Nutrition Survey. www.iuna.net (accessed 10th August 2021)
21. National Diet and Nutrition Survey (2020) Years 9 to 11 of the Rolling Programe (2016/2017 to 2018/2019). https://www.gov.uk/government/statistics/ndns-results-from-years-9-to-11-2016-to-2017-and-2018-to-2019 (accessed 10th August 2021)
22. Ganz T, Nemeth E (2012) Hepcidin and iron homeostasis. *Biochim Biophys Acta* **1823**, 1434-1443.
23. Cao C, O'Brien KO (2013) Pregnancy and iron homeostasis: an update. *Nutr Rev* **71**, 35-51.
24. Rao R, Georgieff MK (2007) Iron in fetal and neonatal nutrition. *Semin Fetal Neonatal Med* **12**, 54-63.
25. Hay G, Refsum H, Whitelaw A *et al.* (2007) Predictors of serum ferritin and serum soluble transferrin receptor in newborns and their associations with iron status during the first 2 y of life. *Am J Clin Nutr* **86**, 64-73.
26. Georgieff MK, Wewerka SW, Nelson CA *et al.* (2002) Iron status at 9 months of infants with low iron stores at birth. *J Pediatr* **141**, 405-409.
27. Rios E, Lipschitz DA, Cook JD *et al.* (1975) Relationship of maternal and infant iron stores as assessed by determination of plasma ferritin. *Pediatrics* **55**, 694-699.
28. Hussain MA, Gaafar TH, Laulicht M *et al.* (1977) Relation of maternal and cord blood serum ferritin. *Arch Dis Child* **52**, 782-784.
29. Hokama T, Takenaka S, Hirayama K *et al.* (1996) Iron status of newborns born to iron deficient anaemic mothers. *J Trop Pediatr* **42**, 75-77.
30. Gaspar MJ, Ortega RM, Moreiras O (1993) Relationship between iron status in pregnant women and their newborn babies. Investigation in a Spanish population. *Acta Obstet Gynecol Scand* **72**, 534-537.
31. Lee S, Guillet R, Cooper EM *et al.* (2016) Prevalence of anemia and associations between neonatal iron status, hepcidin, and maternal iron status among neonates born to pregnant adolescents. *Pediatr Res* **79**, 42-48.
32. Sweet DG, Savage G, Tubman TR *et al.* (2001) Study of maternal influences on fetal iron status at term using cord blood transferrin receptors. *Arch Dis Child Fetal Neonatal Ed* **84**, F40-43.
33. Jaime-Perez JC, Herrera-Garza JL, Gomez-Almaguer D (2005) Sub-optimal fetal iron acquisition under a maternal environment. *Arch Med Res* **36**, 598-602.
34. Shao J, Lou J, Rao R *et al.* (2012) Maternal serum ferritin concentration is positively associated with newborn iron stores in women with low ferritin status in late pregnancy. *J Nutr* **142**, 2004-2009.
35. Kumar A, Rai AK, Basu S *et al.* (2008) Cord blood and breast milk iron status in maternal anemia. *Pediatrics* **121**, e673-677.
36. Basu S, Kumar N, Srivastava R *et al.* (2016) Maternal and Cord Blood Hepcidin Concentrations in Severe Iron Deficiency Anemia. *Pediatr Neonatol* **57**, 413-419.
37. El-Farrash RA, Ismail EA, Nada AS (2012) Cord blood iron profile and breast milk micronutrients in maternal iron deficiency anemia. *Pediatr Blood Cancer* **58**, 233-238.
38. Colomer J, Colomer C, Gutierrez D *et al.* (1990) Anaemia during pregnancy as a risk factor for infant iron deficiency: report from the Valencia Infant Anaemia Cohort (VIAC) study. *Paediatr Perinat Epidemiol* **4**, 196-204.
39. Kilbride J, Baker TG, Parapia LA *et al.* (1999) Anaemia during pregnancy as a risk factor for iron-deficiency anaemia in infancy: a case-control study in Jordan. *Int J Epidemiol* **28**, 461-468.

40. Zhang Y, Jin L, Liu JM *et al.* (2016) Maternal Hemoglobin Concentration during Gestation and Risk of Anemia in Infancy: Secondary Analysis of a Randomized Controlled Trial. *J Pediatr* **175**, 106-110.e102.
41. Chockalingam UM, Murphy E, Ophoven JC *et al.* (1987) Cord transferrin and ferritin values in newborn infants at risk for prenatal uteroplacental insufficiency and chronic hypoxia. *J Pediatr* **111**, 283-286.
42. Georgieff MK, Mills MM, Gordon K *et al.* (1995) Reduced neonatal liver iron concentrations after uteroplacental insufficiency. *J Pediatr* **127**, 308-304.
43. Petry CD, Eaton MA, Wobken JD *et al.* (1992) Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. *J Pediatr* **121**, 109-114.
44. Siddappa AM, Georgieff MK, Wewerka S *et al.* (2004) Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. *Pediatr Res* **55**, 1034-1041.
45. Chelchowska M, Laskowska-Klita T (2002) Effect of maternal smoking on some markers of iron status in umbilical cord blood. *Rocz Akad Med Bialymst* **47**, 235-240.
46. McCarthy EK, Kenny LC, Hourihane JO *et al.* (2017) Impact of maternal, antenatal and birth-associated factors on iron stores at birth: data from a prospective maternal-infant birth cohort. *Eur J Clin Nutr* **71**, 782-787.
47. Poston L, Harthoorn LF, Van Der Beek EM (2011) Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. *Pediatr Res* **69**, 175-180.
48. Jones AD, Zhao G, Jiang YP *et al.* (2016) Maternal obesity during pregnancy is negatively associated with maternal and neonatal iron status. *Eur J Clin Nutr* **70**, 918-924.
49. Garcia-Valdes L, Campoy C, Hayes H *et al.* (2015) The impact of maternal obesity on iron status, placental transferrin receptor expression and hepcidin expression in human pregnancy. *Int J Obes (Lond)* **39**, 571-578.
50. Flynn AC, Begum S, White SL *et al.* (2018) Relationships between Maternal Obesity and Maternal and Neonatal Iron Status. *Nutrients* **10**.
51. Flores-Quijano ME, Montalvo-Velarde I, Vital-Reyes VS *et al.* (2016) Longitudinal Analysis of the Interaction Between Obesity and Pregnancy on Iron Homeostasis: Role of Hepcidin. *Arch Med Res* **47**, 550-556.
52. Dao MC, Sen S, Iyer C *et al.* (2013) Obesity during pregnancy and fetal iron status: is Hepcidin the link? *J Perinatol* **33**, 177-181.
53. Phillips AK, Roy SC, Lundberg R *et al.* (2014) Neonatal iron status is impaired by maternal obesity and excessive weight gain during pregnancy. *J Perinatol* **34**, 513-518.
54. Campbell RK, Tamayo-Ortiz M, Cantoral A *et al.* (2020) Maternal Prenatal Psychosocial Stress and Prepregnancy BMI Associations with Fetal Iron Status. *Curr Dev Nutr* **4**, nzaa018.
55. Menzie CM, Yanoff LB, Denkinger BI *et al.* (2008) Obesity-related hypoferremia is not explained by differences in reported intake of heme and nonheme iron or intake of dietary factors that can affect iron absorption. *J Am Diet Assoc* **108**, 145-148.
56. Charnley M, Newson L, Weeks A *et al.* (2021) Pregnant Women Living with Obesity: A Cross-Sectional Observational Study of Dietary Quality and Pregnancy Outcomes. *Nutrients* **13**.
57. Koenig MD, Klikuszowian E, O'Brien KO *et al.* (2020) Prepregnancy Obesity Is Not Associated with Iron Utilization during the Third Trimester. *J Nutr* **150**, 1397-1404.
58. Jones AD, Shi Z, Lambrecht NJ *et al.* (2021) Maternal Overweight and Obesity during Pregnancy Are Associated with Neonatal, but Not Maternal, Hepcidin Concentrations. *J Nutr* **151**, 2296-2304.
59. Dosch NC, Guslits EF, Weber MB *et al.* (2016) Maternal Obesity Affects Inflammatory and Iron Indices in Umbilical Cord Blood. *J Pediatr* **172**, 20-28.
60. Rao R, Georgieff MK (2001) Neonatal iron nutrition. *Semin Neonatol* **6**, 425-435.

61. Halliday HL, Lappin TR, McClure G (1984) Iron status of the preterm infant during the first year of life. *Biol Neonate* **45**, 228-235.
62. Lackmann GM, Schnieder C, Bohner J (1998) Gestational age-dependent reference values for iron and selected proteins of iron metabolism in serum of premature human neonates. *Biol Neonate* **74**, 208-213.
63. Berglund S, Westrup B, Domellof M (2010) Iron supplements reduce the risk of iron deficiency anemia in marginally low birth weight infants. *Pediatrics* **126**, e874-883.
64. Uijterschout L, Domellof M, Abbink M *et al.* (2015) Iron deficiency in the first 6 months of age in infants born between 32 and 37 weeks of gestational age. *Eur J Clin Nutr* **69**, 598-602.
65. Akkermans MD, Uijterschout L, Abbink M *et al.* (2016) Predictive factors of iron depletion in late preterm infants at the postnatal age of 6 weeks. *Eur J Clin Nutr* **70**, 941-946.
66. Amin SB, Orlando M, Eddins A *et al.* (2010) In utero iron status and auditory neural maturation in premature infants as evaluated by auditory brainstem response. *J Pediatr* **156**, 377-381.
67. Lundstrom U, Siimes MA, Dallman PR (1977) At what age does iron supplementation become necessary in low-birth-weight infants? *J Pediatr* **91**, 878-883.
68. Domellof M, Georgieff MK (2015) Postdischarge Iron Requirements of the Preterm Infant. *J Pediatr* **167**, S31-35.
69. Mukhopadhyay K, Yadav RK, Kishore SS *et al.* (2012) Iron status at birth and at 4 weeks in preterm-SGA infants in comparison with preterm and term-AGA infants. *J Matern Fetal Neonatal Med* **25**, 1474-1478.
70. Shaw JC (1982) Iron absorption by the premature infant. The effect of transfusion and iron supplements on the serum ferritin levels. *Acta Paediatr Scand Suppl* **299**, 83-89.
71. McCarthy EK, Dempsey EM, Kiely ME (2019) Iron supplementation in preterm and low birth weight infants: a systematic review of intervention studies. *Nutr Rev* **77**(12), 865-877.
72. Zhou YB, Li HT, Zhu LP *et al.* (2014) Impact of cesarean section on placental transfusion and iron-related hematological indices in term neonates: a systematic review and meta-analysis. *Placenta* **35**, 1-8.
73. Yao AC, Hirvensalo M, Lind J (1968) Placental transfusion-rate and uterine contraction. *Lancet* **1**, 380-383.
74. Pisacane A (1996) Neonatal prevention of iron deficiency. *BMJ* **312**, 136-137.
75. Boerma T, Ronsmans C, Melesse DY *et al.* (2018) Global epidemiology of use of and disparities in caesarean sections. *Lancet* **392**, 1341-1348.
76. Health Service Executive (2018) *Perinatal Statistics Report 2016*. Dublin, Ireland: Health Service Executive.
77. Georgieff MK, Ramel SE, Cusick SE (2018) Nutritional influences on brain development. *Acta Paediatr* **107**, 1310-1321.
78. Lozoff B, Georgieff MK (2006) Iron deficiency and brain development. *Semin Pediatr Neurol* **13**, 158-165.
79. Georgieff MK (2011) Long-term brain and behavioral consequences of early iron deficiency. *Nutr Rev* **69 Suppl 1**, S43-48.
80. Monk C, Georgieff MK, Xu D *et al.* (2016) Maternal prenatal iron status and tissue organization in the neonatal brain. *Pediatr Res* **79**, 482-488.
81. Wiegersma AM, Dalman C, Lee BK *et al.* (2019) Association of Prenatal Maternal Anemia With Neurodevelopmental Disorders. *JAMA Psychiatry* **76**, 1294-1304.
82. Janbek J, Sarki M, Specht IO *et al.* (2019) A systematic literature review of the relation between iron status/anemia in pregnancy and offspring neurodevelopment. *Eur J Clin Nutr*.

83. Arija V, Hernández-Martínez C, Tous M *et al.* (2019) Association of Iron Status and Intake During Pregnancy with Neuropsychological Outcomes in Children Aged 7 Years: The Prospective Birth Cohort Infancia y Medio Ambiente (INMA) Study. *Nutrients* **11**.
84. Lozoff B, Smith JB, Kaciroti N *et al.* (2013) Functional significance of early-life iron deficiency: outcomes at 25 years. *J Pediatr* **163**, 1260-1266.
85. Choudhury V, Amin SB, Agarwal A *et al.* (2015) Latent iron deficiency at birth influences auditory neural maturation in late preterm and term infants. *Am J Clin Nutr* **102**, 1030-1034.
86. Amin SB, Orlando M, Wang H (2013) Latent iron deficiency in utero is associated with abnormal auditory neural myelination in >/= 35 weeks gestational age infants. *J Pediatr* **163**, 1267-1271.
87. Santos DCC, Angulo-Barroso RM, Li M *et al.* (2018) Timing, duration, and severity of iron deficiency in early development and motor outcomes at 9 months. *Eur J Clin Nutr* **72**, 332-341.
88. Tamura T, Goldenberg RL, Hou J *et al.* (2002) Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. *J Pediatr* **140**, 165-170.
89. McCarthy EK, Murray DM, Hourihane JOB *et al.* (2021) Behavioral consequences at 5 y of neonatal iron deficiency in a low-risk maternal-infant cohort. *Am J Clin Nutr* **113**(4),1032-1041.
90. Grantham-McGregor S, Cheung YB, Cueto S *et al.* (2007) Developmental potential in the first 5 years for children in developing countries. *Lancet* **369**, 60-70.
91. Pfeiffer CM, Looker AC (2017) Laboratory methodologies for indicators of iron status: strengths, limitations, and analytical challenges. *Am J Clin Nutr* **106**, 1606s-1614s.
92. Hoofnagle AN (2017) Harmonization of blood-based indicators of iron status: making the hard work matter. *Am J Clin Nutr* **106**, 1615s-1619s.
93. Georgieff MK (2017) Iron assessment to protect the developing brain. *Am J Clin Nutr* **106**, 1588s-1593s.
94. Brannon PM, Stover PJ, Taylor CL (2017) Integrating themes, evidence gaps, and research needs identified by workshop on iron screening and supplementation in iron-replete pregnant women and young children. *Am J Clin Nutr* **106**, 1703s-1712s.
95. Daru J, Allotey J, Peña-Rosas JP *et al.* (2017) Serum ferritin thresholds for the diagnosis of iron deficiency in pregnancy: a systematic review. *Transfus Med* **27**, 167-174.
96. Pasricha SR, Colman K, Centeno-Tablante E *et al.* (2018) Revisiting WHO haemoglobin thresholds to define anaemia in clinical medicine and public health. *Lancet Haematol* **5**, e60-e62.
97. Domellof M, Dewey KG, Lonnerdal B *et al.* (2002) The diagnostic criteria for iron deficiency in infants should be reevaluated. *J Nutr* **132**, 3680-3686.
98. World Health Organisation (2020) *WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations*. Geneva: World Health Organisation.
99. World Health Organisation (2001) *Iron Deficiency Anaemia. Assessment, Prevention and Control. A guide for programme managers*. Geneva: World Health Organisation.
100. McCarthy EK, Kiely ME, Hannon G *et al.* (2017) Microcytosis is associated with low cognitive outcomes in healthy 2-year-olds in a high-resource setting. *Br J Nutr* **118**, 360-367.
101. Abdullah K, Birken CS, Maguire JL *et al.* (2017) Re-Evaluation of Serum Ferritin Cut-Off Values for the Diagnosis of Iron Deficiency in Children Aged 12-36 Months. *J Pediatr* **188**, 287-290.
102. Rao R, Ennis K, Lubach GR *et al.* (2018) Metabolomic analysis of CSF indicates brain metabolic impairment precedes hematological indices of anemia in the iron-deficient infant monkey. *Nutr Neurosci* **21**, 40-48.

103. Ennis KM, Dahl LV, Rao RB *et al.* (2018) Reticulocyte hemoglobin content as an early predictive biomarker of brain iron deficiency. *Pediatr Res* **84**, 765-769.
104. Marell PS, Blohowiak SE, Evans MD *et al.* (2019) Cord Blood-Derived Exosomal CNTN2 and BDNF: Potential Molecular Markers for Brain Health of Neonates at Risk for Iron Deficiency. *Nutrients* **11**.
105. Pena-Rosas JP, De-Regil LM, Garcia-Casal MN *et al.* (2015) Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev*, Cd004736.
106. Wessling-Resnick M (2017) Excess iron: considerations related to development and early growth. *Am J Clin Nutr* **106**, 1600s-1605s.
107. Ainscough KM, O'Brien EC, Lindsay KL *et al.* (2019) Nutrition, Behavior Change and Physical Activity Outcomes From the PEARS RCT-An mHealth-Supported, Lifestyle Intervention Among Pregnant Women With Overweight and Obesity. *Front Endocrinol (Lausanne)* **10**, 938.
108. Dodd JM, Cramp C, Sui Z *et al.* (2014) The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on maternal diet and physical activity: the LIMIT randomised trial. *BMC Med* **12**, 161.
109. Poston L, Bell R, Croker H *et al.* (2015) Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* **3**, 767-777.
110. Louise J, Poprzeczny AJ, Deussen AR *et al.* (2021) The effects of dietary and lifestyle interventions among pregnant women with overweight or obesity on early childhood outcomes: an individual participant data meta-analysis from randomised trials. *BMC Med* **19**, 128.
111. Hanson M, Barker M, Dodd JM *et al.* (2017) Interventions to prevent maternal obesity before conception, during pregnancy, and post partum. *Lancet Diabetes Endocrinol* **5**, 65-76.
112. Barker M, Dombrowski SU, Colbourn T *et al.* (2018) Intervention strategies to improve nutrition and health behaviours before conception. *Lancet* **391**, 1853-1864.
113. Andersson O, Mercer JS (2021) Cord Management of the Term Newborn. *Clin Perinatol* **48**, 447-470.
114. Hutton EK, Hassan ES (2007) Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. *JAMA* **297**, 1241-1252.
115. McDonald SJ, Middleton P, Dowswell T *et al.* (2013) Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* **7**, Cd004074.
116. Ranjit T, Nesargi S, Rao PN *et al.* (2015) Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. *Indian J Pediatr* **82**, 29-34.
117. Salae R, Tanprasertkul C, Somprasit C *et al.* (2016) Efficacy of Delayed versus Immediate Cord Clamping in Late Preterm Newborns following Normal Labor: A Randomized Control Trial. *J Med Assoc Thai* **99 Suppl 4**, S159-165.
118. Ultee CA, van der Deure J, Swart J *et al.* (2008) Delayed cord clamping in preterm infants delivered at 34 36 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* **93**, F20-23.
119. Andersson O, Hellstrom-Westas L, Andersson D *et al.* (2011) Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. *BMJ* **343**, d7157.
120. Chaparro CM, Neufeld LM, Tena Alavez G *et al.* (2006) Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. *Lancet* **367**, 1997-2004.

121. Kc A, Rana N, Malqvist M *et al.* (2017) Effects of Delayed Umbilical Cord Clamping vs Early Clamping on Anemia in Infants at 8 and 12 Months: A Randomized Clinical Trial. *JAMA Pediatr* **171**, 264-270.
122. Mercer JS, Erickson-Owens DA, Deoni SCL *et al.* (2018) Effects of Delayed Cord Clamping on 4-Month Ferritin Levels, Brain Myelin Content, and Neurodevelopment: A Randomized Controlled Trial. *J Pediatr* **203**, 266-272.e262.
123. Andersson O, Lindquist B, Lindgren M *et al.* (2015) Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial. *JAMA Pediatr* **169**, 631-638.
124. World Health Organisation (2014) *Guideline: Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes*. Geneva: World Health Organisation.
125. Royal College of Obstetricians & Gynaecologists (2015) *Clamping of the Umbilical Cord and Placental Transfusion (Scientific Impact Paper No. 14)*. Royal College of Obstetricians & Gynaecologists.
126. National Institute for Health and Care Excellence (2014) *Intrapartum care: care of healthy women and their babies during childbirth*. National Institute for Health and Care Excellence
127. Knol R, Brouwer E, Vernooij ASN *et al.* (2018) Clinical aspects of incorporating cord clamping into stabilisation of preterm infants. *Arch Dis Child Fetal Neonatal Ed* **103**, F493-f497.
128. Winter C, Macfarlane A, Deneux-Tharaux C *et al.* (2007) Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. *BJOG* **114**, 845-854.
129. Devin J, Larkin P (2018) Delayed cord clamping in term neonates: attitudes and practices of midwives in irish hospitals. *Int J Childbirth* **8**, 4-17.
130. Baker RD, Greer FR (2010) Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics* **126**, 1040-1050.
131. Siu AL (2015) Screening for Iron Deficiency Anemia and Iron Supplementation in Pregnant Women to Improve Maternal Health and Birth Outcomes: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* **163**, 529-536.
132. Siu AL (2015) Screening for Iron Deficiency Anemia in Young Children: USPSTF Recommendation Statement. *Pediatrics* **136**, 746-752.
133. Pavord S, Daru J, Prasannan N *et al.* (2020) UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* **188**, 819-830.
134. Food Safety Authority of Ireland (1999) *Recommended Dietary Allowances for Ireland*. Dublin: FSAI.
135. Scientific Advisory Committee on Nutrition (2010) *Iron and Health*. London: The Stationary Office.
136. EFSA NDA Panel (2015) Scientific Opinion on Dietary Reference Values for iron. *EFSA Journal* **13**, 4254.
137. Institute of Medicine (2001) *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: The National Academies Press.
138. Thompson RA, Nelson CA (2001) Developmental science and the media. Early brain development. *Am Psychol* **56**, 5-15.
139. McCarthy EK, Kiely ME (2019) The neonatal period: A missed opportunity for the prevention of iron deficiency and its associated neurological consequences? *Nutr Bull* **44**, 309-319.

Table 1 Dietary reference values for iron (mg/day) during the first 1,000 days of life*

	FSAI	SACN	EFSA	IOM
Women, >18 years	14	14.8	16	18
Pregnant women, >18 years	15	14.8	16	27
Lactating women, >18 years	15	14.8	16	9
Infants, 0-3 months	1.7	1.7	-	0.27†
Infants, 4-6 months	4.3	4.3	-	0.27†
Infants, 7-12 months	7.8	7.8	11	11
Children, 1-3 years	8	6.9	7	7

FSAI, Food Safety Authority of Ireland[134]; SACN, Scientific Advisory Committee on Nutrition[135]; EFSA, European Food Safety Authority[136]; IOM, Institute of Medicine[137].

* Dietary reference values presented as RDA/PRI/RNI values.

† Adequate Intake.

Figure 1 Developmental milestones in human brain development.

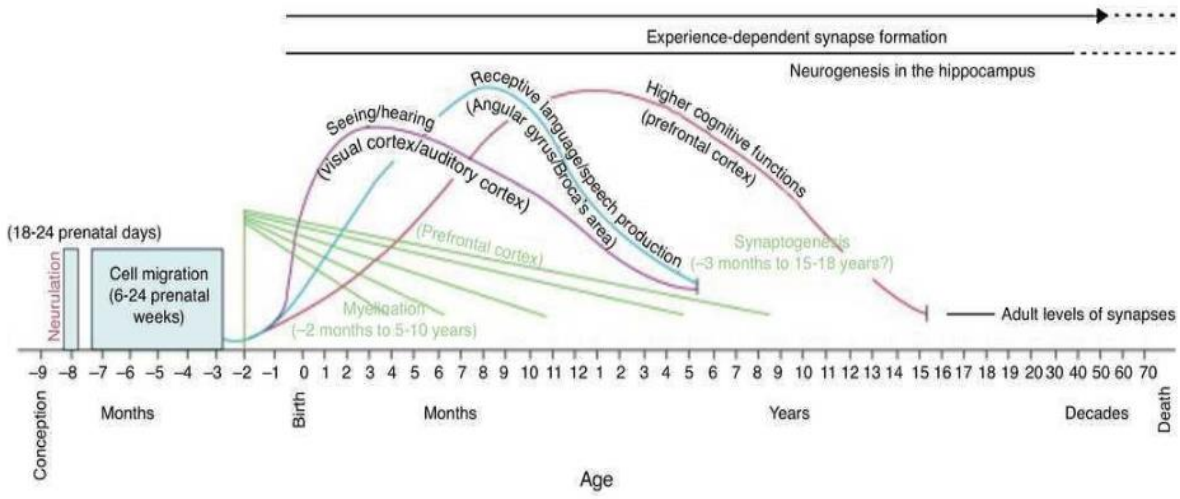

Figure 2 Relationship of storage, transport, supply and functional iron indices to the spectrum of iron status.

Modified from McCarthy and Kiely[139]

	Iron Depletion	Iron Deficiency	Iron Deficiency Anaemia	Iron Overload	Additional considerations for use
Storage Indices					
Ferritin	↓	↓	↓	↑	Confounded by inflammation
Transport + Supply Indices					
Iron	Normal	↓	↓	↑	Confounded by inflammation, diurnal variation
Transferrin	Normal	↑	↑	↓	Diurnal + prandial variation
Transferrin saturation	Normal	↓	↓	↑	Diurnal + prandial variation
Transferrin receptors	Normal	↑	↑	Normal	Assay issues, limited use
Erythrocyte protoporphyrin	Normal	↑	↑	Normal	Low specificity for iron
Functional Indices					
Mean corpuscular volume	Normal	Normal	↓	Normal	Low specificity for iron
Haemoglobin	Normal	Normal	↓	Normal	Low specificity + sensitivity