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

3

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12

13 **Running Title:** Iron deficiency and the developing brain

14

15 **Keywords:** iron, micronutrient deficiency, brain development, malnutrition, maternal
16 obesity, Caesarean section.

17 **Abstract**

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

38 **Introduction**

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

46 Iron stores become depleted if dietary iron intake and/or absorption is inadequate or
47 physiological losses through blood are uncompensated for. Iron deficiency occurs when iron
48 stores are insufficient to meet the needs of an individual; therefore, individuals with increased
49 iron requirements are at the greatest risk. Iron requirements are at their highest during the first
50 1,000 days of life. They increase almost 10-fold during pregnancy, increasing from 0.8
51 mg/day in the first trimester to ~7.5 mg/day in the third trimester⁽⁴⁾. This means close to
52 1000mg of iron must be acquired during the pregnancy to preserve maternal iron balance and
53 support fetoplacental development⁽⁵⁾. As infancy and early childhood is characterised by
54 rapid growth and development, iron requirements per kilogram of body weight are higher
55 from 6-24 months of age than during any other period of life⁽⁶⁾. Failure to meet these
56 increased requirements predisposes pregnant women, infants and young children to iron
57 deficiency and iron deficiency anaemia.

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

64

65 **Iron deficiency in the first 1,000 days**

66 The first 1,000 days arguably represents the period of life with the greatest risk of iron
67 deficiency. In Europe, the prevalence of iron deficiency during pregnancy ranges from 28 to
68 85%, with the highest rates reported in women in their third trimester and in those

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

74

75 *Dietary determinants of iron status*

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

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

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

100

101 *Non-dietary determinants of iron status*

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

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

118

119 *Compromised maternal iron status*

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

131

132 *Disruption to fetal iron delivery and/or demand*

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

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

159

160 *Reduction in iron accretion*

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

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

184

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

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

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

193 concerning. Consistent mechanistic evidence has shown that iron plays a key role in the
194 fundamental neuronal processes of myelination and neurotransmitter and energy
195 metabolism⁽¹¹⁾. Iron deficiency can therefore disrupt these processes, resulting in adverse
196 neurological consequences that often remain long after correction of the deficiency itself.
197 Excellent reviews of the neurobiological effects of iron deficiency are provided elsewhere^{(11;}
198 ^{78; 79)}, with the focus of this review on the observational evidence underpinning the
199 association between iron deficiency and brain development in early life.

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

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

225 considered an important determinant of future educational attainment, career and earning
226 potential and overall quality of life⁽⁹⁰⁾.

227

228 **Challenges in the diagnosis of iron deficiency**

229 In contrast to other nutrients, there is no single biomarker that can truly assess the iron status
230 of an individual or population. Iron status should be considered as a spectrum, moving from
231 the early stage of depleted iron stores to iron deficiency to the final stage of iron deficiency
232 anaemia. A wide range of biomarkers that reflect storage, transport, supply and functional
233 iron are available to assess the different stages of iron status as outlined in **Figure 2**.

234 Additional indicators including hepcidin and reticulocyte haemoglobin content are currently
235 under investigation as potentially useful biomarkers in some populations^(11; 91). However,
236 there are limitations to each biomarker, given that they are frequently confounded by other
237 factors, particularly inflammation or lack specificity and/or sensitivity for iron. Difficulties in
238 standardisation and harmonisation across different labs also present significant challenges to
239 interpretation⁽⁹²⁾.

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

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

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

268

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

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

278

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

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

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

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

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

306

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

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

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

320 stresses that this conclusion is exaggerated and not evidence based⁽¹¹³⁾. Furthermore,
321 improved neurological outcomes have been observed following delayed cord clamping, with
322 increased brain myelination at 4 months and improved fine motor and social development at
323 4 years reported^(122; 123).

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

334

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

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

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

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

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

365

366 **Conclusions**

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

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

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

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391

392 **Conflicts of Interest:** None

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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

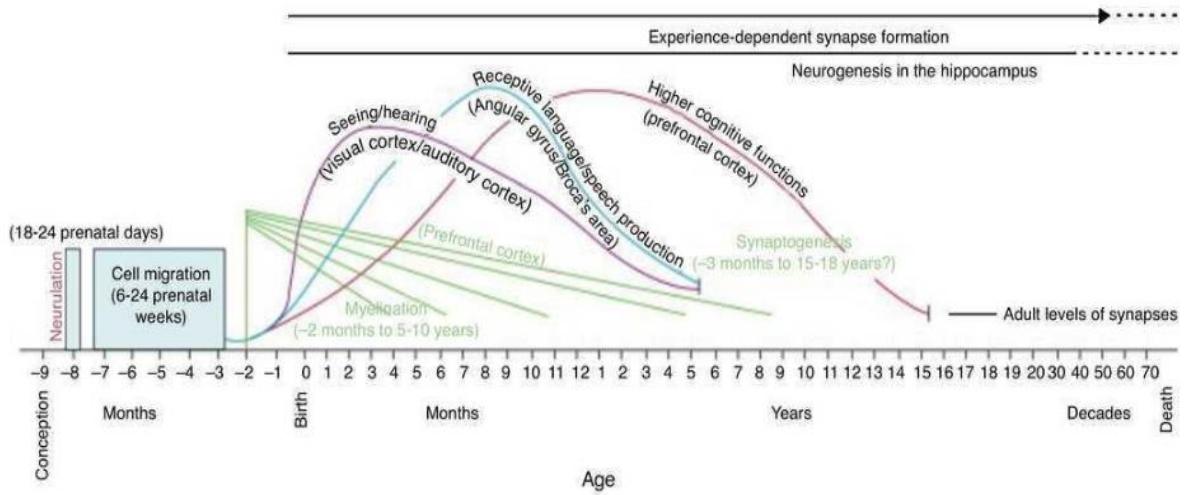
FSAI, Food Safety Authority of Ireland⁽¹³⁴⁾; SACN, Scientific Advisory Committee on Nutrition⁽¹³⁵⁾; EFSA, European Food Safety Authority⁽¹³⁶⁾; IOM, Institute of Medicine⁽¹³⁷⁾.

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

[†] Adequate Intake.

Figure 1 Developmental milestones in human brain development.

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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

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