Review

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Raghavendra B Rao *

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Review

Biomarkers of Brain Dysfunction in Perinatal Iron Deficiency

Raghavendra B. Rao [1,2,*]

[1] Division of Neonatology, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN (USA)
[2] Masonic Institute for the Developing Brain, Minneapolis, MN (USA)
* Correspondence: raghurao@umn.edu

Abstract: Iron deficiency in the fetal and neonatal period (perinatal iron deficiency) bodes poorly to neurodevelopment. Given its common occurrence and the negative impact on brain development, a screening and treatment strategy that is focused on optimizing brain development in perinatal iron deficiency is necessary. Pediatric societies currently recommend a universal iron supplementation strategy for full-term and preterm infants that does not consider individual variation in the body iron status and could lead to undertreatment or overtreatment. Moreover, the focus is on hematological normalcy and not optimal brain development. Several serum iron indices and hematological parameters in the perinatal period are associated with risk of abnormal neurodevelopment, suggesting their potential use as biomarkers for screening and monitoring treatment in infants at risk for perinatal iron deficiency. A biomarker-based screening and treatment strategy that is focused on optimizing brain development will likely improve outcome in perinatal iron deficiency.

Keywords: biomarker; brain; ferritin; hemoglobin; iron; iron deficiency; neurodevelopment; perinatal; reticulocyte hemoglobin; zinc protoporphyrin-to-heme ratio

Introduction

Iron deficiency (ID), the most common micronutrient deficiency in the world, affects 30-60% of pregnancies globally [1–3]. In the United States, 40% of pregnant women have evidence of ID in the third trimester with Black, Hispanic, teens and recent immigrants being at a greater risk [3–6]. Forty to sixty percent of infants born to mothers with ID anemia have evidence of ID in the fetal and neonatal (perinatal) period [7,8]. Additionally, gestational conditions, such as maternal diabetes, obesity, placental dysfunction, and preterm delivery predispose the offspring to brain ID [9–12]. Iron is essential for mitochondrial health, energy production, synaptogenesis, neurotransmission and myelination. Perinatal ID disrupts these processes and impairs brain development, leading to long-term deficits in attention, recognition memory and executive functioning, and neurodevelopmental and intellectual disorders in adolescence and adulthood [7,8,13–18]. Perinatal ID also predisposes to early ID in infancy [19,20], a period when brain development is still active, further compounding the adverse effects. Given the risk of long-term neurological deficits, early diagnosis and prompt treatment are necessary for ensuring normal neurodevelopment in perinatal ID.

Perinatal Iron Metabolism

The fetus is dependent on the mother for iron needs. Regulation of maternal-placental-fetal iron transport is beyond the scope of this review. Excellent reviews are available elsewhere [21–23]. Maternal-fetal iron transport occurs throughout gestation. However, 80% of fetal iron accretion occurs in the third trimester, when daily iron delivery approaches 1-2 mg/kg. Total body iron content of a fetus in the third trimester is 75 mg/kg [24]. Approximately 75 - 80% is in red blood cells (RBC) as hemoglobin, 10% in iron-containing proteins (e.g., cytochromes and myoglobin), and the

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remaining 10 - 15% in storage form, primarily as ferritin [24,25]. The common causes of perinatal ID are given in **Table 1**.

Table 1. Common Causes of Perinatal Iron Deficiency.

Etiology of Iron Deficiency	Underlying Maternal/Placental/Fetal Conditions
Decreased iron delivery	Maternal iron deficiency Placental dysfunction Maternal obesity Maternal inflammatory conditions Chronic placental or fetal-maternal hemorrhage Preterm birth
Tissue iron distribution[1]	Maternal diabetes mellitus Intrauterine growth restriction Maternal smoking ESA administration

[1]Risk of brain iron deficiency without hematological iron deficiency. ESA, erythropoiesis stimulating agent.

Interorgan Prioritization of Iron

Iron is prioritized to RBC over all other organs during negative iron balance. Storage and tissue iron are depleted first in a predetermined order with the liver and skeletal muscle becoming iron deficient prior to the heart and brain [9]. The final competition for available iron is between RBC for hemoglobin synthesis and the brain, with brain becoming iron deficient prior to the onset of anemia [26]. It is brain ID that is responsible for the adverse neurological effects in perinatal ID [27–29]. A similar prioritization favoring RBC over other organs occurs during iron repletion, leaving the brain iron deficient after the resolution of anemia [30]. The efficacy of iron treatment for correcting brain ID and preventing the adverse neurological effects of ID is time sensitive [29,31] and iron transport across the blood brain barrier is developmentally regulated [32,33]. Thus, there is a narrow therapeutic window for correcting brain ID and preventing neurodevelopmental deficits in perinatal ID.

Effects of Perinatal ID on Neurodevelopment

Human data and animal models demonstrate that the hippocampus, a brain region central to recognition or explicit memory, and the striatum, important for implicit memory, are highly vulnerable in perinatal ID [27,34–39]. In human infants, and mouse, rat and piglet models, perinatal ID leads to a smaller hippocampus and recognition memory deficits that persist in childhood despite resolution of ID [27,34,39–49]. Two transgenic mouse models of hippocampal neuron-specific ID confirm that the adverse effects are due to hippocampal neuronal ID and independent of anemia [29,50–52]. Additional studies in full-term infants have demonstrated that perinatal ID is associated with negative emotionality, lower alertness and soothability in the neonatal period [53]; impaired recognition memory and locomotion in infancy [40,54]; and poor mental, psychomotor, cognitive, and behavioral deficits in childhood [41,55]. Perinatal ID due to maternal gestational diabetes is associated with impaired recognition memory at birth [27] and behavioral abnormalities at 5 years of age [56]. In preterm infants, perinatal ID is associated with increased abnormal reflexes indicative of a poor neurobehavioral status at 37 weeks postmenstrual age (PMA) [57], and increased risk of behavioral abnormalities at 7 years of age [42]. In both full-term and preterm infants, perinatal ID is associated with abnormal auditory brain stem responses (ABR) in the neonatal period that are indicative of delayed myelination [58,59].

Biomarkers of Brain Dysfunction in Perinatal ID

Given the risk of long-term neurological impairments and a narrow therapeutic window, biomarkers that predict the risk of brain dysfunction early in the course of perinatal ID, when it is still possible to reverse it with iron treatment are necessary [60]. A biomarker is defined as a molecular, histologic, radiographic, or physiologic characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or

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intervention, including therapeutic interventions [61]. To be of practical use, such biomarkers should be present in an easily accessible compartment (e.g., in blood), not require large specimen volumes or elaborate collection procedures, easily determined in a clinical laboratory with the immediate availability of results. Such a biomarker for prevention of brain dysfunction in perinatal ID does not exist, however, which is a major barrier to optimizing iron status in neonates [62]. Some electrophysiological measures (e.g., ABR and event related potentials [ERP]) are sensitive for early detection of the effects of perinatal ID on the brain [27,40,58,59,63], but either lack specificity (as in the case of ABR) or require expertise for administration and interpretation (as in the case of ERP). Likewise, magnetic resonance imaging is useful for determining the effects of ID on the developing brain regions [34,64], but is not practical for routine screening in the clinic.

A hematology panel consisting of serum iron indices and RBC parameters is typically employed for assessing the iron status in the perinatal period (reviewed in [60,65,66]). However, these parameters are primarily focused on hematological normalcy and lack sensitivity and specificity for brain iron status or brain health [67,68]. Furthermore, the primary focus is on cord blood values [60,66]. While cord blood has practical utility given the relative ease of collection and avoidance of additional phlebotomy loss in neonates, cord blood values by themselves will not provide complete information about the perinatal iron status as they do not account for the postnatal physiological changes (e.g., physiological anemia), pathologic conditions (e.g., cyanotic congenital heart defects), and iatrogenic causes (e.g., phlebotomy losses, RBC transfusions, administration of erythropoiesis stimulating agents [ESA] and iron supplementation), all of which affect the body iron status. Some of the commonly used hematological indices, their advantages and disadvantages are discussed below:

Hemoglobin

As mentioned, majority of the total body iron is in RBCs as hemoglobin. Cord blood hemoglobin levels increase in the third trimester of gestation [69]. Using hemoglobin for screening has practical utility as the method is universally available and inexpensive. However, hemoglobin lacks sensitivity for predicting the risk of ID, impending anemia, brain ID and ID-induced brain dysfunction in infancy [9,10,67,68,70]. Hemoglobin represents the average of values from RBCs of different ages spanning 90 to 120 days and thus is not a good indicator of the current iron status. Gestational conditions associated with chronic *in utero* hypoxia (e.g., maternal diabetes and placental dysfunction) could be associated with brain tissue ID without affecting hemoglobin levels [9,50,51,71,72]. Conversely, a low hemoglobin could be due to physiological reasons (e.g., physiological anemia) or causes other than ID (e.g., hemoglobinopathies, folate deficiency). A recent study found a lack of association between hemoglobin values during the first 24 hours of birth and 2-year neurodevelopment in preterm infants < 32 weeks of gestation [69], highlighting the low sensitivity of hemoglobin as a biomarker of infant brain health.

Serum Ferritin

Serum ferritin (SF) indexes storage iron. SF levels increase between 23 and 41 weeks of gestation [11,73]. Normative cord blood SF values are available for fullterm and preterm infants [11,66]. A decrease in SF is seen only in ID and thus a low SF is a reliable biomarker of ID. A SF level ≤ 75 μg/L in cord blood or in the neonatal period is typically considered evidence of perinatal ID [8,65,71,74]. Such values correlate with slower ABR in full-term and preterm infants [58,59]; abnormal neonatal reflexes at 37 weeks PMA in preterm infants [57]; and poor performance in mental and psychomotor tests at 5 years of age in full-term infants [41,56]. A cord SF < 35 μg/L likely indexes brain ID and is associated with impaired recognition memory at birth in full-term infants of diabetic mothers [27]. A problem with SF is that levels could elevated in inflammatory conditions and after packed RBC transfusions [75,76], which makes SF a poor predictor of ID under these conditions. Similar to low SF, high cord blood SF (≥ 188 μg/L) is also associated with impaired mental and psychomotor development at 5 years of age in full-term infants [41], likely due to the presence of inflammation or other confounders. Consistent with this possibility, a study did not find association between SF > 400 μg/L and neurodevelopmental impairment at 8-12 months of age in 24-32-week gestational age preterm infants after controlling for confounders [77].

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SF in the postnatal period is not a good biomarker of ID, risk of neurodevelopmental deficits or response to iron treatment, especially in extremely low gestational age neonates (ELGAN; gestational age at birth < 28 weeks) [78,79]. A secondary analysis of the NICHD Darbepoetin Trial (Darbe Trial; NCT03169881) found no relationship between SF and evidence of ID (defined as low reticulocyte hemoglobin or low mean corpuscular volume) either in the early (≤ 27 days after birth) or late (≥ 28 days) neonatal period in ELGAN [78]. A balance study in stable, 30 week gestation preterm infants demonstrated a lack of relationship between SF and enteral iron absorption [80]. In another study of ELGAN, there were no relationships between minimum, maximum and median SF values during Neonatal Intensive Care Unit (NICU) stay and Bailey Scales of Infant Development (BSID)-III scores at 24 months corrected age [79]. The correlation between median or maximum SF values and BSID scores improved when infants with evidence of inflammation was excluded from the analysis, highlighting the low sensitivity of SF for predicting neurodevelopmental impairments in the presence of inflammatory conditions.

Urine ferritin correlates with SF [81,82] and offers a non-invasive method for screening for perinatal ID. A urine ferritin < 12 ng/mL corrected for urine creatine and specific gravity has 82% sensitivity and 100% specificity for detecting iron-limited erythropoiesis in neonates at risk for ID, with a positive predictive value of 100% [81]. However, the method may not be feasible in small preterm infants as it requires a relatively large volume of urine, and the assay lacks sensitivity in severe ID [82]. Sensitivity of urine ferritin as a biomarker of brain iron status and health has yet to be determined.

Erythrocyte Zinc Protoporphyrin to Heme Ratio

The protoporphyrin ring, precursor to the heme molecule, can be detected in circulating RBC [65]. Under conditions of iron sufficiency, iron is incorporated into the protoporphyrin ring and only a trace amount of zinc is present in the protoporphyrin ring. This changes during negative iron balance, when zinc is incorporated in the place of iron, giving rise to increased zinc protoporphyrin to heme ratio (ZnPP/H) [83–85]. Thus, increased ZnPP/H indicates iron-deficient erythropoiesis. ZnPP/H in immature RBC has higher sensitivity for detecting mild ID than whole blood ZnPP/H [86]. Reference ZnPP/H values in cord blood and the neonatal period are available for full-term and preterm infants [66,87]. ZnPP/H decreases during the third trimester and inversely correlates with gestational age [83]. Cord blood ZnPP/H is higher in preterm infants and infants at risk for perinatal ID due to maternal ID, diabetes, obesity and intrauterine growth restriction [83,87–90]. A cord blood ZnPP/H > 118 μM/M predicts poor recognition memory at 2 months in full-term infants [40]. A higher cord blood ZnPP/H is also a predictor of ID at 9 months of age [19]. ZnPP/H decreases during the first 6 weeks after birth in preterm infants, followed by an increase [84,91]. Compared with SF, ZnPP/H is affected less by inflammation and packed RBC transfusions [76,85]. Head-to-head comparison shows that ZnPP/H has greater sensitivity for predicting neurodevelopmental deficits in ELGAN than SF [40,79]. In one study, lower ZnPP/H while in the NICU was associated with higher mean BSID-III scores in all three (cognitive, language and motor) domains at 24 months corrected age in ELGAN [79]. Results were no affected when infants with documented inflammation were excluded [79]. A problem with ZnPP/H as a biomarker is that levels could be affected by RBC transfusions, ESA administration and iron treatment [83,85,92].

Reticulocyte Hemoglobin

Reticulocyte hemoglobin content (Ret-Hgb, typically abbreviated as CHr or RET-H*e*, depending on the analyzer used for determination) reflects hemoglobinization in reticulocytes [93]. Ret-Hgb provides a more real time information on bone marrow iron status than hemoglobin since reticulocytes remain in the circulation for a short time (about 48 hours). A low Ret-Hgb indicates the presence of ID. Animal studies show that Ret-Hgb has comparable predictive accuracy for prognosticating ID and IDA as the serum iron indices [70]. Ret-Hgb is affected less by inflammation, diurnal variation or diet than the serum iron indices [94–98]. Additional advantages of Ret-Hgb over serum iron indices are that it can be determined in a small blood volume using a capillary sample and lower cost [99,100]. The small coefficient of variation makes Ret-Hgb also useful for monitoring the iron status of individual infants during ESA administration or iron treatment [101].

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Reference Ret-Hgb values for the first 90 days of birth are available for infants between 22 and 42 weeks of gestation [102,103]. The 5th to 95th percentile reference interval in neonates is 25–38 pg [75,102,103]. Ret-Hgb levels decline after birth in both preterm infants than full-term infants, followed by a slow increase once iron supplementation begins [104,105]. A Ret-Hgb < 29 pg had 85% sensitivity and 73% specificity for detecting ID at 3-4 months corrected age in one study [106]. Ret-Hgb provides better indication of perinatal ID than SF when the two parameters are discordant [75]. On the negative, a low Ret-Hgb can be seen in certain hemoglobinopathies, such as α and β thalassemia, and all analyzers do not provide Ret-Hgb.

Soluble Transferrin Receptor

Soluble transferrin receptor (sTfR) is a cleaved fragment of the transmembrane transferrin receptor that is derived primarily from reticulocytes [65,66]. sTfR is a marker of intracellular iron status and is increased in tissue ID and iron-deficient erythropoiesis. sTfR is not affected by inflammation. The ratio of sTfR to SF gives total body iron status and is useful for monitoring response to iron treatment [107]. A recent study demonstrated an association between increased sTfR at 5 months of age and poor cognitive function at 5 months and 5 years, suggesting sTfR's biomarker potential for predicting long-term neurodevelopmental impairments [108]. Similar data for sTfR in the perinatal period are not available.

Hepcidin

Hepcidin is the central regulator of iron absorption, cycling and storage in the body. Hepcidin is downregulated during ID, which promotes iron absorption in the gastrointestinal tract. Hepcidin-based iron regulation is active in newborn infants [109–112]. Reference ranges for cord blood hepcidin are available from 24 to 42 weeks of gestation [113]. Serum hepcidin levels double during the first month after birth in full-term infants. A hepcidin level < 16 ng/mL at 4 months of age indicates ID [111]. As with SF, it is possible to determine hepcidin in urine. Urine hepcidin level correlates with serum hepcidin level in preterm infants [114] and offers a non-invasive screening method. Urine hepcidin/creatinine ratio correlates positively with SF and negatively with ZnPP/H in ELGAN [109]. Hepcidin is affected by RBC transfusions, ESA administration, iron treatment and inflammation [109,110,113–115]. There are no data on hepcidin's role as a biomarker of brain dysfunction in perinatal ID.

Maternal Peripartum Iron Biomarkers and Infant Neurodevelopment

Maternal ID during pregnancy is the most common cause of perinatal ID [1–3]. In addition to causing perinatal ID and affecting iron-dependent processes in the developing brain, maternal peripartum ID is associated with poor mother-infant interaction due to maternal depression, stress, and lower cognitive functioning, further impacting offspring neurodevelopment [116,117]. In a prospective study of 132 mother-full-term infant dyads from a well-nourished population at low-risk for ID, the associations between maternal peripartum iron status (hemoglobin, SF, sTfR, sTfr:SF ratio and plasma iron at 3 months postpartum) and infant cognitive function at 3 months and 9 months were determined using sophisticated electrophysiological tests [63]. Better maternal peripartum iron status was associated with better infant cognitive performance overall. Higher maternal plasma iron was associated with faster speed of processing and better memory; higher hemoglobin with better attention and memory; and lower sTfR and higher sTfR/SF ratio with lower neural response variability, all at 9 months [63]. There was a negative association between maternal plasma iron and infant neural response variability, indicating slower adaptation to stimuli with higher maternal plasma iron.

Biomarkers of Iron-Dependent Brain Health

The above-mentioned biomarkers primarily index iron status in the heme compartment and not brain iron status or brain health. Molecular biomarkers of iron-dependent brain health are needed for optimizing brain development through early detection and treatment. Two recent developments in this area are reviewed below:

In a study involving human newborn infants at risk for perinatal ID due to maternal anemia, diabetes or obesity, cord blood exosomal contactin-2 and brain derived neurotrophic factor (BDNF), both of which are important for brain development [34,118], correlated with cord blood SF [12].

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Exosomes are small, cell-derived vesicles found in all biofluids, carrying the same classes of molecules as the parent cell and function as a snapshot of their cell of origin. Exosomal contactin-2 levels were lower in male infants at risk for perinatal ID, while BDNF levels were higher in female infants, suggesting their potential use as sex-specific biomarkers of brain health in perinatal ID [12].

Our research using a well characterized nonhuman primate model of infantile ID [30,119–124] and proteomic and metabolomic analyses of paired serum and cerebrospinal fluid (CSF) samples has discovered serum biomarkers of metabolic dysfunction in the brain in the preanemic stage of ID [67,70,121,125–128]. Several neurologically important metabolites (dopamine, serotonin, and *N*-acetyl-aspartyl-glutamate) were present in the sera in the preanemic period and perturbed by parenteral iron treatment [126–128]. Additional studies in this model confirmed the presence of many neurologically important proteins and metabolites representing lipid metabolism, precursors of neurotransmitters, purines, and xenobiotic molecules, and acute phase proteins in the serum and CSF in the preanemic period [67,126]. Among these, homostachydrine and stachydrine demonstrated parallel changes of comparable magnitude in the two compartments [67]. Homostachydrine and stachydrine are derivatives of pipecolic acid betaine and proline betaine, respectively. Whereas the biological role of homostachydrine has yet to be completely understood, stachydrine is known to have neuroprotective effects [129]. Lower homostachydrine and stachydrine in ID is consistent with our previous study in this model [128]. That study also showed that both metabolites increased by 12-folds following parenteral iron treatment [128]. Given that nonhuman primate infants have similar trajectory of brain development and metabolic demand as human infants, and the two species have identical metabolites and in similar concentrations in the sera [130,131], these data have translational relevance. Thus, homostachydrine and stachydrine could serve as biomarkers of impending neurological impairment and response to iron treatment in perinatal ID.

Our recent study also evaluated the sensitivity of conventional iron panel and RBC indices for predicting the risk of metabolic brain dysfunction in our nonhuman primate model [67]. Serum iron indices (transferrin saturation [TSAT], total iron binding capacity and unbound iron binding capacity) and RET-H*e*, but not hemoglobin and other RBC indices, predicted the future risk of metabolic brain dysfunction. The predictive accuracy of RET-H*e* was comparable to that of serum iron indices. A RET-H*e* < 30 pg at 2 weeks of age accurately predicted the risk of abnormal CSF metabolite profile at 4 months of age in all infants [67]. While these results are promising, corroborating studies involving structural and functional outcomes in human infants are necessary before recommending Ret-Hgb for screening and treatment of perinatal ID in clinical practice .

Biomarker-based Iron Supplementation for Optimizing Neurodevelopment

Pediatric societies in North America and Europe currently recommend a universal iron supplementation strategy for both full-term and preterm infants [132–135]. There is no uniformity in iron dose, time of initiation and duration of supplementation among the recommendations. The iron status of individual infants is not considered and thus there is a potential for under- or over-treatment. Moreover, hematological normalcy is the focus of these recommendations and not optimization of brain development. Recent data suggest that a standardized biomarker-based iron dosage strategy addresses some of these limitations and results in higher cumulative iron dose, fewer transfusions, and potentially better neurodevelopment without increasing morbidities in preterm infants [45,136,137]. A biomarker-based supplementation strategy would also avoid or delay unnecessary iron supplementation in iron-replete infants [136].

Studies reporting a biomarker-based iron supplementation strategy, typically in the context of ESA administration in ELGAN, have used TSAT, SF or ZnPP/H for determining the time of initiation of supplementation and dosage adjustments [45,71,136,137]. Among these, only the study by German et al has evaluated the effects on neurodevelopment [45]. This secondary analysis of ELGAN enrolled in the Preterm Erythropoietin (Epo) Neuroprotection Trial (the PENUT Trial; NCT01378273) [138] found that a standardized iron supplementation strategy with dosage adjustments based on SF or ZnPP/H at 14 days and 42 days after birth resulted in higher daily iron delivery at 60 days in the placebo and Epo groups (3.6 mg/kg in the placebo group and 4.8 mg/kg in the Epo group; range, 0 to 14.7 mg/kg; IQR 2.1-5.8 mg/kg) than the dose currently recommended by the pediatric societies (2-3

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mg/kg per day) [132,134]. There was a positive association between cumulative iron dose at 60 days and BSID-III cognitive scores at 2 years of age. Higher cumulative iron dose was also associated with better, but statistically not significant. motor and language scores. In all three domains, infants treated with Epo had better scores than those treated with placebo [45]. A similar association between cumulative iron dose at 90 days and BSID scores were not present, highlighting the importance of a postnatal age-specific dosage strategy. The recently completed Darbe trial (NCT03169881), and two ongoing trials (Iron Supplementation and Neurodevelopmental Outcome in ELGANs; NCT04691843, and the Darbe Plus IV Iron to Decrease Transfusions While Maintaining Iron Sufficiency in Preterm Infants; DIVI: NCT05340465), all of which employ a biomarker-based iron dosage strategy and neurodevelopment as outcome are expected to provide additional information.

There are limitations for instituting a biomarker-based iron supplementation strategy. A single biomarker may not be sensitive for predicting both the risk of brain dysfunction and efficacy of treatment. For example, whereas SF may be useful for monitoring for the risk of brain ID (e.g., during ESA therapy) in ELGAN [71], it does not appear to be sensitive for assessing response to iron treatment. A recent study found negative association between SF and cumulative iron dosage, an opposite effect than expected [78]. It is also probably futile to aim for normalization of SF during iron treatment since storage iron is the last compartment to get replenished. In a previous study, despite close monitoring for ID during ESA therapy using TSAT (TSAT < 20% is conventionally used as an indicator of ID in infancy [139]) and meticulously adjusting iron dose to maintain TSAT > 20%, 60% of ELGAN had evidence of ID (SF < 75 μg/L) at the conclusion of ESA therapy [71]. An RBC based biomarker is probably better for monitoring response to iron therapy since iron is prioritized to the RBC for heme synthesis during treatment [78,80,83]. Both ZnPP/H and Ret-Hgb appear to be better biomarkers for this purpose. Both are altered in the preanemic period and respond to iron treatment [78,92,105]. Our recent data in nonhuman primate studies suggest that Ret-Hgb may be superior to ZnPP/H for predicting the risk of metabolic brain dysfunction in infantile ID [67,70]. The small coefficient of variation of Ret-Hgb is also conducive for monitoring response iron treatment in individual patients [101]. Corroborating studies in human infants are needed before a biomarker-based screening and treatment strategy could be recommended for clinical practice.

5. Conclusions

Perinatal ID is common and has negative effects on neurodevelopment. Ensuring perinatal iron sufficiency through attention to maternal health and nutrition, perinatal prevention measures (e.g., delayed umbilical cord clamping and limiting phlebotomy losses) and timely iron supplementation is important for infant neurodevelopment. Current screening and treatment strategy focused on hematological normalcy is insufficient for ensuring optimal brain development of infants at risk for perinatal ID. An individualized biomarker-based screening and treatment strategy focused on brain protection is needed. A single biomarker is unlikely to be adequate for this purpose. A panel of biomarkers indexing the hematological and brain iron status is necessary for ensuring optimal brain development in perinatal ID.

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