

Iron deficiency in pregnancy

Michael K. Georgieff, MD

Why Is Iron Important in Biology and Maternal–Fetal Medicine?

Iron is so fundamental to cellular functions that its uptake by cells is a highly conserved process across species. The mechanism by which iron is taken up from the extracellular environment by plants, yeast, and mammals is remarkably similar. Mammalian cells incorporate iron into the porphyrin ring of hemoproteins as well as into enzymes, where the iron moiety is essential for those enzymes' activities. Examples of the former include hemoglobin, myoglobin, and cytochromes. Examples of the latter encompass a wide range of enzymes from hydroxylases that mediate fundamental intermediary cellular metabolism to demethylases that modify the chromatin of DNA and thus gene expression.

Iron sufficiency is essential for oxygen delivery to the maternal–placental–fetal unit to support the increased oxygen consumption demand of pregnancy.¹ Maintenance of adequate maternal hemoglobin concentrations supports the oxygen demands of the 3 components of the unit. Beyond oxygen delivery, iron in cytochromes catalyzes the generation of ATP at a time when the fetal oxygen consumption rate is very high, driven largely by the structural development of fetal organs.² Of these, the brain is particularly “greedy,” accounting for an astounding

Iron is essential for the function of all cells through its roles in oxygen delivery, electron transport, and enzymatic activity. Cells with high metabolic rates require more iron and are at greater risk for dysfunction during iron deficiency. Iron requirements during pregnancy increase dramatically, as the mother's blood volume expands and the fetus grows and develops. Thus, pregnancy is a condition of impending or existing iron deficiency, which may be difficult to diagnose because of limitations to commonly used biomarkers such as hemoglobin and ferritin concentrations. Iron deficiency is associated with adverse pregnancy outcomes, including increased maternal illness, low birthweight, prematurity, and intrauterine growth restriction. The rapidly developing fetal brain is at particular risk of iron deficiency, which can occur because of maternal iron deficiency, hypertension, smoking, or glucose intolerance. Low maternal gestational iron intake is associated with autism, schizophrenia, and abnormal brain structure in the offspring. Newborns with iron deficiency have compromised recognition memory, slower speed of processing, and poorer bonding that persist despite postnatal iron repletion. Preclinical models of fetal iron deficiency confirm that expected iron-dependent processes such as monoamine neurotransmission, neuronal growth and differentiation, myelination, and gene expression are all compromised acutely and long term into adulthood. This review outlines strategies to diagnose and prevent iron deficiency in pregnancy. It describes the neurocognitive and mental health consequences of fetal iron deficiency. It emphasizes that fetal iron is a key nutrient that influences brain development and function across the lifespan.

Key words: anemia, biomarkers, brain, brain development, epigenetics, ferritin, fetal growth restriction, fetus, gestational diabetes, hemoglobin, hepcidin, hippocampus, iron, iron deficiency, mental health, metabolism, nutrition neurodevelopmental disorder, placenta, pregnancy, prematurity, preterm birth

60% of the total fetal oxygen consumption rate.² This high human fetal brain oxygen consumption rate is due to the structural development of both neurons and glia and far exceeds the brain oxygen consumption rate of other mammalian species.² The fetal brain develops from a smooth bilobed structure at 24 weeks of gestation to a complex sulcated and gyrated structure at term that looks far more like a mature adult brain than like its earlier fetal counterpart.³ The increased surface complexity reflects the massive cellular differentiation of the brain in multiple brain regions and processes that include the hippocampus, the striatum, and the process of myelination.⁴

Why Does Pregnancy Increase the Need for Iron?

The onset of pregnancy can be considered a case of impending iron deficiency, as evidenced the high rate of the disorder

during gestation. In low- and middle-income countries, the rate approaches 80%, whereas estimated rates in well-resourced countries approach 45% depending on the sensitivity of the markers used to detect it.^{5,6} The serum concentration of hepcidin, which is regulated by maternal iron status, is extremely low during pregnancy.¹ Since hepcidin is a negative regulator of intestinal iron absorption, a low level indicates a high requirement for iron.¹

Pregnancy increases maternal iron demand for 3 reasons. Maternal plasma and blood volumes are increased during pregnancy.¹ Each extra gram of hemoglobin that the mother synthesizes requires an addition 3.46 mg of elemental iron. In addition, the fetus requires iron for its own metabolic and oxygen delivery needs as well as the loading of its comparatively large endogenous iron stores that will be used in the first 6

From the Division of Neonatology, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN.

Received Jan. 24, 2020; revised Feb. 28, 2020; accepted March 3, 2020.

The authors report no conflict of interest.

The work was supported by grants 5R01 HD-29421, R01 NS-099178, R01 HD-089989, and R01 HD-094809 from the National Institutes of Health.

Corresponding author: Michael K. Georgieff, MD. georg001@umn.edu

0002-9378/\$36.00

© 2020 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.ajog.2020.03.006>

months of postnatal life.^{7,8} The placenta is a highly metabolically active organ with large iron requirements. It has the capacity to store iron in resident reticuloendothelial cells to provide a buffer against periods of low maternal iron supply.^{7–9} Overall, pregnancy requires an additional 1 g of iron, relatively equally divided between the mother and the fetus.

Postnatal Iron Status During Early Childhood Depends on Fetal Iron Loading

Postnatal iron deficiency is extremely common in infants and toddlers, with rates approaching 80% in low- and middle-income countries. In well-resource countries in Europe and in the United States, the rate of iron deficiency in children ranges from 9% to 45%.^{10,11} Postnatal iron deficiency has been convincingly linked to short- and long-term neurodevelopmental abnormalities.¹²

Until recently, postnatal iron deficiency was thought to be due to a combination of poor dietary iron intake and blood loss (due to intestinal infections). However, a recent large randomized trial of pregnant women in a Chinese population with a moderate rate of iron deficiency demonstrated that postnatal iron deficiency in the offspring was driven to a large degree by the iron status of the neonate and thus was a function of fetal iron loading.¹³ Previous studies had shown that neonatal non-anemic iron deficiency, as defined by low cord serum ferritin concentrations, negatively affects neurologic and behavioral functions in the neonatal period and confers long-term risks to neurodevelopment.^{14–19} Children born with lower fetal iron loading have lower iron stores at 9 months of age and a greater risk of postnatal iron deficiency.^{20,21} Thus, proper fetal iron loading has taken on greater importance in public health strategies to combat postnatal iron deficiency and its long-term neurodevelopmental risks.

The fetus maintains a relatively constant 75 mg of iron per kilogram of body iron during the last trimester.^{7,22} Fetal iron can be divided into 3

compartments; red cells, storage iron mostly in the liver, and non-heme, non-storage tissue iron.⁷ Red cells contain 55 mg of iron per kilogram body weight as hemoglobin and this represents the largest compartment. The amount of fetal iron in hemoglobin can be estimated by assuming 3.46 mg of iron per gram of hemoglobin and a blood volume of 85 mL per kilogram body weight.⁷ Normal values for hemoglobin concentration in term babies range from 133 to 184 g/L.²³ Risks for fetal anemia include acute fetal–maternal or fetal–placental hemorrhage and severe maternal iron deficiency when maternal hemoglobin concentration is less than 90 g/L.²⁴

Iron stores are found mostly in the liver at the end of gestation and represent 12 mg per kilogram body weight.⁷ Iron stores are proportionately larger in neonates than in older infants, children, and adults. The mean cord serum ferritin concentration of the term infant is 170 $\mu\text{g/L}$ and the fifth percentile is 59.^{13,25} Storage iron can be estimated from the serum ferritin concentration by using nomograms that relate them to liver iron content.²⁵ Negative fetal iron balance can be recognized clinically by a low cord serum ferritin concentration, which indicates loss of fetal iron stores.²⁶ Reduced ferritin concentrations occur in infants born to iron-deficient mothers with serum ferritin concentrations $<13.4 \mu\text{g/L}$,¹³ iron sufficient mothers with hypertension during gestation,²⁷ mothers who smoke cigarettes,²⁸ and mothers with glucose intolerance/diabetes mellitus during pregnancy.^{29,30} Twins can have discordant iron loading where one twin may be profoundly iron deficient.³¹

The smallest compartment is made up of the non-heme, non-storage tissues, including the brain and the heart, and comprises approximately 8 mg per kilogram body weight.⁷ No biomarkers index this compartment, yet much of the symptomatology of iron deficiency, including fatigue and altered brain function, stem from iron deficiency at the tissue level.^{32,33}

An important concept of fetal iron metabolism is that iron is prioritized to red cells over all other compartments

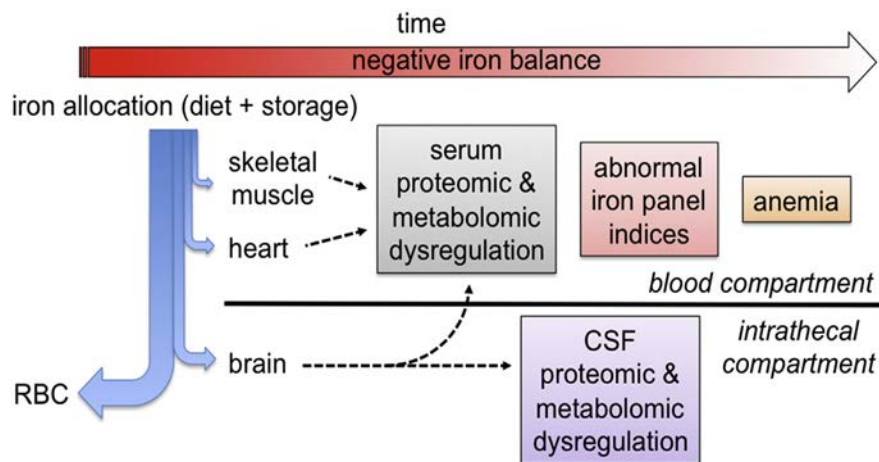
including the brain (Figure 1).^{34–37} Consequently, anemia represents the end stage of the iron deficiency process and is not a sensitive marker of tissue level iron deficiency including brain iron deficiency.³⁶ Because of the prioritization of fetal iron to the red cells, the iron status of these tissues must be inferred from the serum ferritin.³⁴ Iron status of the fetal and neonatal brain can be assessed from the serum ferritin concentration and the demonstrated relationship between reduced liver iron stores and compromised brain iron status.^{30,37} Fundamentally, tissue iron is at risk once fetal iron stores have been exhausted.^{30,34,37} To that end, newborn ferritin concentrations $<76 \mu\text{g/L}$ (25th percentile) in humans have been associated with abnormal neonatal neurologic function including poorer recognition memory^{15,17} and slower speed of processing (longer interwave latencies) on brainstem evoked responses.¹⁶

The maternal gestational conditions that compromise fetal and neonatal iron status are remarkably common,²⁶ yet routine measurement of iron status in the neonate is not performed. Conversely, the fully iron loaded neonate, who receives the benefit of delayed cord clamping and is growing at the rate described by the World Health Organization growth curves, has enough iron to maintain adequate iron delivery to supply the growing tissues and expanding red cell mass for up to 4–6 months.³⁸ Delayed cord clamping improves hemoglobin status at 2 months of age.³⁹

Biomarkers of Iron Status and Diagnosis of Iron Deficiency in Pregnant Women

Traditionally, the measurement of hemoglobin concentration has been used for patients of all ages to screen for iron status because so much of anemia worldwide is due to iron deficiency. The wide availability, ease of measurement, and low cost of hemoglobin measurement are advantages particularly in low-resource areas. Normal values for hemoglobin concentration are published and are easily accessed so that the diagnosis of anemia is not problematic.

FIGURE 1
Iron prioritization during fetal and neonatal iron deficiency^{34–37}



The relative distributional flow of iron is indicated by the thickness of the *blue arrows*. The red blood cells receive the primary allocation followed sequentially by the brain, the heart, and skeletal muscle.^{34–37} As negative iron balance progresses over time (*red arrow*), iron-dependent metabolic dysregulation of the skeletal muscle and heart is first noted by alterations in the serum metabolome.³⁶ Progressive worsening of iron deficiency subsequently negatively affects brain metabolism at approximately the same time that serum iron panels (eg, ferritin, %TSAT) become abnormal.³⁶ Iron deficiency results in anemia only in the final stage of the process.^{34–37}

CSF, cerebrospinal fluid; RBC, red blood cell; %TSAT, % total iron binding capacity saturation.

Georgieff. Iron deficiency in pregnancy. *Am J Obstet Gynecol* 2020.

Nevertheless, there are significant concerns with relying solely on hemoglobin screening. Because iron incorporation into hemoglobin is a highly prioritized process, anemia is the end-stage result of negative iron balance. Thus, hemoglobin concentration lacks the sensitivity to detect early stages of iron deficiency, when there are already physiologic effects at the tissue level. In addition, conditions other than iron deficiency cause anemia, including hemoglobinopathies, hemolysis, and inflammation/chronic disease. Reliance on hemoglobin concentration alone lacks sufficient sensitivity and specificity to diagnose iron deficiency in pregnancy. Iron-specific biomarkers, such as serum ferritin, % total iron binding capacity saturation (%TSAT), and hepcidin can be used to distinguish iron deficiency anemia from other causes of anemia.

The serum ferritin concentration indexes the body's storage iron capacity. Ferritin is stored in reticuloendothelial cells and released to the red cells for hemoglobin synthesis and to the tissues

for iron-dependent enzymes and hemoproteins. Both the liver and the placenta have remarkable ability to store iron as ferritin to buffer the mother and the fetus from wide swings in iron availability. Ferritin also acts as an intracellular regulator of the labile iron pool by releasing iron when needed via regulated chaperone molecules such as NCOA4.⁴⁰ Clinically, the finding of low serum ferritin concentration is highly diagnostic for iron deficiency.⁴¹ Standards for normal ferritin concentrations in pregnant women are available and easily accessed in practice.

However, elevated or even normal serum ferritin concentrations may be difficult to interpret because ferritin is an acute phase reactant, rising when systemic inflammation is present.⁴² A high ferritin may represent true total body iron overload or simply a shift of iron into ferritin as a response to inflammation.⁴² A normal ferritin concentration may mask an iron-deficient state if inflammation is present. Current recommendations are to measure a

biomarker of inflammation, such as C-reactive protein, if interpretation of serum ferritin in the setting of inflammation or infection.⁴² Measurement of serum ferritin requires specialized equipment and more blood than measurement of hemoglobin, although the global availability of the test is expanding rapidly. Overall, serum ferritin, if available, should be used in conjunction with hemoglobin concentration to more precisely define iron status in pregnancy.⁴²

Other iron biomarkers show promise in refining the diagnosis of iron deficiency in pregnant women. %TSAT is computed by dividing the serum iron level by the total iron-binding capacity and multiplying times 100. It reflects the percentage of iron binding sites on serum iron transport proteins that are occupied by iron molecules. Serum iron concentrations decrease early during negative iron balance, thereby decreasing the %TSAT. In stage 2 iron deficiency, transferrin concentrations increase to optimize iron binding capacity for transport, which drives the %TSAT even lower. All of these changes occur before microcytosis or anemia. Measurement of %TSAT has confirmed the tenuous iron status of a large number of pre-anemic women with iron deficiency.⁶ Reticulocyte hemoglobin concentration also identifies pre-anemic, pre-microcytic iron deficiency and thus can serve as an early biomarker of iron deficiency. Its advantage is that most equipment that measures hemoglobin concentration also has the capacity to measure reticulocyte hemoglobin.

In the future, measurement of serum hepcidin concentrations may provide the most information about who should and should not receive iron supplementation. Hepcidin is the master regulator of intestinal iron absorption and iron distribution from the reticuloendothelial cells.⁴³ Hepcidin is synthesized by the liver in response to iron status and inflammation. Hepcidin is a negative regulator, which means that high concentrations reduce intestinal iron absorption and promote iron sequestration, whereas low levels increase intestinal iron absorption and

iron release from reticuloendothelial cells. High %TSAT indicating iron sufficiency or high levels of intraleukin-6, a pro-inflammatory cytokine, increase hepcidin synthesis and release. Low % TSAT is found in iron deficiency and suppresses hepcidin. Patients with low hepcidin levels likely require iron and will respond to iron therapy, whereas those with high hepcidin levels due to iron sufficiency or iron overload do not require additional iron and will not absorb dietary iron.⁴³

The beginning of pregnancy is characterized by very low hepcidin concentrations, indicating a state of negative iron balance, and providing strong evidence that iron needs during pregnancy are high.¹ Women with marginal or even adequate iron status in the prepregnancy state are thus prone to iron deficiency when they become pregnant.

Iron Deficiency and Iron Deficiency Anemia

Iron deficiency and iron deficiency anemia are not synonymous. Iron deficiency is a state of negative iron balance where iron supply does not meet iron demand, whereas iron deficiency anemia defines the condition when hemoglobin synthesis has been limited by the lack of iron and the person is anemic as a consequence. Because iron is prioritized to red blood cells for hemoglobin synthesis, iron deficiency proceeds through multiple non-anemic stages before anemia ensues. Iron deficiency anemia can thus be thought of as the end stage of the iron-deficiency process. Iron stores are mobilized during the first stage of iron deficiency, resulting in reduced %TSAT and ferritin concentrations, respectively. This process reflects the body's attempt to maintain iron delivery to the red cells and non-heme tissues including the brain. However, when placed in direct competition for iron, the red cells will be prioritized over the brain.^{35–37} Children with pre-anemic iron deficiency demonstrate abnormal brain and behavioral function,⁴⁴ indicating the likely presence of brain tissue-level iron deficiency before the appearance of

anemia. Genetic models of neuronal-specific iron deficiency without anemia confirm that most of the neurocognitive phenotype of iron deficiency anemia is not due to the anemia.^{33,45}

Iron Supplementation During Pregnancy

The major reasons to maintain an iron-sufficient state during pregnancy are to protect the health of the mother, improve pregnancy outcomes, and foster fetal development. A recent systematic review demonstrates that iron deficiency in the first and second trimesters is associated with increased maternal morbidity and an increased risk of adverse pregnancy outcomes defined as low birthweight, prematurity, or intra-uterine growth restriction.⁴⁶ Randomized controlled trials of iron supplementation of iron-deficient pregnant women show that iron therapy reduces the rates of these morbidities.⁴⁶ Little debate exists as to whether iron-deficient pregnant women should have their iron deficiency treated.^{47,48}

Nearly 2 billion of the 7.5 billion people on the planet are iron deficient, making it the most common micronutrient deficiency in the world.⁵ Iron deficiency predominantly affects women, their fetuses, and their offspring.^{5,49} Such stark statistics combined with the evidence that pregnancy induces negative iron balance¹ has led governing bodies to consider whether universal supplementation with iron should be policy.^{5,50} The Office of Dietary Supplements at the National Institutes of Health recently held a workshop to consider the question whether iron-sufficient pregnant women should receive iron supplementation.⁴⁸ The question was considered because many women are not iron deficient and because a small body of emerging research suggests an increased risk of glucose intolerance in iron-sufficient pregnant women treated with iron.⁵¹ This area deserves further, adequately powered studies and exploration of potential underlying mechanisms (eg, oxidative stress, microbiome alterations) before policy decisions can be made.

The Short- and Long-Term Effects of Gestational Iron Deficiency on the Fetus

Fortunately, during mild maternal iron deficiency, iron is prioritized to the fetus.^{8,24} However, during moderate and severe iron deficiency, the entire maternal-placental-fetal unit becomes iron deficient, with significant short- and long-term consequences to the fetus. These consequences also occur in fetuses of iron-sufficient mothers who nevertheless have gestational conditions that compromise fetal iron delivery. These maternal conditions include hypertension, smoking, diabetes mellitus, and twinning.^{26–31} Insufficient fetal iron, whether due to maternal iron deficiency or to gestational conditions that compromise maternal fetal iron delivery, results in 3 risks to the fetus.

The immediate risk is to fetal brain development. Low maternal iron intake in the third trimester results in altered neonatal brain structure, including alterations in gray matter that index less-complex dendritic architecture.⁵² Non-anemic iron-deficient newborns with cord serum ferritin concentrations <40 $\mu\text{g/L}$ have compromised recognition memory processing¹⁵ as do 2-month-old infants with cord serum ferritin concentrations <76 $\mu\text{g/L}$.⁵³ The early age at which these abnormalities are detectable strongly implicate abnormal fetal as opposed to postnatal brain development due to iron deficiency. Recognition memory is mediated in large part by the hippocampus, which is a highly metabolic and rapidly developing structure during the late fetal and early neonatal period, making it more vulnerable to the lack of a critical substrate that supports energy metabolism.⁵⁴

The second risk is to long-term brain development. Fetal/neonatal iron deficiency is associated with long-term neurocognitive dysfunction despite spontaneous repletion of iron stores by 9 months of age.^{18,20} Low neonatal iron status reduces recognition memory performance at 3.5–4 years of age, even though the infants are no longer iron deficient.¹⁸

The third risk is postnatal iron deficiency in infancy and toddlerhood and its attendant neurodevelopmental sequelae. Infants who were iron underloaded as fetuses have poorer iron status at 9 months of age and thus a greater risk of becoming iron deficient.²⁰ Iron deficiency during infancy and toddlerhood is associated with slower speed of processing, poorer motor function and increased social dysfunction during the acute phase of iron deficiency. It confers a risk of significant long-term neuro-morbidities including depression and anxiety in adulthood.^{55–58} One reason proper fetal iron loading is important is that human milk is very low in iron. Breast milk may be the only dietary source for the infant in the first 6 postnatal months and thus the infant relies on the iron stored during fetal life to support hemoglobin synthesis and organ development for that period.^{37,38}

The Link Between Fetal or Early Postnatal Iron Status and Long-Term Neurocognitive and Mental Health

Maternal–fetal iron status has been linked to a number of neurocognitive and mental health disorders in the offspring, driven in part by the timing of iron deficiency during pregnancy. Low maternal iron intake at the time of conception is associated with a greater risk of autism in the offspring.⁵⁹ Low iron intake during the second trimester increases the risk of schizophrenia in the offspring by 30%.⁶⁰ Infants born with low serum ferritin concentrations, reflecting reduced fetal iron loading, have poorer recognition memory at birth,¹⁵ 2 months of age,⁵³ and 3.5 years of age.¹⁸ They have poorer school performance at 5–6 year of age¹⁴ and difficulty with planning and attention at 10 years of age.¹⁹ Infants with onset of iron deficiency in early postnatal life, likely driven by inadequate fetal iron loading,¹³ demonstrate slower speed of neural processing at the time of their deficiency.⁵⁵ The slower speed of neural processing persists beyond the period of iron deficiency and despite treatment.⁶¹ The infants have a greater risk of cognitive and socioemotional problems including anxiety and depression in their

second decade of life and into young adulthood.⁵⁸ The resultant loss of education and job potential can be considerable.⁴⁹ Thus, ensuring fetal nutritional and in particular iron health can be seen as an investment in the next generation and society going forward.

The Mechanisms Underlying Iron Deficiency Effects on the Young Brain

Iron is essential for the proper functioning of all cells, including those that comprise the brain. The negative effects of developmental iron deficiency on the brain have been well described in preclinical models over the past 45 years,¹² particularly in the domains of monoamine neurotransmitter metabolism,^{62,63} neuronal and glial energy metabolism,^{64,65} myelination,⁶⁶ and gene regulation.^{67–69} The alterations in the brain induced by iron deficiency are highly consistent with the acute and long-term neurobehavioral deficits that have been described in humans.¹²

Monoamine neurotransmitters, eg, dopamine, serotonin, and norepinephrine, are synthesized by the iron-containing hydroxylases-tyrosine hydroxylase and tryptophan hydroxylase. In the human, the regulation of these neurotransmitters is highly shaped between mid-gestation and 3 years' postnatal age. Research dating from the mid-1970s to the present in preclinical models indicates that early life iron deficiency alters the concentrations of the neurotransmitters, their receptors, and their reuptake mechanisms acutely while iron deficient,^{62,63} and more importantly, long-term into adulthood despite iron repletion.⁷⁰ These neurochemical changes underlie behavioral changes in the preclinical models and the behaviors are similar to those seen in humans, where anxiety, hesitancy, and mood disorders have been documented.^{12,71}

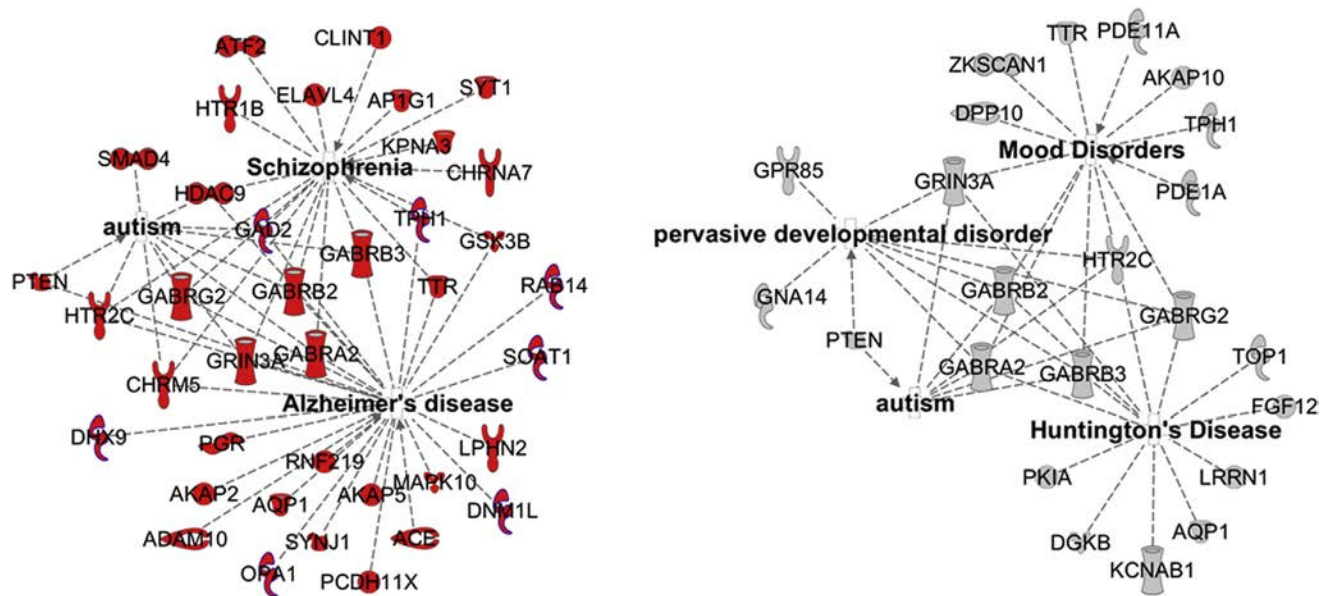
As noted previously, the fetal brain is a highly metabolic organ, consuming 60% of the total fetal oxygen consumption rate.² This high metabolic rate serves the purpose of cellular differentiation and function. Iron is essential in this process through its role in cytochromes in the generation of ATP. Neuronal iron deficiency to the degree found in human

newborns reduces oxygen consumption rate by 60%, which in turn results in a more primitive and simple neuronal structure and poorer brain mitochondrial health.^{65,72} Among the brain regions that are most rapidly developing in the last trimester, the hippocampus is foremost. The hippocampus resides at the center of the recognition memory system that mediates spatial and fact learning. The hippocampus in humans begins to differentiate rapidly at 28 weeks gestation and continues to be highly active in its development until approximately 2 years of age.⁴ Fetal iron deficiency in preclinical models compromises hippocampal synaptic plasticity and structural gene expression,^{73,74} metabolism,⁶⁴ electrophysiologic capacity,^{75,76} and recognition memory behavior acutely and into adulthood despite iron repletion in the neonatal period.^{33,45} These findings provide biological plausibility for the neurocognitive changes documented in iron-deficient newborns.^{15,17,18}

In the human, rapid myelination of the brain begins at 32 weeks of gestation and extends into the first 2 years of postnatal life. Iron-containing enzymes are important in the synthesis of fatty acids integral to myelin and early life iron deficiency alters the fatty composition of myelin and results in a hypomyelinated nervous system.⁶⁶ Hypo- and dysmyelination would result in slower speed of neuronal processing, a finding that is present in iron deficient neonates and infants.^{16,55,61} Myelin effects persist into adulthood in the preclinical models.⁶⁸

More recently, iron's role in fetal and neonatal gene expression has been demonstrated in preclinical models and has been used as a way of demonstrating a mechanism underlying the long-term effects of early-life iron deficiency. Rodents with fetal iron deficiency modeling the degree of brain iron deficiency seen in humans demonstrate a reduction in the expression of individual synaptic plasticity genes essential for development and function,^{73,74,77} as well as networks of genes underlying critical neural processes and mental health conditions, including autism,

FIGURE 2

Gene networks affected by gestational iron deficiency and choline supplementation⁶⁹

Adult hippocampal gene networks negatively affected by gestational iron deficiency

Adult hippocampal gene networks recovered by prenatal choline in spite of gestational iron deficiency

Georgieff. Iron deficiency in pregnancy. *Am J Obstet Gynecol* 2020.

schizophrenia and mood disorders.⁶⁹ These long-term gene changes are likely epigenetically driven, particularly by alterations to iron containing histone demethylases of the JARID family.⁷⁸

Based on the understanding of the biology, it should not be surprising that iron deficiency compromises brain acutely in the fetus and newborn. However, it is the long-term effects that are concerning from a societal perspective and thus the etiologies of and potential therapies for the long-term effects are a topic of intense investigation.

The long-term effects can be conceptualized by 2 basic mechanisms that are not mutually exclusive: the critical period mechanism and the epigenetic modification of chromatin mechanism. The brain is not a homogenous organ; instead, its various areas and processes are distinct entities that develop on different trajectories.⁴ A period of rapid growth and differentiation often

constitutes a critical period,⁷⁹ wherein lack of substrates necessary for proper development result in permanent structural abnormalities.^{45,79,80} Such a period has been identified in the fetal/neonatal period for the mouse hippocampus.⁴⁵ Iron deficiency that is not corrected during that period results in long-term structural deficits accompanied by neurocognitive abnormalities.⁴⁵

The epigenetic mechanism is rooted in the concept of the Developmental Origins of Adult Health and Disease.^{81,82} Many regulatory setpoints for genes that control multiple metabolic processes are set in late fetal life, a concept popularized by David Barker and known initially as the “Barker Hypothesis” in the 1990s.⁸³ The observation that similar principles of “fetal setpoint anticipation” apply to the brain became evident in the early 2000s with the demonstration that the risk for several adult mental health conditions including schizophrenia are

driven in part by fetal conditions.⁸⁴ Fetal iron status appears to follow this pattern. Low maternal iron intake in the second trimester is associated with a 30% increased risk of schizophrenia.⁶⁰ Pre-clinical models demonstrate that a network of genes underlying schizophrenia are activated by fetal iron deficiency.⁶⁹ These gene networks continue to show abnormal expression in the formerly iron deficiency adult brain, providing biological plausibility to the epidemiologic finding in humans.^{60,69} The finding that these changes to gene networks are prevented by feeding a diet rich in a methyl donor (choline) support the hypothesis that the long-term effects may be epigenetic in nature (Figure 2).⁶⁹ A similar line of research demonstrates a link between low first-trimester iron intake and the risk of autism in humans,⁵⁹ with elucidation of the involved gene networks in the preclinical fetal iron deficiency model.⁶⁹

In summary, the preclinical science across multiple investigative platforms, including molecular biology, cellular biology, electrophysiology, structure, and behavior, have provided a convincing plausibility to the role of fetal iron in brain development and the role of fetal iron deficiency in the short- and long-term neurobehavioral abnormalities observed in humans.⁸²

Pre- and Periconceptional Iron and the Argument for a Life-Cycle Effect of Nutrients

Ongoing research indicates that a woman's nutritional status heading into pregnancy influences the brain

development of the offspring. Periconceptional iron and folate iron intake are both related to the subsequent risk of autism in the offspring with lower intakes associated with higher risks.^{59,85} Undernutrition is not the only problem. Overnutrition in the form of maternal obesity is a risk factor. Elevated prepregnancy body mass index independent of gestational weight gain increases the risk of mental health and neurodevelopmental disorders in the offspring.⁸⁶

Conclusion

The information presented in this review shifts the conversation about the role of nutrition in ensuring childhood brain

health from solely focusing on postnatal nutrition to focusing on prenatal and even preconceptional nutrition. In this way, it argues for policies that promote maternal nutritional health heading into pregnancy, followed by close attention to provision of critical nutrients such as iron during pregnancy. This life-cycle approach to nutrition can be seen as an investment in the mental health of the next generation and an investment in society. ■

REFERENCES

1. Fisher A, Nemeth E. Iron homeostasis during pregnancy. *Am J Clin Nutr* 2017;106(suppl):1567S–74S.
2. Kuzawa CW. Adipose tissue in human infancy and childhood: an evolutionary perspective. *Am J Phys Anthropol* 1998;27(suppl):177–209.
3. Cowan MW. The development of the brain. *Sci Am* 1979;241:113–33.
4. Thompson RA, Nelson CA. Developmental science and the media. Early brain development. *Am Psychol* 2001;56:5–15.
5. World Health Organization. Iron deficiency anaemia: assessment, prevention and control: a guide for programme managers. 2015. Available at: www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf 2015. Accessed April 10, 2020.
6. Auerbach M, Abernathy J, Juul S, Short V, Derman R. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. *J Matern Fetal Neonatal Med* 2019;3:1–4.
7. Oski FA. The hematologic aspects of the maternal-fetal relationship. In: Oski FA, Naiman JL, eds. *Hematologic problems in the newborn*, ed 3. Philadelphia: WB Saunders; 1982. p. 32–3.
8. Cao C, O'Brien KO. Pregnancy and iron homeostasis: an update. *Nutr Rev* 2013;71:35–51.
9. McArdle HJ, Gambling L, Kennedy C. Iron deficiency during pregnancy: the consequences for placental function and fetal outcome. *Proc Nutr Soc* 2014;73:9–15.
10. van der Merwe LF, Eussun SR. Iron status of young children in Europe. *Am J Clin Nutr* 2017;106(suppl):1663S–71S.
11. Gupta PM, Perrine CG, Mei Z, Scanlon KS. Iron, anemia and iron deficiency anemia among young children in the United States. *Nutrients* 2016;8:E330.
12. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of early iron deficiency in infancy. *Nutr Rev* 2006;64:S34–43.
13. Shao J, Lou J, Rao R, et al. Maternal serum ferritin concentration is positively associated with newborn iron stores in women with low ferritin status in late pregnancy. *J Nutr* 2012;142:2004–9.

GLOSSARY OF TERMS:

C-reactive protein: A protein generated by the liver during conditions of inflammation, such as infection.

Dysmyelination: Abnormal biochemical composition of myelin.

Ferritin: The intracellular storage protein for iron. Measurement of ferritin in the serum or plasma likely comes from ferritin shed from senescent cells and reflects the intracellular storage pool.

Glia: Non-neuronal cells in the brain including oligodendrocytes that make myelin, astrocytes that serve multiple functions including nutrient delivery, and microglia that traffic neurons during development and can generate pro-inflammatory responses.

Hepcidin: A protein generated by the liver in response to iron sufficiency or inflammation that inhibits iron absorption from the intestine and sequesters iron in macrophages.

Labile iron pool: The intracellular iron that is not bound in active enzymes or hemoproteins or stored in ferritin and thus is available for use.

Methyl donor: Compounds that through their metabolism can donate a methyl group that can bind to DNA components such as cytosine—guanine islands or histones and thereby alter gene expression. Multiple nutrients such as choline, betaine, folate can act as methyl donors.

Monoamine neurotransmitters: Dopamine, serotonin, and norepinephrine are the neurotransmitters that are synthesized by iron containing enzymes tyrosine hydroxylase and tryptophan hydroxylase where iron is critical to the enzymatic function and thus the concentration of neurotransmitter produced.

Neurocognitive: Brain functions related to reasoning, learning and memory, and higher functions (eg, multi-tasking, attention, inhibition, working memory).

Neurodevelopment: The process of rapid brain growth and differentiation that takes place in the period of time from conception through early adulthood.

Transferrin saturation: Transferrin is the major binding protein for iron circulating in the serum. Under normal physiologic conditions, up to two ferric iron molecules are bound to transferrin molecule.

Oxygen consumption rate: The cellular metabolic rate of oxygen in the process of ATP generation as set by the mitochondria.

Synaptic plasticity: The ability of neurons to respond to external influences and thereby modify their anatomic structure and functional output. The term is often used to reflect the flexibility of the functioning brain.

14. Tamura T, Goldenberg RL, Hou J, et al. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. *J Pediatr* 2002;140:165–70.
15. Siddappa AM, Georgieff MK, Wewerka S, Worwa C, Nelson CA, deRegnier R-A. Auditory recognition memory in iron-deficient infants of diabetic mothers. *Pediatr Res* 2004;55:1034–41.
16. Amin SB, Orlando M, Eddins A, MacDonald M, Monczynski C, Wang H. In utero iron status and auditory neural maturation in premature infants as evaluated by auditory brainstem response. *J Pediatr* 2010;156:377–81.
17. Geng F, Mai X, Zhan J, Xu L, Georgieff M, Shao J, Lozoff B. Timing of iron deficiency and recognition memory in infancy. *Nutr Neurosci* 2020 [Epub ahead of print].
18. Riggins T, Miller NC, Bauer PB, Georgieff MK, Nelson CA. Consequences of low neonatal iron status due to maternal diabetes mellitus on explicit memory performance in childhood. *Dev Neuropsychol* 2009;34:762–79.
19. Jabès A, Thomas KM, Langworthy S, Georgieff MK, Nelson CA. Functional and anatomic consequences of diabetic pregnancy on memory in 10-year-old children. *J Dev Behav Pediatr* 2015;36:529–35.
20. Georgieff MK, Wewerka SW, Nelson CA, deRegnier R-A. Iron status at 9 months of infants with low iron stores at birth. *J Pediatr* 2002;141:405–9.
21. Zhao G, Guobin X, Zhou M, et al. Prenatal iron supplementation reduces maternal anemia, iron deficiency, iron deficiency anemia in a randomized clinical trial in rural china, but iron deficiency remains widespread in mothers and neonates. *J Nutr* 2015;145:1916–23.
22. Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. *Growth* 1976;40:329–41.
23. Lorenz L, Peter A, Poets CF, Franz AR. A review of cord blood concentrations of iron status parameters to define reference ranges for preterm infants. *Neonatology* 2013;104:194–202.
24. O'Brien KO, Zavaleta N, Abrams SA, Caulfield LE. Maternal iron status influences iron transfer to the fetus during the third trimester of pregnancy. *Am J Clin Nutr* 2003;77:924–30.
25. Saarinen UM, Siimes MA. Serum ferritin in assessment of iron nutrition in healthy infants. *Acta Paediatr Scand* 1978;67:745–51.
26. Siddappa AJ, Rao R, Long JD, Widness JA, Georgieff MK. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. *Neonatology* 2007;92:73–82.
27. Chockalingam UM, Murphy E, Ophoven JC, Weisdorf SA, Georgieff MK. Cord transferrin and ferritin levels in newborn infants at risk for prenatal uteroplacental insufficiency and chronic hypoxia. *J Pediatr* 1987;111:283–6.
28. Sweet DG, Savage G, Tubman TR, Lappin TR, Halliday HL. Study of maternal influences on fetal iron status at term using cord blood transferrin receptors. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F40–3.
29. Georgieff MK, Landon MB, Mills MM, et al. Abnormal iron distribution in infants of diabetic mothers: spectrum and maternal antecedents. *J Pediatr* 1990;117:455–61.
30. Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK. Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. *J Pediatr* 1992;121:109–14.
31. Ru Y, Pressman EK, Guillet R, Katzman PJ, Vermeylen F, O'Brien KO. Umbilical cord hepcidin concentrations are positively associated with the variance in iron status among multiple birth neonates. *J Nutr* 2018;148:1716–22.
32. Blayney L, Bailey-Wood R, Jacobs A, et al. The effects of iron deficiency on the respiratory function and cytochrome content of rat heart mitochondria. *Circ Res* 1976;39:744–8.
33. Carlson ES, Tkac I, Magid R, et al. Iron is essential for neuron development and memory function in mouse hippocampus. *J Nutr* 2009;139:672–9.
34. Georgieff MK. Iron assessment to protect the developing brain. *Am J Clin Nutr* 2017;106:1588S–93S.
35. Zamora TG, Guiang SF III, Georgieff MK, Widness JA. Iron is prioritized to red blood cells over the brain in phlebotomized anemic newborn lambs. *Pediatr Res* 2016;79:922–8.
36. Rao R, Ennis K, Lubach G, Lock E, Georgieff MK, Coe C. Metabolomic analysis of CSF indicates brain metabolic impairment precedes hematological indices of anemia in the iron-deficient infant monkey. *Nutr Neurosci* 2016;6:1–9.
37. Georgieff MK, Schmidt RL, Mills MM, Radmer WJ, Widness JA. Fetal iron and cytochrome c status after intrauterine hypoxemia and erythropoietin administration. *Am J Physiol* 1992;262:R485–91.
38. Lonnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. *Am J Clin Nutr* 2017;106:1681S–7S.
39. Grajeda R, Perez-Escamilla R, Dewey KG. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of age. *Am J Clin Nutr* 1997;65:425–31.
40. Philpott CC, Jadhav S. The ins and outs of iron: escorting iron through the mammalian cytosol. *Free Rad Biol Med* 2019;133:112–7.
41. Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem* 1998;44:45–51.
42. Suchdev PS, Williams AM, Mei Z, et al. Assessment of iron status in settings of inflammation: challenges and potential approaches. *Am J Clin Nutr* 2017;106:1626S–33S.
43. Coffey R, Ganz T. Iron homeostasis: an anthropocentric perspective. *J Biol Chem* 2017;292:12727–34.
44. Lozoff B, Clark KM, Jing Y, Armony-Sivan R, Angeilli ML, Jacobson SW. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. *J Pediatr* 2008;152:696–702.
45. Fretham SJB, Carlson ES, Wobken J, Tran PV, Petryk A, Georgieff MK. Temporal manipulation of transferrin receptor-1 dependent iron uptake identifies a sensitive period in mouse hippocampal neurodevelopment. *Hippocampus* 2012;22:1691–702.
46. Dewey KG, Oaks BM. U-shaped curve for risk associated with maternal hemoglobin, iron status or iron supplementation. *Am J Clin Nutr* 2017;106:1694S–702S.
47. Georgieff MK, Krebs NF, Cusick S. The benefits and risks of iron supplementation in pregnancy and childhood. *Ann Rev Nutr* 2019;39:121–46.
48. Brannon PM, Stover PJ, Taylor CL. 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* 2017;106:1703S–12S.
49. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA; International Child Development Steering Group. Child development: risk factors for adverse outcomes in developing countries. *Lancet* 2007;369:145–57.
50. Siu AL; US Preventative Services Task Force. Screening for iron deficiency anemia and iron supplementation in pregnant women to improve maternal health and birth outcomes: US Preventative Services Task Force Recommendation Statement. *Ann Intern Med* 2015;163:529–36.
51. Zhang C, Rawal S. Dietary iron intake, iron status and gestational diabetes. *Am J Clin Nutr* 2017;106:1672S–80S.
52. Monk C, Georgieff MK, Xu D, et al. Maternal prenatal iron status and tissue organization in the neonatal brain. *Pediatr Res* 2015;79:482–8.
53. Geng F, Mai X, Zhan J, et al. Impact of fetal-neonatal iron deficiency on recognition memory at 2 months of age. *J Pediatr* 2015;167:1226–32.
54. Georgieff MK, Innis S. Controversial nutrients in the perinatal period that potentially affect neurodevelopment: essential fatty acids and iron. *Pediatr Res* 2005;57:99R–103R.
55. Roncagliolo M, Garrido M, Walter t, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. *Am J Clin Nutr* 1998;68:683–90.
56. Angulo-Kinzler RM, Peirano P, Lin E, Algarin C, Garrido M, Lozoff B. Twenty-four-hour motor activity in human infants with and without iron deficiency anemia. *Early Hum Dev* 2002;70:85–101.
57. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. *Arch Pediatr Adolesc Med* 2006;160:1108–13.

58. Lukowski AF, Koss M, Burden MJ, et al. Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. *Nutr Neurosci* 2010;13:54–70.
59. Schmidt RJ, Tancredi DJ, Krakowiak P, Hansen RL, Ozonoff S. Maternal intake of supplemental iron and risk of autism spectrum disorder. *Am J Epidemiol* 2014;180:890–900.
60. Insel BJ, Schaefer CA, McKeague IW, Susser ES, Brown AS. Maternal iron and the risk of schizophrenia in offspring. *Arch Gen Psychiatry* 2008;65:1136–44.
61. Algarin C, Peirano P, Garrido M, Pizzaro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. *Pediatr Res* 2003;53:217–23.
62. Youdim MB, Yehuda S. The neurochemical basis of cognitive deficits induced by brain iron deficiency: involvement of dopamine-opiate system. *Cell Mol Biol* 2000;46:491–500.
63. Felt BT, Beard JL, Schallert T, et al. Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. *Behav Brain Res* 2006;171:261–70.
64. Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK. Perinatal iron deficiency alters the neurochemical profile of the developing rat hippocampus. *J Nutr* 2003;133:3215–21.
65. Bastian TW, von Hohenberg WC, Mickelson DJ, Lanier LM, Georgieff MK. Iron deficiency impairs developing hippocampal neuron gene expression, energy metabolism and dendrite complexity. *Dev Neurosci* 2016;38:264–76.
66. Ortiz E, Pasquini JM, Thompson K, Felt B, Butkus G, Beard J, Connor JR. Effect of manipulation of iron storage, transport, or availability on myelin composition and brain iron content in three different animal models. *J Neurosci Res* 2004;77:681–9.
67. Carlson ES, Stead JDH, Neal CR, Petryk A, Georgieff MK. Perinatal iron deficiency results in altered developmental expression of genes mediating energy metabolism and neuronal morphogenesis in hippocampus. *Hippocampus* 2007;17:679–91.
68. Clardy SL, Wanx X, Zhao W, et al. Acute and chronic effects of developmental iron deficiency on mRNA expression patterns in the brain. *J Neural Transm Suppl* 2006;71:173–96.
69. Tran PV, Kennedy BC, Pisansky MT, Won K-J, Gewirtz JC, Simmons RA, Georgieff MK. Prenatal choline supplementation diminishes early-life iron deficiency induced preprogramming of networks associated with behavioral abnormalities in the adult rat hippocampus. *J Nutr* 2016;146:484–93.
70. Unger EL, Hurst AR, Georgieff MK, et al. Behavior and monoamine deficits in pre- and peri-natal iron deficiency are not corrected by early postnatal moderate or high iron diet in rats. *J Nutr* 2012;142:2040–9.
71. Wachs TD, Pollitt E, Cueto S, Jacoby E, Creed-Kanashiro H. Relation of neonatal iron status to individual variability in neonatal temperament. *Dev Psychobiol* 2005;46:141–53.
72. Bastian T, Von Hohenberg W, Georgieff MK, Lanier L. Chronic energy depletion due to iron deficiency impairs dendritic mitochondrial motility during hippocampal neuron development. *J. Neurosci* 2019;39:802–13.
73. Tran PV, Carlson ES, Fretham SJ, Georgieff MK. Early-life iron deficiency anemia alters neurotrophic factor expression and hippocampal neuron differentiation in male rats. *J Nutr* 2008;138:2495–501.
74. Brunette KE, Tran PV, Wobken JD, Carlson ES, Georgieff MK. Gestational and neonatal iron deficiency alters apical dendrite structure of CA1 pyramidal neurons in adult rat hippocampus. *Dev Neurosci* 2010;32:238–48.
75. Jorgenson LA, Sun M, O'Connor M, Georgieff MK. Fetal iron deficiency disrupts the maturation of synaptic function and efficacy in area CA1 of the developing rat hippocampus. *Hippocampus* 2005;15:1094–102.
76. Pisansky MT, Wickham RJ, Su J, et al. Iron deficiency with or without anemia impairs prepulse inhibition of the startle reflex. *Hippocampus* 2013;23:952–62.
77. Tran PV, Fretham SJB, Carlson ES, Georgieff MK. Long-term reduction of hippocampal BDNF activity following fetal-neonatal iron deficiency in adult rats. *Pediatr Res* 2009;65:493–8.
78. Tran PV, Kennedy BC, Lien YC, Simmons RA, Georgieff MK. Fetal iron deficiency induces chromatin remodeling at the Bdnf locus in adult rat hippocampus. *Am J Physiol Integr Comp Phys* 2015;308:R276–82.
79. Hensch TK. Critical period regulation. *Annu Rev Neurosci* 2004;27:549–79.
80. Jorgenson LA, Wobken JD, Georgieff MK. Perinatal iron deficiency alters apical dendritic growth in hippocampal CA-1 pyramidal neurons. *Dev Neurosci* 2003;25:412–20.
81. Hanson MA, Poston L, Gluckman PD. DOHaD—the challenge of translating science to policy. *J Dev Orig Health Dis* 2019;10:263–7.
82. Barks AK, Hall AM, Tran PV, Georgieff MK. Iron as a model nutrient for understanding the nutritional origins of neuropsychiatric disease. *Pediatr Res* 2019;85:176–82.
83. Curran GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. *Circulation* 1996;94:1310–5.
84. Bale TL, Baram TZ, Brown AS, et al. Early life programming and neurodevelopmental disorders. *Biol Psychiatry* 2010;68:314–9.
85. Schmidt RJ. Maternal folic acid supplements associated with reduced autism risk in the child. *Evid Based Med* 2013;18:e53.
86. Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. *Front Neurosci* 2015;9:194.