REVIEW ARTICLE

Iron Deficiency in Newborn Infants: Global Rewards for Recognizing and Treating This Silent Malady

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Abstract

Iron deficiency can exist at birth. Even if iron is sufficient at birth, deficiency can develop during the neonatal period, or during infancy, or during childhood. Iron deficiency can exist despite a normal hematocrit and a normal blood hemoglobin concentration, because anemia is a very late manifestation of iron deficiency. It is likely that adverse neurodevelopmental consequences occur during perinatal biochemical iron deficiency, despite a normal hematocrit and hemoglobin. Consequently, measuring those parameters is a very insensitive method for perinatal iron deficiency screening. This review focuses on potentially better practices for diagnosing perinatal iron deficiency, including recent advances in understanding the pathogenesis of this condition, and also on practical means of treatment, and on global rewards of so doing.

Keywords: Anemia, Erythropoiesis, Erythroferrone, Diagnosis, Hepcidin, Iron, Treatment.

Newborn (2022): 10.5005/jp-journals-11002-0021

Preamble

Saving lives of babies who would otherwise die is a magnificent aim. However, insuring that survivors have full functionality, the best possible health, and maximal potential intellect must also be part of that aim. One "silent malady" that sometimes thwarts best possible health outcomes of neonatal survivors is a deficiency in the element iron during critical perinatal periods. Survivors of premature birth are particularly susceptible to this problem, as are survivors who were born small for gestational age, or were infants of diabetic mothers, or were born to a mother with obesity, because each of those conditions impedes fetal/neonatal iron accretion in unique and often unseen ways.[1,2]

As this global society endeavors to find new ways to improve neonatal survival, and also strives to produce the best possible long-term outcomes for babies, efforts are needed to assure perinatal iron sufficiency. Global dividends will result from improved methods to recognize neonates who are at-risk, and to diagnose and adequately manage them so as to see that their future is not jeopardized by the silent malady of perinatal iron deficiency.

Central to understanding perinatal iron deficiency is the realization that it is a spectrum, not a dichotomous variable of iron deficiency vs iron sufficiency.[3,4] Table 1 groups the spectrum of perinatal iron deficiency into three recognizable entities. These can be considered as early, mid-, and late manifestations of iron deficiency, or perhaps mild, moderate, and severe iron deficiency. Another terminology scheme, which is the one we used in Table 1, is biochemical iron deficiency, iron-limited erythropoiesis, and iron deficiency anemia.

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How to cite this article: Christensen RD, Bahr TM, Ward DM. Iron Deficiency in Newborn Infants: Global Rewards for Recognizing and Treating This Silent Malady. Newborn 2022;1(1):97–103.

Source of support: This work was supported in part by grant U54DK110858 from the U. S. Public Health Service.

Conflict of interest: None

Table 1: One categorization of the spectrum of perinatal iron deficiency

Category of iron deficiency	*Iron metrics are below the lower reference interval*	*Erythrocyte size and Hemoglobin content are below the lower reference interval*	*Hematocrit and Hemoglobin are below the lower reference interval*
Biochemical iron deficiency	YES	NO	NO
Iron-limited erythropoiesis	YES	YES	NO
Iron-deficiency anemia	YES	YES	YES

Note: Reference intervals for iron metrics, erythrocyte size and hemoglobin content, and hematocrit and hemoglobin differ for women vs neonates, and in neonates, they differ on the basis of gestational age at birth and postnatal age. For reference ranges for women, see "Anemias during Pregnancy and the Postpartum Period," Chapter 43, RT Means, Jr. in Wintrobe's Clinical Hematology, 14th Edition, Wolters Kluwer, Philadelphia, 2019. For reference ranges for neonates, see "Reference Intervals in Neonatal Hematology," Chapter 24, RD Christensen, in Neonatal Hematology, 3rd edition, Cambridge University Press, New York, 2021

Biochemical iron deficiency exists when metrics indicate that the iron supply is low. This means the biochemical iron measurements are below the lower reference interval (5th percentile) for age. However, in biochemical iron deficiency, the red blood cell size and hemoglobin content are normal, and the subject is not anemic. In contrast, the next phase is iron-limited erythropoiesis, which exists when biochemical iron deficiency is present and there is evidence of erythrocyte microcytosis and hypochromia. Perhaps the subtlest such evidence is an elevation in the Micro-R% and the HYPO-He%.[5,6] These parameters equate to the percent of erythrocytes that have a mean corpuscular volume (MCV) below 60 fL and have a mean corpuscular hemoglobin (MCH)below 16 pg/dL, respectively. As iron deficiency worsens further, the MCV and MCH fall to a point where they both are below the 5th percentile lower reference interval, and microcytosis and hypochromia are recognizable on a stained blood film. However, at this intermediate phase of iron deficiency, the hemoglobin and hematocrit remain within the reference range; thus, anemia does not exist. Only with more severe iron lack will the hemoglobin and hematocrit fall below their lower reference intervals, revealing iron deficiency *anemia*, accompanying biochemical iron deficiency and iron-limited erythropoiesis. Thus, iron deficiency anemia is not a subtle sign of low iron, but rather is an extreme condition where iron is in such short supply that erythropoiesis is failing and anemia has resulted.[4,7]

One unknown, but critically important aspect of perinatal iron deficiency involves the issue of iron-limited *neurodevelopmental impairment*. Specifically, exactly when during the spectrum of worsening iron deficiency does a human fetus or newborn infant begin to have inadequate iron to support normal neurodevelopment? Does this point occur only once iron deficiency *anemia* has developed, or is the fetus/neonate at risk when biochemical iron deficiency or iron-limited erythropoiesis has occurred? Although more work must be done to define this clearly in humans, animal experimentation suggests that once iron-limited erythropoiesis is present, impaired neurodevelopment has already occurred.[8–10]

The Iron Endowment at Birth

The *iron endowment* is a concept for the sum of all the iron a newborn baby has at birth. This includes all the iron in storage, such as that in ferritin and hemosiderin, plus the iron within heme-containing molecules like hemoglobin and myoglobin, plus that in the circulation, generally bound to transferrin, plus that in the hundreds of different iron-containing enzymes and cofactors. In fact, it is estimated that 6–7% of all human enzymes are iron dependent.[11] Obviously, a newborn baby's entire iron endowment is derived from transplacental passage of iron from the mother during gestation. One of the falsehoods previously dogmatically taught was that a fetus, being a parasite, invariably takes sufficient iron from its mother, even at her own peril, so the fetus will be iron sufficient at birth. That statement is not true. Pregnant women who have critically low iron reserves deliver babies who have critically low iron reserves.[12–14] Moreover, some pregnant women have defective mechanisms for transferring iron to her fetus.[15] Also, preterm birth virtually always results in a lower-than-normal iron endowment. Unfortunately, an inadequate iron endowment is not rare, and two common reasons for it are the perennial problem of preterm birth and the relatively new problem of obesity in pregnancy.[16–19]

Relevance of the Perinatal Erythropoietin/Erythroferrone/Hepcidin Axis

Iron deficiency in newborn infants can result in substantial and persistent neurocognitive dysfunction.[1,2,8–10,20,21] Consequently, efforts are needed to prevent or to promptly and adequately treat this deficiency. However, enteral iron supplementation will not always prevent or treat neonatal iron deficiency. In fact, the success of enteral iron dosing depends, in part, on the integrity of the patient's iron homeostatic mechanisms. Those mechanisms are well described in adults, but studies are only beginning in neonates.[22–24]

The iron-regulatory hormonal axis includes erythropoietin (Epo), erythroferrone (ERFE), hepcidin, and ferroportin. In brief (Fig. 1), when Epo binds to cognate receptors on the surface of erythroid progenitors, erythrocytic clonal proliferation occurs. The Epo-stimulated erythroid progenitors rapidly produce ERFE and ERFE blood levels consequently rise.[25] High circulating levels of ERFE suppress hepcidin production by the liver.[26] Elevated hepcidin levels trigger the degradation of ferroportin, the iron exporter that moves iron from the enterocyte or macrophage to plasma, thereby inhibiting the absorption of enteral iron and preventing the mobilization of iron from storage.[12,13] In contrast, low hepcidin levels (seen with high ERFE levels) foster the absorption of enteral iron through ferroportin-mediated iron transport.

Premature Birth Cheats the Iron Endowment

The iron endowment at birth is needed to support development and growth throughout the neonatal period and infancy. A term "neonate" has a relatively high hematocrit at birth that gradually falls over the first weeks following birth, yielding some additional iron bioavailable for early iron needs. An adequate iron endowment plus this extra iron stored in the "excess" erythrocytes typically constitutes a sufficient iron supply despite a relatively iron-poor diet during the first several months of neonate life.[27]

When birth occurs prematurely, the iron endowment is compromised. Premature delivery deprives the fetus of the iron that should be transferred during the final weeks of pregnancy. Since 60–70% of the total body content of iron in a term "fetus" is obtained during the last trimester of pregnancy, premature birth can result in a very low iron endowment. If not made up for in some way, this low endowment may be inadequate to fully support neurodevelopment and other iron-dependent functions over the coming months. At birth preterm neonates generally do not have the high hematocrits typical of term neonates. As shown in Figure 2, the more preterm at birth, the lower the hematocrit will be.[28,29] Moreover, preterm neonates, particularly those who require neonatal intensive care unit (NICU) care, are sometimes subjected to repeated blood testing for clinical management, which further diminishes their iron supply. Since 1 mL of blood typically contains about 0.5 mg of iron, the removal of 30 mL/kg of blood or more, over the first weeks in a NICU, will diminish the iron supply by 25–30%.

The Epidemic of Obesity and its Effects on Maternal and Fetal Iron

The widespread consumption of a "western style" diet, plus a sedentary lifestyle, is leading to a global epidemic of obesity.[30,31]

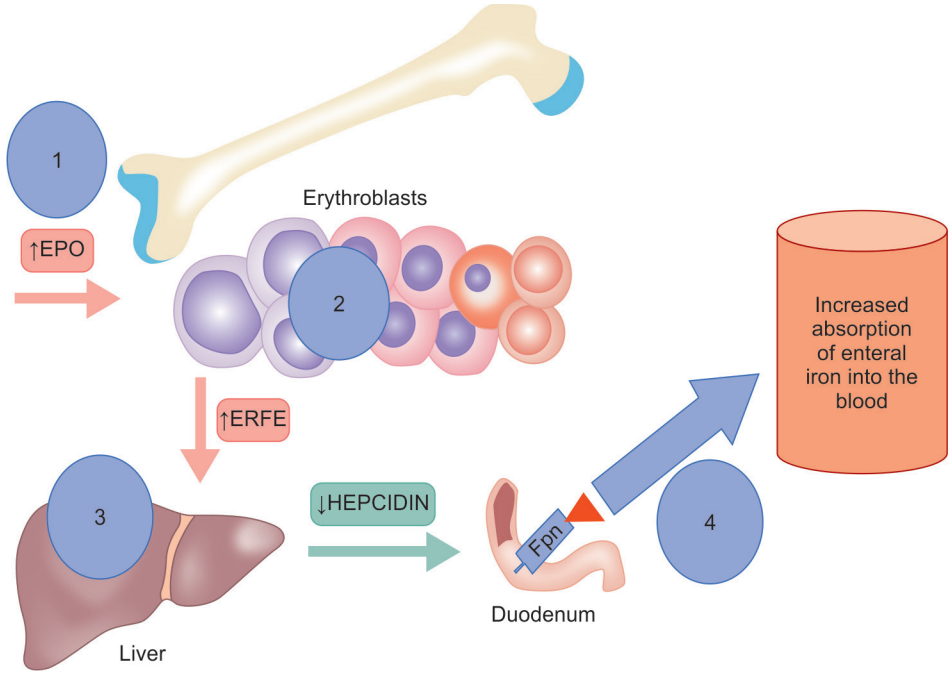

Fig. 1: The erythropoietin axis. Schematic representation of the erythropoietin (EPO), erythroferrone (ERFE), hepcidin, and ferroportin (Fpn) axis, as it pertains to the regulation of intestinal iron absorption. (1) High EPO levels; (2) Stimulate erythroblasts to produce ERFE; (3) High ERFE levels reduce hepcidin production in the liver; (4) Low hepcidin levels facilitate the absorption of enteral iron through ferroportin[24]

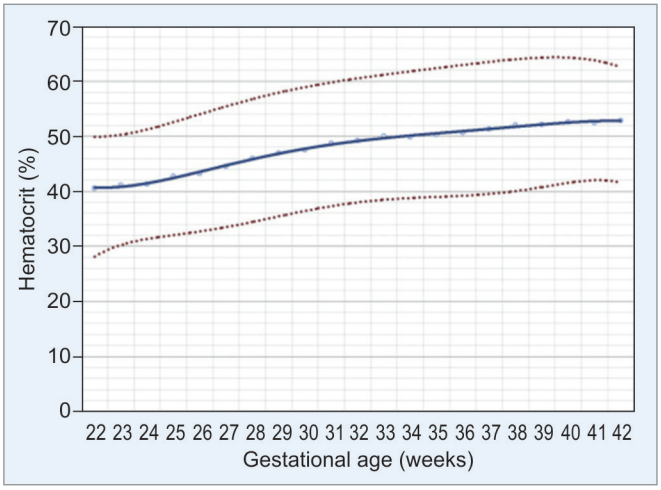

Fig. 2: Hematocrit on the day of birth according to gestational age, from 22 to 42 weeks. The figure was produced using over 350,000 hematocrit values from Intermountain Healthcare. The lower and upper dotted lines represent the lower reference interval (5th percentile) and the upper reference interval (95th percentile), and the middle solid line is the median[28,29]

Iron deficiency is particularly frequent in obese patients, as a result of adiposity-associated inflammation, and the consequent high blood levels of hepcidin.[32,33] During healthy pregnancy, maternal hepcidin levels are low, which is essential to increase the absorption of iron from the maternal diet, and to mobilize iron from maternal storage sites to produce the hemoglobin needed for increasing maternal red blood mass during pregnancy, and for the iron needed for the fetus. As shown in Figure 3, high maternal levels of hepcidin bind to ferroportin on syncytiotrophoblasts, thereby blocking maternal-to-fetal iron transfer. Consequently, high levels of hepcidin can interfere with maternal absorption of dietary iron and also block the transfer of maternal iron to the fetus.[23]

Phillips et al. demonstrated that women with a pre-pregnancy body mass index ≥30 kg/m^2, or excessive gestational weight gain, delivered offspring with lower serum ferritin concentrations, compared to non-obese women or those without excessive gestational weight gain.[16] Recent studies in pregnant animal models suggest that maternal hepcidin levels determine embryo iron endowment. Specifically, Sangkhae et al. showed that higher levels of maternal hepcidin caused maternal iron restriction, resulting in lower embryo weight, increased incidence of embryo anemia, and increased embryo mortality.[23] These observations support the idea that obesity, through the mechanism of elevated hepcidin levels, can render fetuses at risk of reduced iron delivery.

Iron Lack and Perinatal Brain Development

Iron plays an important role in many neurodevelopmental processes, and animal studies indicate that iron sufficiency in pregnancy and infancy is particularly important for neurodevelopment.[34] Even so, many questions remain regarding how iron deficiency in the human fetus and neonate impacts neurodevelopment, and how the timing and severity of the iron lack result in subsequent specific developmental problems. Available studies support improved neurodevelopmental outcomes with either iron supplementation or delayed umbilical cord clamping at birth, which is associated with a larger iron endowment.[35] However, it is not clear, from human studies, whether a prompt and effective treatment of perinatal iron deficiency completely reverses the adverse neurodevelopmental effects of iron lack.[36]

It is clear that iron sufficiency during the neonatal period is important for erythropoiesis, mitochondrial respiration, nucleic acid replication, and immune function.[37] Iron sufficiency is particularly

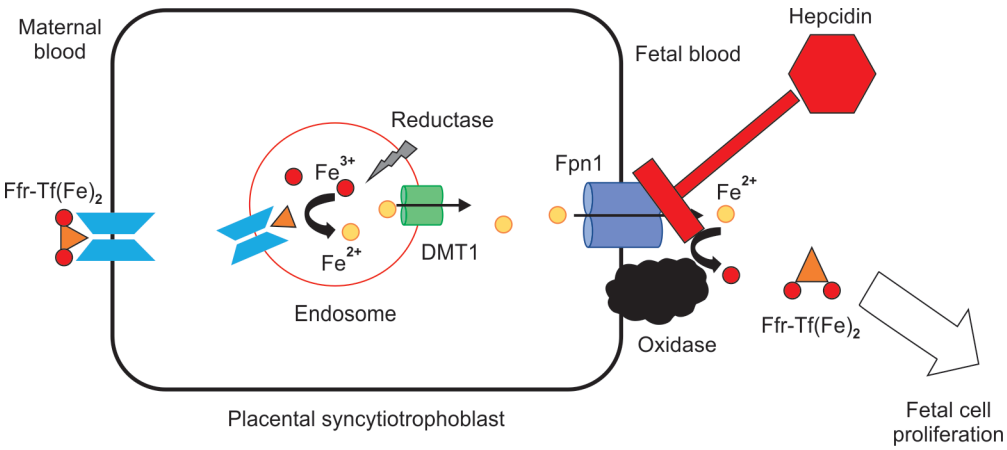

Fig. 3: Placental Iron Transport. Maternal iron is delivered to the placenta by transferrin (Tf)-mediated endocytosis. Iron is released from an intracellular compartment by divalent metal transport (DMT1). Iron can then be stored as ferritin or utilized for heme synthesis in the placental cells. Iron is transported out of the placental cells by ferroportin (Fpn1) providing iron to fetal Tf for delivery throughout the fetus. However, high levels of hepcidin will block the movement of iron from the syncytiotrophoblast into the fetal circulation

crucial for neonates receiving treatment with recombinant erythropoietin because inadequate iron availability during accelerated erythropoiesis can deplete iron stores and precipitate multiorgan iron deficiency.[38,39] Moreover, due to the prioritization of iron stores to support erythropoiesis over the iron needs of other organs, it is possible that even moderate iron limitation could result in deficient brain iron.[40] Neonatal animal models suggest that deficient brain iron can cause neurological damage that persists even after the iron deficiency is corrected.[8,10,20,34,41] Consequently, avoiding iron deficiency in neonates who are receiving erythropoietin treatment is an important facet of assuring their optimal neurodevelopment.

Developing Practical Ways to Identify Neonatal Iron Deficiency

As a screening method to detect neonatal/infant iron deficiency, measuring the hematocrit or blood hemoglobin level will not do. Why? Because, by the time iron deficiency has caused neonatal *anemia*, iron-deficient *neurodevelopmental damage* has probably already occurred.[1,8,40] Thus, screening for iron deficiency by looking for anemia is like closing the barn door after the horse already escaped. The basis for the insensitivity of anemia as a screen for iron deficiency is due to the natural prioritization of iron trafficking to support erythropoiesis above the priority to support normal neurodevelopment.[40] Perhaps nature decided that when iron deficiency is present, it is better for the baby to be alive with some degree of neurodevelopmental impairment than to be dead from severe anemia with an intact brain.

Iron deficiency can be confirmed in neonates in a sophisticated but expensive battery of tests, including serum iron, transferrin, transferrin saturation, serum ferritin, soluble transferrin receptor, zinc protoporphyrin-to-heme ratio, Micro-R and HYPO-He values, and reticulocyte hemoglobin content (RET-He).[6,42] However, the large volume of blood required and the costs of the combined tests dictate that typically just one screening test is used. Serum ferritin might be the most common single test for assessing iron sufficiency in NICU patients; however, serum ferritin has the disadvantage that it requires phlebotomy, and some clinical laboratories require 1 mL of serum for ferritin testing. Moreover, the serum ferritin can be artifactually elevated by inflammation, rendering the test less informative during inflammatory states, which are not uncommon in NICU patients. Non-invasive tests for iron status, such as urine ferritin, have inherent advantages over serum-based testing, but might also be flawed by artifactually elevated urinary ferritin levels during inflammation.

Though serum ferritin level is commonly used to screen neonates for iron deficiency,[43] it is not well validated in extremely preterm neonates. A more recent method used to assess iron stores is the RET-He, which measures the hemoglobin within reticulocytes. The RET-He serves as a metric of the iron available for hemoglobin production during the previous several days.[6,7,44] The validity of RET-He as a marker of iron status has been well studied in adult and pediatric patients.[45] However, like ferritin, limited data validate RET-He as a marker of iron status in preterm neonates.[45–48]

Ishikawa et al. reported that healthy adults in Japan had urine ferritin levels about 5% of their serum ferritin levels, with a correlation coefficient of 0.79.[49] On that basis, we speculated that measuring urinary ferritin might be a useful non-invasive way to screen NICU patients for iron deficiency. Specifically, we hypothesized that a low concentration of ferritin in the urine might identify neonates who are iron deficient. In a pilot study, we measured paired serum/urine ferritin from healthy adults, healthy term neonates, growing preterm neonates, and children with very high serum ferritin levels from liver disorders or iron overload.[50] In that study, we detected ferritin in every urine sample and found a correlation with serum ferritin (correlation coefficient 0.78). Those findings led us to further evaluate urinary ferritin as a potential screen for iron deficiency.

In a subsequent study, we found[51] (1) that it was highly feasible to obtain urine samples from NICU patients; (2) ferritin was measurable in every urine sample collected, with the same laboratory method used for measuring serum ferritin; (3) dividing the urinary ferritin concentration by the urinary creatinine improved the correlation with serum ferritin; (4) a low urine ferritin (either <10 ng/mL or <12 ng/mL) performed well statistically in identifying iron-limited erythropoiesis; and (5) some affirmation of the association between maternal obesity and neonatal iron deficiency. These findings encourage us to pursue using urine to assess a neonate's iron status, without phlebotomy. Such monitoring is particularly relevant

among NICU patients receiving erythropoiesis-stimulating factors, because of the potential to cause iron-limited neurodevelopmental delay if their iron supplementation is inadequate.

New, inexpensive, rapid, reliable, and non-invasive means are needed to identify iron deficiency in neonates. Urinary methods are particularly attractive, especially if they could be as simple as a dip-stick method.[49–51] Other creative potential methods might involve testing saliva.

Developing More Effective Treatments for Neonatal Iron Deficiency

Advances are needed to generate enteral iron preparations for neonates that are better absorbed and have fewer adverse effects. In most investigations, neonates seem to tolerate ferrous sulfate fairly well, but just as in older children and adults, constipation and other gastrointestinal symptoms (e.g., emesis) have been reported.[52] In one of our studies of iron dosing in a multihospital collaborative group, we did not find emesis to be a common problem in preterm neonates receiving ferrous sulfate as early as 10–14 days after birth.[44] In adults with iron deficiency, vitamin C given along with the enteral iron improves the iron absorption.[53] This has not been formally investigated in neonates but should be. Also, other preparations of enteral iron should be tested in neonates, looking for better absorption, fewer adverse effects, lower costs for large underserved populations, and greater effectiveness.

Some iron-deficient neonates seem to require very high doses of enteral iron in order to increase their serum ferritin or RET-He levels.[38] Perhaps some of this refractoriness is on the basis of high hepcidin levels accompanying inflammatory conditions.[54] This theory is consistent with one of our pilot studies.[44] Identifying iron-deficient neonates who have high hepcidin levels, or who have other mechanisms causing refractoriness to enteral iron treatment, could permit the use of intravenous iron for those unlikely to respond to high enteral dosing. Clearly, new oral preparations of iron and also improvements in intravenous iron administration are needed for neonates as are better non-invasive means of monitoring the efficacy of iron treatment, as are ways to make these improvements practical and inexpensive.[55]

Studies in infant rhesus monkeys, classified as iron deficient on the basis of hematological values, affirm the importance of iron for normal brain development.[56] Neuroimaging studies indicated that a history of iron deficiency was associated with smaller total brain volumes, primarily due to significantly less total gray matter. These brain differences were evident even after iron treatment and recovery from the iron-deficiency anemia. These experiments highlight the importance of early detection and preemptive supplementation to limit the neural consequences of neonatal iron deficiency.

Global Rewards for Doing this Better

Posit 1: Iron deficiency during the neonatal period results in an average diminution in the adult IQ of five points. The truth here is unknown. However, in one study, the mean IQ of iron-deficient children was 91.5 ± 2.3 compared to 97.5 ± 3.2 in controls.[57] Individual readers can decide whether they believe the assumption in Posit 1 is plausible or not. We submit it is reasonable, or perhaps even an underestimate of the harm that iron deficiency during that critical period of neurodevelopment can produce.

Posit 2: At least 10% of the world's population have had iron deficiency during their neonatal period. Although we know of no clear data, the world health organization (WHO) estimates that 80 percent of the world's population has insufficient iron and that 30 percent have iron deficiency anemia.[58] So what do you think about Posit 2? Plausible or not?

Posit 3: Prevention, or timely detection and treatment, of neonatal iron deficiency will avert a 5-point IQ drop. If you think all three posits are ridiculous, you can stop reading this section, because you will not agree with the Results and Conclusions below. However, if you think these assumptions are at least theoretical possibilities with some merit, keep reading.

Result 1: About 790 million people alive today (10% of the world's population as of May 2021) each have five fewer IQ points than they "should have" on the basis that they had neonatal iron deficiency. Thus, the world's population right now has 3,950,000 fewer IQ points because of neonatal iron deficiency.

Result 2: Each one-point increase in IQ is associated with $500 more income per year. A report on global economy and intelligence, published in 2016, calculated that one IQ point is associated with measurably higher adult productivity, wages, and capital and that this is the case for individuals in poor and rich countries.[59] In the USA, one IQ point was associated with a $500/year higher income.

Conclusion

If these estimates are even somewhat close to accurate, prevention or timely treatment of neonatal iron deficiency would enrich the world by a minimum of 2 trillion dollars every year. However, having more money and a higher gross world product are not the only reasons we should work to eliminate neonatal iron deficiency. Might *you* have had iron deficiency as a neonate? How would *you* like to have five more IQ points? How would their quality of life be enriched if the people you know with a low IQ had five more points each?

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