Does Iron Deficiency Cause Low Birth Weight, Prematurity, Anemia, and Mortality in Early Infancy?

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Observational studies over the past 30 years document a strong association between maternal anemia and birth outcomes such as low birth weight (LBW), prematurity, infant anemia, and mortality for either mother or infant. There is a consistent U-shaped curve relating maternal Hb to these outcome measures. High Hb in the second or third trimester likely reflects a failure of proper expansion of the maternal plasma volume while a low Hb may reflect both abnormal volume expansion and/or Hb production. The true proportion of anemia due to iron deficiency in most studies is unknown so the attribution of iron deficiency to these outcomes is speculative. The timing, during pregnancy, of maternal iron status evaluation is critical to determining if there is a ‘causal’ relationship between iron nutriture, anemia, and maternal and infant outcomes. Biologically feasible concepts include increased mortality due to poor immune functioning, improper neonatal growth and development secondary to anemia and poor placental delivery of iron to the fetus, insufficient iron for proper hormonal and neuronal regulation of pregnancy, and poor oxygenation of the fetal tissues when maternal anemia is quite severe. LBW is a strong predictor of mortality and LBW babies are at greater risk of developing anemia during infancy. Other recent studies demonstrate that low plasma ferritin at birth is related to poorer cognitive development of the child at 5 years of age. Insufficient delivery of iron to developing brain tissue is a feasible explanation for this relationship. Associations of maternal iron status and anemia with maternal and fetal outcomes do exist but plausible biological ‘causal’ linkages are lacking in most cases.
Iron Balance in Pregnancy

Iron deficiency continues to be a leading cause of anemia in many parts of the world despite significant efforts over the past 3 decades to eradicate this nutrient deficiency disorder [1]. The burden of iron deficiency is especially profound during the periods of high iron requirements during pregnancy and early infant growth and development. The estimated prevalence of iron deficiency in pregnancy varies from 30% in industrialized countries to >60% in other less developed parts of the world. The disparity likely represents a myriad of effects of access to health care, dietary quality and quantity, and reproductive frequency. There is little evidence that racial/genetic backgrounds significantly impinge on the relationship of iron deficiency anemia and pregnancy outcomes.

Iron requirements increase quite dramatically during pregnancy for expansion of the maternal blood volume, placental growth, and fetal growth. Quantitatively, these requirements change from <1 mg Fe/day in a reproductive age female to a median requirement of 4.6 mg Fe/day and a 90th percentile requirement of nearly 6.75 mg Fe/day by the third trimester [2]. Maternal iron stores are usually limited in women and the capacity to increase the efficiency of absorption of dietary iron appears to maximize at around 40% for non-heme iron in the second trimester. Given the fact that there are limited stores and an upper limit to dietary intake, iron balance is very difficult to maintain. When there is insufficient dietary and reserve iron to meet the demands, essential body iron from maternal pools are sacrificed with a resulting maternal iron deficiency. The adaptive responses in placental transfer of iron with severe iron deficiency includes upregulation of placental ferritin receptors and presumably an increase in placental-fetal transfer of iron [3, 4]. Chorionic somatotropin levels are correlated with transferrin levels in anemic mothers, but not in non-anemic mothers suggesting this placental trophic hormone could play a role in this adaptive process [5]. Animal models of the direct effects of iron deficiency on placental adaptation document that tumor necrosis factor-α levels are significantly increased [6].

What Are the Consequences of This Negative Iron Balance?

The consequences of depletion of the essential body pools of iron include anemia, altered neuroendocrine metabolism, altered energy metabolism, depressed immune functioning, and changes in behavior and cognition [7]. To date, the impact of each of these ‘consequences’ on maternal and fetal survival, fetal growth, and postnatal development have not been examined. Thus a ‘causal’ role for tissue iron deficiency, apart from anemia is nearly impossible to ascertain at this time. Allen [8] reviewed some possible biologically feasible routes of impact of iron deficiency on pregnancy outcomes in her recent review, but there is little new data to support or reject these hypotheses. The
possible causal routes considered included direct and indirect effects of anemic hypoxia, placental delivery of iron, and alterations in hormonal control of pregnancy due to alterations in the stress – hypothalamic-pituitary-adrenal axis system [8]. The possibilities of causal effects due to altered renal control of blood volume through neural regulation of the renal perfusion and altered cellular metabolic activity due to mitochondrial insufficiency of iron-dependent respiration are also distinct routes of investigation.

**The Relationship of Maternal Anemia to Birth Outcomes**

Several recent conferences have had significant discussions regarding the relationship of maternal anemia to birth outcomes [8–11]. These analyses include relationships to maternal mortality, fetal mortality, fetal growth retardation, pregnancy complications, and a small amount on infant growth. The fundamental conclusions of those authors will not be contested in this brief review of the literature but will be summarized with the very recent observations since those reviews will be presented. As will become obvious with this review, a vast majority of studies on anemia and pregnancy outcome have focussed on anemia and not clear documentation of iron status. In those studies that do measure iron status (with ferritin, transferrin saturation (TSAT), etc.) there is frequently a problem of timing during pregnancy for the collection of the sample. Thus, the assurance that relationships between anemia and pregnancy and iron deficiency anemia and pregnancy outcome are identical cannot be reached.

**Anemia and Birth Weight, Gestational Age, and Infant Mortality**

Most reviewers of the scientific literature will agree that there is a U-shaped curve relationship between the maternal hemoglobin concentration and the proportion of LBW infants [8–11]. The cause of the elevation in prevalence of LBW infants at the upper end of the distribution of Hb is believed to be improper expansion of the maternal plasma volume [12] while insufficient erythropoiesis and poor volume expansion may be associated with the low Hb concentrations at the other end of the distribution curve. The optimal maternal Hb for minimal incidence of LBW varies in the published literature (table 1). As the guideline suggested by the WHO for defining anemia in pregnancy (100 g/l) is usually above these values, it is possible to view these optimal Hb concentrations as being erroneous. The hemoglobin concentration, and the definition of ‘anemia’ are trimester dependent with a clear nadir of concentration in mid gestation. Since many of these studies did not use finite times of sampling the variations may well reflect the timing of sampling and not true discrepancies in the relationship of data to outcomes [10].
The severity of anemia appears to be an additional factor associated with an increased risk of LBW and prematurity with severe anemia (Hb <80 g/l) having a median risk of 4.9 across these 6 studies and moderate anemia having a median risk of approximately 2.0. The causes of anemia were not known in most studies thus the contribution of iron deficiency anemia cannot be evaluated. In a study of pregnancy outcome where malaria is endemic, Verhoeff et al. [18] reported a relative risk (RR) of 1.6 for intrauterine growth retardation if maternal Hb was <80 g/l at booking compared to a RR of 1.4 (not significant) if moderate anemia was present at delivery. Interestingly, the prevalence of anemia decreased from 23.6 to 11.4% between booking and delivery. In this study of 1,423 live-born singleton births in rural Malawi there was no benefit of iron-folate administration during pregnancy on intrauterine growth retardation. The authors did observe, however, a significant reduction in the prevalence of prematurity with micronutrient supplementation. In contrast, malaria intervention, even in mid gestation was effective in promoting fetal growth.

**Maternal Anemia and Mortality**

Maternal mortality is correlated with the severity of severe anemia in pregnancy [19]. In his review of reports from 1950 to 1999 Rush, [19] examined
the relationship of maternal anemia, usually at delivery, with both antepartum and postpartum death. He arrived at the conclusion that severe anemia (Hb 6–7 g/l or Hct 0.14–0.25) is associated with an increased rate of maternal death (table 2). In very severe anemia the death rate may be as high as 20, greater than the comparison group of minimum mortality [20]. While no causal relationships between iron deficiency anemia and mortality have been demonstrated in these studies, there is a reproducible observation of an association.

What Is the Relationship Iron Deficiency Anemia to Pregnancy Outcomes?

Maternal iron stores in pregnancy will decline rapidly in the first trimester to mid pregnancy resulting in an alteration in sensitivity of measures to maternal iron status; that is, ferritin will work well before 10–14 weeks and will become ‘insensitive’ thereafter [26]. Only in the past decade have investigators begun to utilize a battery of assessment parameters to document iron deficiency. Given the known biology of iron requirements during pregnancy, it is predictable that measures of iron deficiency erythropoiesis (transferrin receptor (TfR), zinc protoporphyrin (ZPP), TSAT) become more useful by the second trimester as there is less and less adequate iron delivery to bone marrow. Plasma or serum ferritin is no longer useful in the majority of pregnant women beyond the first trimester [3]. Thus the strength of association of ‘iron status’ to pregnancy outcome can realistically utilize ferritin, TfR, ZPP, and TSAT in the first trimester, and is reduced to utilizing

Table 2. Maternal mortality and severity of maternal anemia

<table>
<thead>
<tr>
<th>Severity of anemia</th>
<th>Range of relative risks</th>
<th>Country of study and sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or unknown severity of anemia (Hct 0.25–0.29)</td>
<td>0–3.84</td>
<td>Lampur [21], n = 73,048 Nigeria [20], n = 19,217 Indonesia [22], n = 36,062 Guinea [23], n = 13,191 Punjab [24], n = 35,565 Malawi [25], n = 3,740</td>
</tr>
<tr>
<td>Severe anemia (Hct 0.14–0.25)</td>
<td>1.05–5.9</td>
<td>Lampur Nigeria Indonesia Punjab Malawi</td>
</tr>
<tr>
<td>Very severe anemia (Hct &lt;0.14)</td>
<td>1.34–20</td>
<td>Nigeria [20]</td>
</tr>
</tbody>
</table>
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TfR, ZPP, and TSAT in the second and third trimesters (and ferritin in a small percentage of pregnancies). In addition, authors need to have sufficient sample size of non-iron-deficient anemic and iron-deficient anemic pregnancies to conclude an effect of iron deficiency apart from anemia. Being cognizant of this biology, separate research groups have computed RRs for the impact of iron deficiency anemia on pregnancy complications while controlling for other causes of anemia [11, 18, 27]. In a study in Camden, N.J., Scholl and Hediger [27] showed that iron deficiency anemia in the first trimester was more strongly related to prematurity and LBW (RR = 3.1) than anemia of any cause later in pregnancy. They concluded from this that iron deficiency in the first trimester was important but anemia at other times had little effect. In a study in Malawi, Verhoeff et al. [18] collected samples early in pregnancy and also at mid gestation. In their evaluation within the context of coexistence of anemia associated with malaria, they observed an RR of 6.0 for LBW of iron deficiency early in pregnancy but not in late pregnancy. A third study measured iron status in Chinese mothers very early pregnancy (<8 weeks) and observed that moderate iron deficiency anemia conferred a RR of 2.96 for prematurity and LBW [16]. These three studies, taken together, suggest that iron deficiency anemia has a similar impact on fetal growth and development as does anemia in general.

Is Ferritin a Good Indicator of ‘Risk’ for Complications?

The utility of ferritin as an indicator of maternal iron stores loses sensitivity by the middle of the second trimester and has little sensitivity as a predictor of poor fetal outcomes as a result [28]. Several studies have now observed a relationship of elevated ferritin with preterm birth, LBW, and also preeclampsia [28–31]. Higher ferritin concentrations may be more an indication of upper genital tract infection and a subsequent development of spontaneous preterm delivery. For example: Lao et al. [31] recently reported on an analysis of birth outcomes for 488 non-anemic women. They observed a significant inverse relationship between maternal ferritin quartiles and infant birth weight with an increased risk of prematurity and neonatal asphyxia in those mothers with the highest quartile of ferritin. Tamura et al. [30, 32] observed a similar relationship in an analysis of the Preterm Prediction Study of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units network conducted from 1992 to 1996. Regardless of the gestational age at sampling (19, 26 and 36 weeks), ferritin in the highest quartile was associated with the lower mean birth weights than those in the other three quartiles of ferritin. The adjusted odds ratio was significant, however only at the 26-week sample with an odds ratio of 2.0 for premature delivery and 2.7 for small birth weight (<1,500 g). The 2002 follow-up analysis utilized cervical ferritin concentrations at 22–24 weeks of gestation and
showed an adjusted odds ratio of very premature delivery (<32 weeks) to be as high as 6.3. There was a strong correlation with other markers of inflammation from cervical fluid. These studies suggest that elevations of ferritin in mid gestation increase the risk for pregnancy complications.

**Are There Relationships of Maternal Iron Status to Other Fetal Outcome Measures?**

*Infant Development*

There are other associations between maternal ferritin and fetal and infant outcomes: 278 children of 5 years of age were studied for psychometric evaluations as a function of their cord blood ferritin values obtained at birth [33]. The children were compared by their cord blood ferritin in the two median ferritin quartiles: those in the lowest quartile scored lower on a number of tests including language ability, fine motor skills, and tractability. Since cord blood ferritin is correlated with maternal iron status, these data suggest that poor iron status at birth is related to later infant development. The intervention study of Presozio et al. [34] reached a similar conclusion regarding the benefit of iron supplementation in pregnancy on infant scores in tests of motor and mental development at 12 months of age. Research in South Africa contributes to this point [35]. In an intervention study with more than 150 iron-deficient anemic and non-anemic mothers, the authors observed that infants of iron-deficient anemic mothers had lower developmental scores, assessed with the Griffith scale at 9 months of age, than infants of mothers who were not anemic. All infants in this study were of full gestational age and weight, thus intrauterine growth failure was excluded. All severe maternal anemia (<85 g/l) was excluded. These authors also bring forward an interesting concept regarding postnatal maternal anemia and infant development: is it possible that iron deficiency during lactation alters maternal behavior and results in a change in infant development? These anemic mothers had increased amounts of depression and altered mother–child interactions compared to iron-supplemented mothers. While our focus in the past has been on biological roles of iron on infant development these observations suggest that other pathways also exist.

*Infant Iron Status*

A recent small Canadian study of 75 moderately anemic mothers showed a highly significant correlation between maternal Hb in the third trimester with the infant Hb at 9 months of age [36]. In contrast, a recent report from Amman, Jordan, with 232 infants followed for 1 year after birth had such high prevalence rates of infant anemia, >70%, that it was impossible to determine a strength of association of infant anemia with maternal iron status. The authors did determine that there was about 40% more anemia in the infants
of anemic mothers at 12 months of age than in the infants of non-anemic mothers [37]. In Mexico, there were high prevalence rates of maternal anemia, >85%, but the prevalence of infant anemia was only 7.5% in the neonates [38]. This weak relationship at birth and a stronger relationship over the ensuing 12 months of life, are recent examples of the concept that iron-depleted and moderately anemic mothers provide sufficient delivery of iron for infant growth and erythropoiesis in utero, but fail to provide sufficient iron for normal growth and development over the next 12 months of life.

**Conclusion**

The relationship of iron deficiency anemia to pregnancy outcomes cannot be separated clearly for the relationship of all-cause anemias to outcomes at this time. The recent studies in the past 2 years add small amounts of additional information to the conclusions reached by the recent reviewers of this topic [8–11]. Clearer documentation of iron status now suggests that moderate iron deficiency in pregnancy will have ramifications in infant development at >6 months of age, but only severe anemia will have effects on gestational age, weight, maternal and neonatal mortality.

**References**

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Discussion

**Dr. Sazawal:** The question is: with increasing support for using the transferrin receptor and the realization that it is dependent on erythropoiesis, what is your feeling about using it in malaria areas where there is a faster delivery of red cells, given hemolysis, happening all the time in these conditions?

**Dr. Beard:** That is a very good question. The big advantage of the transferrin receptor is that it is generally not responsive to inflammatory processes, so it is not an acute phase reactive protein. The disadvantage, as I pointed out, is the fact that it is sensitive to anything that drives erythropoiesis. So, if you have a clinical situation in which erythropoietic drive is accelerated, you are going to falsely suggest that iron status is low. I think you need to readjust or reevaluate your cutoff values in that situation. Renal dialysis patients for instance are given erythropoietin as a normal course of treatment, but you cannot use the soluble transferrin receptor as a valuable, reasonable measure, so I think the same situation applies there.

**Dr. West:** Has any work been done on ratio indicators among these individual iron status indicators, ferritin over, transferrin receptor and so forth and try to sort it out?

**Dr. Beard:** What Dr. West is referring to is taking the ratio of transferrin receptor to ferritin and trying to improve its sensitivity. That work has been done and it works reasonably well. It will not necessarily work in pregnancy because in fact the ferritin has reached quite a low plateau value, whereas the transferrin receptor can continue to increase. So I think that perhaps in the second trimester as ferritin is coming down and the soluble transferrin receptor is on the upward slope, it could be a very nice sensitive indicator, and certainly in the first trimester it will work very nicely as well.

**Dr. Verhoef:** We have done some studies on transferrin receptor in malaria and the pattern that seems to emerge is that in asymptomatic malaria there is an increase in transferrin receptor which would be compatible with what Dr. Beard is saying, that there is increased erythropoiesis to compensate fully hemolyzed red blood cells. There seem to be some discrepancies in studies in terms of the effects of acute malaria. Some studies suggest a decrease in transferrin receptor, and this is compatible with a decrease in erythropoiesis which contributes to the anemia observed. So I agree that transferrin receptor malaria is certainly not a good indicator for iron status. It could perhaps be an interesting thing to use on erythropoiesis because there are a lot of questions there on malaria as well, as I indicated.

**Dr. Beard:** If you provide iron supplements in an intervention approach in your malaria populations, are you able to demonstrate that you can knock the transferrin receptor down?

**Dr. Verhoef:** Yes, we have shown that cross-sectionally. We have also shown this prospectively in a trial that we did in children who were originally without infection but then developed an infection. On the other hand we had children who had current or recent infection at baseline and then became negative for malaria. In both cases the pattern seems to be consistent: in the first case as expected transferrin receptor increases, and in the other situation it decreases. So all this supports the idea that it is perhaps a causal relationship. This work will be published shortly. In pregnancy that is now the issue, if you look at some of the studies that have been carried out using transferrin receptor in pregnancy you can see that in the third trimester of pregnancy transferrin receptor levels are almost the same as in nonpregnant women, and if you look at the few papers that have assessed transferrin receptor in early pregnancy, in certainly the first two trimesters you see a considerable decrease in transferrin receptor which seems to corroborate evidence that erythropoiesis is actually suppressed during the first two trimesters of pregnancy. Therefore I think that also in the first two trimesters you probably can’t use it, perhaps you could use it...
in the third trimester, but I think that some more work needs to be done to validate this.

**Dr. Young:** You indicated that Dr. Allen’s stress response hypothesis remains viable. Yet the cortisol findings, as I judge them, don’t seem to provide any strong support for the hypothesis. What needs to be done in order to either validate or invalidate this hypothesis?

**Dr. Beard:** The limitation to our study is that our institutional review board for the use of human subjects on campus requires that if we detect any hemoglobins under 10.5 we need to treat and not to include these subjects in the study. As you saw from table 1 in terms of birth outcomes, in almost all cases the hemoglobin concentration at which the strongest relationship was seen, was less than that. I think that in order to really test Dr. Allen’s hypothesis, one would have to do the cortisol work in populations in which you would be able to find mothers in the first trimester, that is where the action really is, and do not only baseline cortisols but the stress response, the area-under-the-curve response, and give them a stimulus. We gave them a string of numbers which they had to recite forward and backward, and that was enough of a stress to get a corticotropin-releasing hormone, adrenocorticotropic hormone and cortisol response. It doesn’t have to be anything too fancy to do it. We evaluated the salivary cortisol. I was one of the first people to publish a paper on salivary cortisol and I am not particularly enamored by it. That is because so much of that capability is dependent on how you collect spit. There are a lot of tricks to collecting saliva and if you don’t do it the same way as somebody else did it, you are going to come up with very different numbers.

**Dr. Allen:** The Centers for Disease Control and Prevention [1] did a very nice randomized control study of iron supplementation in non-anemic pregnant women in the United States. They found that the women to whom they gave 30 mg iron/day, starting in the middle of the pregnancy for about 8 weeks, produced infants that averaged 206 g heavier than controls. The prevalence of low birth weight was reduced from 17 to 4%. This is an excellent trial. Of course many of these women became iron-deficient during pregnancy even if they were not when they started the study, but having no iron-deficient women at baseline enabled them to justify the randomized controlled trial. This is the sort of innovative design that I think could be used by more investigators.

**Dr. Beard:** I think that is a very good idea. I think when we talk more about psychomotor things tomorrow, it is important to realize that nearly all those studies that will be addressed were done in full-term otherwise healthy infants at anywhere between 12 and 18 months of age, and the authors in nearly all of those studies purposely excluded infants that were small-for-gestational age or premature or had any other risk factors for poor fetal growth. So in fact what we don’t know and one of the huge holes in the literature right now, is what is the impact of maternal iron deficiency, intrauterine iron deficiency on mental growth and the later functioning. We have really excluded that unfortunately. So the point here is that while we have every indication to think that there are irreversible changes associated with iron deficiency somewhere in the first year and half of life, we mustn’t automatically exclude from your thinking that iron deficiency in the fetal period is not sensitive to abnormalities in brain functioning and development. I think much of the story that you heard about iodine, could also be the same for iron deficiency and brain development.

**Dr. Christian:** I think it was in the 2nd or 3rd slide of your presentation in which you showed that plasma volume expansion is higher among women who are supplemented with iron compared to those who don’t receive iron, suggesting that iron supplementation increases plasma volume expansion. Do you think that could be one of the reasons why there is masking of an increase in hemoglobin concentrations
related to iron supplementation and that we are not able to demonstrate larger increases with studies that have been done previously?

Dr. Beard: That is an interesting idea. I suspect it is still viable that you can give additional iron, but you don't know where it goes and you don't really see a change in hemoglobin concentration. You assume that the intervention didn't work, when in fact you really did have a positive benefit in terms of blood volume expansion. The problem, of course, is how you really measure blood volume expansion in a reasonable fashion, and certainly doing it in field trials would be very difficult.

Dr. Christian: What was the reference for those data?

Dr. Beard: I will get it for you.

Dr. Azizi: I was very interested to see your data on the thyroid, ferritin deficiency or iron deficiency and the effect on the thyroid hormones. Iron is a very interesting element for the thyroid and the metabolism of thyroid hormones because iodine is working through many of the enzymes and into peroxidase in the thyroid. Animal studies [2, 3] actually show that you can have problems with thyroxine and triiodothyronine, and increase thyroid-stimulating hormone (TSH) in some animals that have severe iron deficiency. Actually in the human this is not really the case. There are studies showing the relationship between iodine and iron from Zimmermann et al. [4–7] in Switzerland. They show that when iodine is supplemented in iodine deficiency, those who have iron deficiency actually do not respond as well. Recently in a cross-sectional study in school children in Iran, we have also shown that there is a relationship between those who have low ferritin and high goiter prevalence: the goiter prevalence increases in those who actually have low ferritin. I was wondering if there is any influence on iron or the interrelationship between iron and iodine or thyroid hormone in the first 6 months of life?

Dr. Beard: We were the ones that did all those animal studies on iron deficiency and thyroid metabolism back when I was interested in temperature regulation. We published a human study in 1991 [8] in which iron-deficient women were placed in cold water for about 1 h. We studied the metabolic and also the thyroid hormone responses to this, and found that the subjects were sluggish and their metabolic response ability to upregulate thyroid hormone was less than that of body weight-matched and control subjects. I was thinking that we now have some clue as to how it might work, and this is why I think in pregnancy it is an issue. One of the key neurotropic regulators of the thyroid response is going to be dopamine. So in situations of high extracellular dopamine there is suppression of thyrotropin-releasing hormone (TRH) release and of course regulation of TSH and so on. It is quite clear in the animal literature that iron-deficient rats have an elevation in extracellular dopamine. There is a defect in the dopamine transporter and what happens then is that extracellular dopamine is likely to be elevated in the hypothalamic region that controls TRH secretion. So if I were to do the experiment now and I could actually image hypothalamic TRH secretion, my suggestion would be that it is a dopamine-based abnormality, as well as what you suggest is thyroid peroxidase in the thyroid gland itself, I think that the data are quite clear.

Dr. Al Awar: In our areas in Middle East we have to consider that anemia is quite commonly due to the chronic hemoglobinopathy, and many women who have anemia either before or during pregnancy are at thalassemic risk. Now if iron supplements are given routinely to these women before or during pregnancy, they actually become overloaded with iron. The same will apply to their infants. My other question, does anemia due to causes other than iron deficiency have the same sequels? Are there any studies showing that in those cases it would have the same sequels as iron deficiency anemia?

Dr. Beard: You have a very good point about the thalassemia threat and that certainly is something that one needs to be conscious of. Whether or not there are
effects of anemia that are quite clear relative to functioning: there are, but I don’t know that they are very well explored. There are a lot of anecdotal observations in the clinical literature about lethargy, about poor performance in a number of different dimensions [9] but I don’t think we can describe the biochemical abnormalities. Whether or not anemia itself is responsible for the things that we know happen in pregnancy, in newborns and in iron-deficient anemic adults is unknown. I think we are often mistaken in trying to say something is due to tissue iron deficiency versus anemia. In reality we need to think about it as a continuum of the deficiency state. It is very unusual for somebody to be truly iron-deficient without having some aspects of anemia. They may actually be far below the cutoff value, and yet they may have insufficient oxygen transport. I am sorry it is not a complete answer for you.

**Dr. Young:** I just recall that there is a protein called hypoxia factor, is that correct? What happens to that in anemic states?

**Dr. Beard:** There are a number of hypoxia-inducible factors, these are transcription factors that modify the transcription of a number of proteins, specifically in the gut. They upregulate iron absorption by upregulating the amount of two of the key iron uptake proteins called divalent metal transporter-1 and metal transporter protein-1. These are two proteins that are responsible for taking iron into the enterocyte and exporting it from the enterocyte, and they are responsive to hypoxia. If we did an absorption study at a high altitude, one of the first things that would be noticed is that iron absorption would be upregulated, independent of the iron status. So there are really two fundamental mechanisms for regulating iron absorption, the hypoxia model and then the whole body iron status regulator model.

**References**