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Maternal, Fetal and Placental Regulation of Placental Iron Trafficking

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Abstract

The human placenta is a highly specialized organ that is responsible for housing, protecting, and nourishing the fetus across gestation. The placenta is essential as it functions among other things as the liver, lungs, and gut while also playing key immunological and endocrine roles.[1] The structure and transport capacity of this temporary organ must evolve as gestation progresses while also adapting to possible alterations in maternal nutrient availability. All nutrients needed by the developing fetus must cross the human placenta. Iron (Fe) is one such nutrient that is both integral to placental function and to successful pregnancy outcomes. Iron deficiency is among the most common nutrient deficiencies globally and pregnant women are particularly vulnerable. Data on the partitioning of Fe between the mother, placenta and fetus are evolving yet many unanswered questions remain. Hepcidin, erythroferrone and erythropoietin are regulatory hormones that are integral to iron homeostasis. The mother, fetus and placenta independently produce these hormones, but the relative function of these hormones varies in each of the maternal, placental, and fetal compartments. This review will summarize basic aspects of Fe physiology in pregnant women and the maternal, fetal, and placental adaptations that occur to maintain Fe homeostasis at this key life stage.

Keywords

placenta; IRE/IRP; ferroportin; transferrin receptor; hepcidin

INTRODUCTION

Iron is the 4th most abundant mineral on the Earth's crust by weight, but it exists in an oxidized form (ferric Fe) that is very poorly absorbed. Poor dietary quality, parasitic infections and low dietary iron bioavailability contribute to Fe deficiency (ID) being among the most common nutrient deficiencies in the world.[2] Pregnant women are particularly vulnerable to ID due to the substantial increase in Fe requirements that occur at this life

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stage.[3] Severe maternal ID limits hemoglobin production and results in Fe deficiency anemia (IDA). It has been estimated that nearly 56.4 million pregnancies worldwide occur in the context of maternal anemia.[2] Maternal anemia increases the risk of adverse birth outcomes and can cause irreversible adverse effects on neurodevelopmental outcomes in the offspring. To help protect body iron stores, humans have no regulatable means of excreting excess Fe once absorbed.[3] In a typical, non-pregnant adult, less than 2 mg of absorbed Fe per day is needed to maintain Fe balance. At least ten times this amount of Fe (20–25 mg) is released into circulation daily from the catabolism of senescent red blood cells.[4] Iron that enters the circulation is used predominantly by bone marrow erythroblasts to support erythropoietic demands. Absorbed Fe that exceeds daily Fe requirements is stored primarily in the liver and spleen but when excess stores are present, Fe can also accumulate in the pancreas, heart, and endocrine organs.[5]

Three regulatory hormones are utilized to coordinately regulate Fe absorption, recycling, storage, and utilization. The first hormone, erythropoietin (EPO), was identified ~50 y ago.[6] Erythropoietin is produced by the kidney in response to hypoxia to stimulate RBC production. Iron utilization increases when EPO is produced to support the increased erythropoietic demands. A second Fe regulatory hormone, hepcidin, was discovered in 2001.[7] Concentrations of this negative Fe regulatory hormone are low to undetectable in those with IDA, concentrations decrease in those with increased erythropoietic drive, and hepcidin production increases in response to inflammation or infection.[8] Hepcidin binds to ferroportin (FPN1), which is both the receptor for hepcidin and the only non-heme Fe export protein in the body. Interactions between hepcidin and ferroportin block Fe release from storage sites and prevent Fe from being exported from the enterocyte into the body.[9] A third regulatory hormone, erythroferrone (ERFE), was identified in 2014 and it functions as an erythroid regulator.[10] ERFE is produced by erythroid tissue in response to elevations in EPO, and ERFE then suppresses hepcidin production by inhibiting bone morphogenic signaling in hepatocytes.[11] When pregnancy occurs, women must make significant adaptations to supply nearly 300 mg of Fe to the fetus and placenta while also supporting expansion of the maternal red blood cell mass. In sum, approximately 1000 mg of Fe are needed to support a typical singleton pregnancy.[12]

PLACENTAL DEVELOPMENT AND IRON TRANSPORT

Histiotrophic Nutrition

Humans have a hemochorial placenta whereby maternal blood is in direct contact with the chorionic epithelium. The human placenta begins to develop 7–9 days post-fertilization when the blastocyst implants in the uterine lining. In normal early placentation, cytotrophoblasts invade the maternal uterine tissues as extravillous trophoblast (EVT). This EVT invades smooth muscle, blood vessels and uterine glands to remodel these structures to support and sustain the early embryo and fetus.[13] In early stages of placentation the maternal spiral arteries are blocked by the EVT, forcing the early embryo to obtain its nutrients and required growth factors from uterine glands via a process known as histiotrophic nutrition.[14] Studies have found that by day 11–12 the syncytiotrophoblast (STB) has direct contact with uterine gland secretions.[15] The STB takes up nutrients

released by the uterine glands (such as glycoproteins) by phagocytosis.[16] Because the placenta is not supplied with maternal blood via the maternal spiral arteries in early gestation, the embryo exists in a relatively hypoxic environment and the majority of metabolism is thought to be anaerobic.[16]

Maternal blood transports Fe primarily in the form of non-heme Fe bound to the plasma protein transferrin (Tf), as di-ferric transferrin. Target tissues such as the STB express transferrin receptor 1 (TfR1) which internalizes di-ferric Tf via receptor-mediated endocytosis. The fetal liver can synthesize Tf as early as 29 days of gestation,[17] and this Fe transport protein is found at high levels in fetal plasma as early as 13–14 weeks of gestation.[18] Few studies to date have evaluated placental Fe trafficking at these early stages of gestation. Limited data on Fe distribution in the first trimester fetus are available from a study of 15 first trimester pregnancies (8–11 weeks of gestation).[19] High concentrations of ferritin were found in the exocoelomic cavity and low concentrations of Tf were found in the coelomic fluid or amniotic fluid leading the authors to conclude that little Tf-bound Fe was utilized by the developing embryo during these early stages of gestation.[18]

Hemotrophic Nutrition

At approximately the 12–13th week of pregnancy, the maternal spiral arteries become fully remodeled and function as low resistance, high-capacity arteries. A failure to appropriately remodel the spiral arteries results in a placenta that is poorly perfused, which may increase the risk of intrauterine growth retardation (IUGR), preterm birth (PTB) or preeclampsia (PE).[14] Once spiral arteries release blood into the intervillous space, nutrients and gases in maternal blood bathe the STB, and the fetus obtains its nutrition directly from the maternal blood supply in a process referred to as hemotrophic nutrition.[14] Because this cell layer is a syncytium, i.e., there are no paracellular spaces, substances must pass through the STB transcellularly.

NET IRON ACCRETION BY THE DEVELOPING FETUS

Some of the only data evaluating the tempo of human fetal Fe acquisition were compiled by Widdowson et al. in the 1950's based on a chemical analysis of 13 immature fetuses and 6 full term, stillborn infants.[20] Her data are reproduced below (Figure 1). The human fetus weighs approximately 1,100 grams at the end of the second trimester of pregnancy but its weight more than triples to approximately 3,500 g by term.[21] Relating stage of gestation to Fe accretion, less than one-third of total fetal Fe is accumulated by the end of the second trimester, leaving >70% of the total Fe endowment of the fetus to be accumulated over the last 90 days of gestation.

IRON TRAFFICKING ACROSS THE PLACENTA

All Fe trafficking across the STB is transcellular and unidirectional. Maternal di-ferric Tf is taken up by TfR1 on the apical side of the STB and endocytosed into the cell. The resulting endosomes are acidified, Fe is released from Tf and Fe is exported out into the cytosol via divalent metal transporter 1 to be used by the placenta to support mitochondrial

or other cellular functions or to be stored within placental tissue as ferritin. If not needed by the placenta, Fe can be exported across the fetal side of the placenta by FPN1 and then must cross the fetal endothelium before entering fetal circulation (Figure 2). A recent murine study utilized an immunogold electron microscopy approach to show that the fetal endothelium does not express FPN1 indicating other Fe trafficking mechanisms are utilized to transfer Fe across the fetal endothelium.[22] Some of the Fe trafficking proteins in the human placenta are unique to the placenta including the ferroxidase, zyklopen, which oxidizes ferrous to ferric Fe.[23] A recent murine study that knocked zyklopen out globally or in the fetal component of the placenta found that zyklopen was not essential for placental transfer of iron to the fetus.[24] Loss of this ferroxidase in animals ingesting a standard rodent diet, did not significantly impact fetal Fe status or placental iron content at E18.5. However, maternal, but not fetal loss of zyklopen, was associated with a significant increase in placental size.[24] Unlike other cells that can export Fe into the systemic circulation, if the placenta does not export Fe to the fetus it must either restrict uptake of Fe from maternal circulation or store excess intracellular Fe over the course of gestation.

The placenta is exposed to maternal hormones that are delivered via maternal circulation, hormones that are independently produced by the fetus, and hormones that are produced by the placenta itself. Maternal erythropoietin, hepcidin and erythroferrone bathe the STB. These hormones are not thought to cross the STB into fetal circulation.[25] The fetus independently makes these same three regulatory hormones starting in early gestation.[7, 25–27] Finally, the placental tissue itself produces these three regulatory hormones.[28] Over the past 20 years there has been a marked increase in research evaluating relationships between maternal Fe status and the neonatal Fe endowment at birth. Increased attention has been focused on the elemental composition of the placenta, and on factors that influence placental Fe content (p[Fe]) and Fe trafficking proteins. Murine models have been developed to help isolate the effects of individual hormones and regulatory proteins on the neonatal Fe stores and use of stable Fe isotopes and biomedical mass spectrometry have provided opportunities to evaluate Fe trafficking in vivo and the individual roles of maternal, fetal, and placental factors on these processes.

MATERNAL REGULATION OF PLACENTAL FE TRAFFICKING

The apical layer of the STB is exposed to variable maternal concentrations of Fe regulatory hormones and di-ferric Tf that occur in response to Fe insufficiency or excess throughout gestation. Many human studies have confirmed that women with depleted Fe stores (as measured by low serum ferritin, low total body Fe or increased soluble TfR) have increased placental TfR1 protein abundance allowing the placenta to better scavenge Fe from maternal circulation.[29–34] Using stable Fe isotopes, we evaluated non-heme intestinal Fe absorption in pregnant women and found that intestinal absorption of non-heme iron increased on average by 1.5% for every 10 ug/L decrease in maternal serum ferritin.[35] The mediator of this altered absorptive response is hepcidin and maternal hepcidin has been found to be significantly inversely associated with absorption of non-heme Fe during pregnancy.[36, 37] A significantly greater transfer of maternally absorbed Fe to the fetus was also found in women with low hepcidin, as evaluated by a greater enrichment of stable Fe isotope in the neonate at birth.[36, 37]

The predictive ability of individual maternal Fe biomarkers and regulatory hormones to identify women with ID and IDA was recently evaluated in two cohorts of pregnant women.[38] Of all indicators measured, the hepcidin/erythropoietin ratio was the strongest predictor of maternal IDA. This ratio may be particularly helpful as it captures maternal responses to both ID and hypoxia.[38] To date no studies have evaluated this ratio and its possible associations with placental Fe trafficking proteins or p[Fe].

In human studies, pre-pregnancy samples are typically not available to characterize the early changes in iron regulatory hormones that occur after pregnancy is established. Animal models provide unique opportunities to answer these questions while manipulating the Fe content of the diet. Studies in mice have found that that hepcidin decreases early in pregnancy but the signal responsible for this early suppression of maternal hepcidin has yet to be identified.[34]

Ferroportin is responsible for exporting non-heme Fe from the human placenta but data on associations between maternal Fe status and placental ferroportin protein abundance and transcript expression are inconsistent. A large study of placental tissue obtained from pregnant adolescents found no significant associations between placental FPN1 and maternal Fe status.[32] Issues with the FPN1 antibody used may have impacted this finding, but a similar lack of an association was recently reported in lean and obese adult pregnant women using a well validated FPN1 antibody.[34] Findings in pregnant women to date differ from recent murine data that show FPN1 abundance decreases when severe maternal ID is induced.[34, 39] This response may be a protective mechanism to maintain p[Fe] as discussed in more detail below.

FETAL REGULATION OF PLACENTAL FE TRAFFICKING

Multiple studies have evaluated Fe status biomarkers in umbilical cord blood to identify possible fetal determinants of p[Fe] and placental Fe trafficking.[30–32, 37, 40] Recent data from both preterm and term newborns have confirmed that the human fetus has an intact EPO-ERFE-Hepcidin axis.[27, 40] Evaluation of these hormones in relation to a panel of Fe biomarkers at birth showed that umbilical cord hepcidin and the hepcidin/erythropoietin ratio were the strongest determinants of neonatal Fe and hematological status.[40] delaney To provide another means of evaluating the ability of the fetus to respond to its internal Fe environment, we utilized a multiple birth model to characterize factors that may contribute to placental Fe transport and Fe status at birth. Towards this goal, inter- and intrauterine variance in Fe biomarkers and regulatory hormones were evaluated in twin or triplet fetal-placental units in the context of a fixed maternal environment.[41] Significant variability in Hb and hepcidin was observed between siblings and 64% of the intrauterine variance in Hb was explained by cord hepcidin. More variability in Hb and hepcidin was observed between siblings sharing an intrauterine environment than was evident between unrelated neonates, highlighting the regulatory role of fetal hepcidin and its ability to respond to fetal Fe status.[41]

While the fetus appears to sense and respond to its internal Fe environment, it may have little control over placental Fe transport under typical conditions. Data from 154 mother-

newborn pairs found that neonatal Fe status at birth was not significantly associated with placental TfR or FPN1 mRNA expression or protein abundance.[32] Fetal Fe status was also not significantly associated with other placental non-heme Fe trafficking proteins (divalent metal transporter 1 (DMT1), hepcidin and zyklopen).[32] A similar lack of any significant association between neonatal ferritin stores at birth and placental ferroportin (mRNA and protein) was found in a recent study of 42 newborns born to obese or non-obese adult women.[34]

The effects of fetal hepcidin on fetal Fe stores has also been explored using several unique mouse models.[42] These data highlighted the significant autocrine effects of fetal hepcidin on hepatic hepcidin production which allows the fetal liver to accrue sufficient Fe to support hepatic hematopoiesis. In contrast to the significant effects of hepcidin on the liver, fetal hepcidin had no significant effect on placental ferroportin expression.[42] Reductions in fetal liver Fe stores were also associated with a decrease in fetal hemoglobin suggesting that fetal hepatic Fe stores are transferred to erythroid progenitors either directly or indirectly or that there may be paracrine effects of hepatocellular hepcidin on hepatic erythroid progenitors.[42, 43]

PLACENTAL REGULATION OF IRON TRAFFICKING

The placenta has high metabolic demands and a per kilogram oxygen consumption that meets or exceeds the oxygen demands of the brain or of tumor tissue and that is higher than either the mother or the fetus.[44, 45] Adequate cellular Fe stores are needed to support this high energy demand. To date, little attention has been focused on the Fe content of the human placenta or on factors that may be associated with variability in p[Fe]. The last dietary intake recommendations for Fe were published in 2001.[46] Iron intake requirements for pregnant women at that time were estimated using a factorial approach assuming the average term placenta contained 90 mg of Fe.[47] This value appears to have been based on 1961 report evaluating p[Fe] in a group of 49 primarily low-income pregnant women, with highly variable Hb concentrations (8–14 g/dL) and newborn birth weights (1.5 to 4.2 kg) and 3 of the women studied gave birth to twins.[48] Many other publications have reported data on human p[Fe] since that time using more precise analytical approaches in larger, more homogenous study populations.[31, 49–74] A summary of these data suggests that the average p[Fe] is only 41 ± 13 mg assuming placental weight is 496 g.[75]

The placenta is the gatekeeper for Fe transfer to the fetus, but few data are available on whose needs predominate should maternal Fe availability be limited. Animal models provide opportunities to manipulate the maternal diet to cause ID, sufficiency, or excess. Using this approach two recent studies in mice found that p[Fe] is largely independent of dietary manipulations and the placenta prioritizes its Fe content at the expense of the fetus when maternal Fe availability is limited which the authors have referred to as the "selfish placenta" concept.[34, 76, 77] Another recent murine study also found a similar upregulation of placental TfR1 and downregulation of placental FPN1 under maternal ID conditions.[39] Highly specialized cellular mechanisms are known to protect cellular Fe stores under low Fe conditions using the Fe regulatory protein and Fe response element (IRP/IRE) signaling pathway which post transcriptionally controls mRNA translation or

stability of cellular Fe trafficking genes that contain Fe response elements.[78] When intracellular Fe availability is limited, the placenta protects its own Fe supply by increasing the expression of TfR1 and downregulating the expression of FPN1 through the IRE/IRP system. These changes reduce non-heme Fe export from the placenta conserving Fe for placental functions.[34] Placental hepcidin is not involved in this regulatory process,[34] consistent with human data finding no significant associations between placental hepcidin expression with maternal, placental or neonatal Fe stores.[32] This coordinate regulation of placental TfR1 and FPN1 has been utilized to obtain an estimate of the placental iron deficiency index (PIDI).[34] Lower PIDI ratios have been found in humans with low Fe stores and in mouse models of severe ID.[34]

Relationships between maternal Fe status and p[Fe] were recently evaluated in 101 placentas obtained from multiple birth neonates and in 132 placentas obtained from neonates born to pregnant adolescents (n=132).[75] In adult women carrying multiple fetuses, p[Fe] was significantly higher in anemic compared to non-anemic women and low maternal Fe status was associated with higher p[Fe] consistent with the premise of the placenta prioritizing Fe for its own metabolic demands when maternal Fe stores are limited. However, in the pregnant adolescent cohort, a significantly lower p[Fe] was observed in adolescents with limited Fe stores. The observed differences between these two obstetric populations were also evident when comparing the relative prevalence of maternal versus newborn anemia in these two cohorts. In pregnant women with available data on p[Fe], 44% of women carrying multiple fetuses were anemic at term (35 ± 2 weeks) but only 30% of the adolescents were anemic at term in spite of delivering their newborns on average 5 weeks later (40 ± 1 week) than the multiple gravidas. In contrast, 14% of neonates born to women carrying multiples were anemic at birth while 26% of neonates born to the pregnant adolescents were anemic at birth (p=0.05).[75] Similar alterations in nutrient partitioning have been reported in sheep models of adolescent pregnancy.[79] More data are needed in diverse obstetrical populations to evaluate determinants of Fe partitioning when there are conditions that alter maternal Fe requirements (biological immaturity, chronic infection or disease, severe maternal obesity, concurrent micronutrient deficiencies, gestational diabetes, etc.).

There are many challenges when evaluating placental responses to ID as recently highlighted.[39] Alterations in placental Fe trafficking proteins and regulatory systems at term provide clues about maternal Fe sufficiency across gestation, but human placental samples cannot be obtained until pregnancy ends, limiting the ability to intervene in real time. Variable findings between studies may be a consequence of differences in the timing or magnitude of maternal ID across gestation. There are additional issues when sampling the human placenta and more work is needed to understand sources of variability that may occur due to the site of sampling.[75, 80–82] Tissue samples from the placental disk contain STB but also other cell types (smooth muscle, immune cells, endothelial cells, macrophages) that may confound measures of transporter expression. Finally, women that suffer from ID are often deficient in multiple other micronutrients making it difficult to isolate placental responses that can be attributed only to constrained Fe availability. A final challenge that is increasingly appreciated are the differences in placental responses that may occur between the male and the female placenta.[83]

SEX DIFFERENCES IN PLACENTAL IRON TRAFFICKING

Placental efficiency can be estimated by evaluating the ratio between the mass of the fetus to the mass of the placenta with greater placental efficiency being evident when lower placental weights result in larger birth weights. The male fetus prioritizes nutrients to support its own growth making it more dependent on optimal maternal nutritional status over pregnancy.[83] This is thought to contribute to the increased risk of adverse birth outcomes observed among males when the mother experiences nutritional insults during pregnancy.[83, 84] A recent murine study directly evaluated the impact of fetal sex on placental responses to maternal ID in a model that established ID prior to pregnancy.[39] Placental tissue was isolated at E14 and transcriptomic and proteomic analyses of placental homogenates were undertaken and compared as a function of placental sex. Analysis of the RNA-Seq data identified six genes that were similarly up- (Tfrc, Slc11a2, Gypa, Hemgn) or downregulated (Tmcc2, Cts6) in both the male and female placentas. However, an additional 154 differentially expressed genes were uniquely impacted by ID in the male placentas.[39]

NON-HEME IRON IS NOT THE ONLY FORM OF IRON AVAILABLE TO THE PLACENTA

Research on placental Fe trafficking has focused on non-heme Fe but this is not the only form of Fe that is ingested in the typical diet nor is it the only form of Fe that is available for placental use. Iron is ingested as inorganic Fe, heme Fe or as ferritin. In the body, inorganic Fe is transported in blood bound to Tf, but Fe also circulates as non-transferrin bound Fe (NTBI). Tissues internalize NTBI using ZIP14 and ZIP8 which are both highly expressed in the human placenta.[85] Pregnant women that ingest animal protein also consume heme Fe. Heme Fe may be released intravascularly from RBC catabolism and heme may be exported intact from cells that express heme export proteins. The placenta richly expresses heme trafficking proteins,[86] and heme scavenging by the placenta is not unusual as some carnivorous mammals have placentas that contain hemophagous regions. These regions heavily depend on heme catabolism to meet fetal and placental Fe requirements.[87, 88] Iron can also be ingested in the diet as ferritin and ferritin is found within the maternal circulation. Ferritin is taken up into cells by the receptor scara5 which is also expressed by the placenta.[86, 89, 90] Greater attention to these alternate forms of iron is needed to fully understand Fe partitioning and maternal, placental, and fetal utilization of variable iron sources across gestation.

CONCLUSIONS

Complex interactions occur between the mother, placenta, and fetus to meet the Fe demands of pregnancy. At least 3 regulatory hormones are needed to coordinately regulate Fe balance and ensure that maternal Fe stores and dietary Fe supply can be mobilized to meet gestational Fe demands. It is likely that an additional Fe regulatory signal suppresses hepcidin early in gestation, but this has yet to be identified. The placenta functions as a unique entity and regulates its own internal Fe environment to support the heavy metabolic demands of this organ across pregnancy. When maternal Fe availability is limited, the placenta may sequester Fe for its own use even at the sake of the developing fetus. The

fetus has an intact EPO-ERFE-Hepcidin axis, and fetal hepcidin functions in an autocrine fashion to ensure Fe is available for the fetal liver. Fetal hepcidin does not appear to regulate placental Fe export and the ability of the fetus to compensate for maternal ID is limited. Currently, few normative data are available on Fe biomarkers in the human newborn at birth. These normative data are needed to identify newborns with insufficient Fe stores at birth. Targeting newborns at this time will allow interventions to be initiated in a timely fashion. Characterization of newborn status is also needed to establish dietary Fe intake requirements for pregnant women that meet both maternal Fe demands and that are sufficient to fully endow the newborn with adequate Fe reserves at birth. The placenta is now known to play a larger regulatory role than previously appreciated and may prioritize Fe to support its own essential functions at the expense of the fetus. This fetally derived organ responds to Fe deprivation but these adaptive responses differ as a function of fetal sex and greater attention to fetal sex is needed when studying Fe homeostasis across gestation. The regulatory interactions between the maternal-placenta-fetal unit are complex and may be altered under conditions of biological immaturity, chronic inflammatory disease, maternal obesity, or other metabolic diseases in ways that have yet to be elucidated. Animal models provide unique opportunities to investigate maternal, placental, and fetal iron partitioning but human studies are needed to validate the translational impact of these findings. Iron is found in multiple different forms in the body and in the diet yet most research to date has focused only on the metabolism of non-heme Fe. More attention to the overall maternal diet and impact of variable Fe sources on maternal, placental, and fetal Fe homeostasis across gestation is needed to support positive maternal and neonatal birth outcomes

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Abbreviations:

DMT1	divalent metal transporter 1
EPO	erythropoietin
ERFE	erythroferrone
EVT	extravillous trophoblast
Fe	iron
FPN	ferroportin
ID	iron deficiency
IDA	iron deficiency anemia
IRP	iron regulatory protein
IRE	iron response element
NTBI	non-transferrin bound iron

p[Fe]	placental Fe content
STB	syncytiotrophoblast
sTfR	serum soluble transferrin receptor
Tf	transferrin
TfR1	transferrin receptor 1

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Highlights:

- The placenta may prioritize Fe for its own use when maternal Fe status is limited.
- The placental IRP/IRE system plays a key role in placental Fe trafficking.
- Fetally derived hepcidin does not impact placental iron transporter expression.
- Placental responses to Fe deficiency vary as a function of fetal sex.
- More data on placental utilization of heme, non-heme and NTBI are needed.

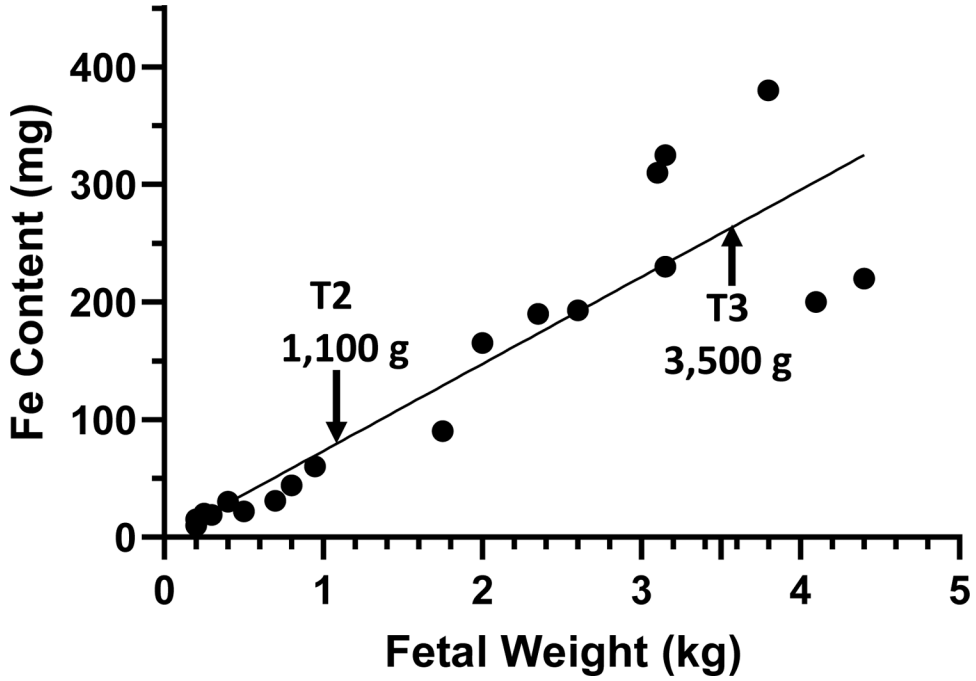

Figure 1:

Widdowson et al evaluated the iron content of the human fetus by chemical analysis and plotted total body iron content as a function of fetal weight in 13 immature fetuses (< 17 weeks of gestation) and in 6 stillborn, term infants (> 3 kg).[20] The estimated average weight of a fetus at the end of the second (1,100 g) and third trimester of pregnancy (3,500 g) are shown above. Using these data, by the end of the 2^{nd} and 3^{rd} trimester of pregnancy the human fetus has accrued roughly 70 mg and 260 mg of iron respectively. With this rate of observed accretion, only approximately 27% of the iron endowment at birth is obtained over the first two trimesters of pregnancy leaving 70% of the iron reserve at birth to be transported across the placenta to the fetus over the last 90 days of pregnancy. (Figure modified from Widdowson et. al.).[20]

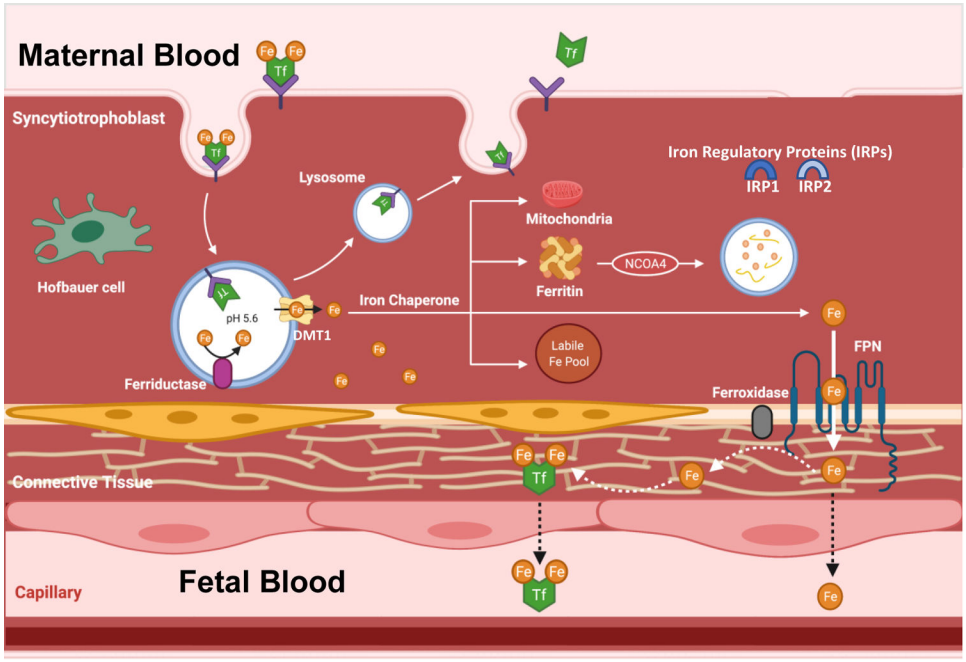

Figure 2:

Non-heme iron (Fe) is transferred from maternal circulation to the fetus across the syncytiotrophoblast (STB). Maternal diferric-transferrin (Tf) binds to transferrin receptor 1 (TfR1) on the apical side of the STB where it is internalized into clathrin coated endosomes. The endosomes are acidified by proton pumps, causing ferric Fe (Fe^{3+}) to be released from TfR. Fe^{3+} is then reduced to ferrous Fe (Fe^{2+}) by a ferrireductase (STEAP) and is exported into the cytosol by divalent metal transporter 1 (DMT1). The remaining apotransferrin is recycled back to the apical membrane of the STB where the more basic extracellular pH causes the apotransferrin to be released from TfR1 allowing it to reenter maternal circulation and bind more Fe^{3+}. The Fe^{2+} that enters the cytosol of the STB can bind to intracellular Fe chaperones such as poly C binding protein (PCBP) and can be utilized by placental mitochondria or stored within the STB as ferritin. Some Fe may remain in the intracellular labile iron pool. Under low intracellular Fe conditions, the iron regulatory proteins (IRP), IRP1 and IRP2, bind to iron response elements (IRE) on iron regulated genes such as FPN1 and TfR1. These IRP-IRE interactions post-transcriptionally regulate IRE-containing genes leading to changes that allow the placental tissue to retain Fe for its own metabolic demands (such as increasing the expression of TfR1 and decreasing the expression of FPN1). If Fe is not utilized by the placenta, Fe^{2+} can be exported across the fetal side of the STB by FPN1 where it is again oxidized by a ferroxidase into Fe^{3+}. The fate of this Fe^{3+} and the process used to transfer Fe^{3+} across the fetal endothelium (either as diferric-Tf or as non-transferrin bound iron) has not been confirmed in humans. Figure adapted from [91] by Youri Jung using Biorender.com.