JCI The Journal of Clinical Investigation

The selfishly selfless placenta

Nermi L. Parrow, Robert E. Fleming

J Clin Invest. 2020;130(2):590-592. https://doi.org/10.1172/JCI134272.

Commentary

Although iron deficiency continues to pose a problem for pregnant women and fetal development, an incomplete understanding of placental adaptation to limited iron availability has hindered efforts to identify optimal supplementation strategies. In this issue of the *JCI*, Sangkhae et al. used mouse models and human placentas to explore maternal, placental, and fetal responses to alterations in iron status during pregnancy. The authors identified molecular mechanisms that limit placental ability to upregulate iron transport in the setting of severe iron deficiency and explored a potential marker of placental maladaptation.

The selfishly selfless placenta

Nermi L. Parrow[1] and Robert E. Fleming[1,2]

[1]Department of Pediatrics and the [2]Edward A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, Missouri, USA.

Although iron deficiency continues to pose a problem for pregnant women and fetal development, an incomplete understanding of placental adaptation to limited iron availability has hindered efforts to identify optimal supplementation strategies. In this issue of the *JCI*, Sangkhae et al. used mouse models and human placentas to explore maternal, placental, and fetal responses to alterations in iron status during pregnancy. The authors identified molecular mechanisms that limit placental ability to upregulate iron transport in the setting of severe iron deficiency and explored a potential marker of placental maladaptation.

Deficiency anemia in pregnant women

Iron deficiency during pregnancy continues to present a major public health concern. Even in developed parts of the world, most women of reproductive age require supplemental iron to meet the estimated needs of pregnancy. Although the placenta will continue to extract iron from the mother, even at the expense of maternal iron stores, correlations between markers of maternal and newborn iron status raise concern that fetal iron accrual may be suboptimal in the setting of maternal iron deficiency — possibly in the absence of maternal anemia (1, 2). Nonetheless, determining which pregnant women and/or their fetuses may benefit from iron supplementation has been difficult, and official guidelines vary significantly (3, 4). The Centers for Disease Control and Prevention recommends iron supplementation for all pregnant women (4). The American Congress of Obstetrics and Gynecology recommends universal screening of pregnant women for iron deficiency anemia (5). On review of the issue, the US Preventive Services Task Force concluded that "current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in pregnant women to prevent adverse maternal health and birth outcomes" (6). The issue is a timely one, as the British Society for Haematology published its guidelines last month, recommending a more tailored approach (7).

The placental compartment

Much of the difficulty in determining optimal maternal iron supplementation during pregnancy arises from uncertainty in distinguishing adaptive versus maladaptive events — for both the fetus and the mother — and appropriate markers for these events. Clarity requires a better understanding of the fundamental mechanisms of iron transfer at the interface between mother and fetus, i.e., the placenta (8). In this issue of the *JCI*, Sangkhae et al. present insights into placental regulation of iron metabolism (9) that challenge certain paradigms and serve to identify novel markers to assist in the identification of settings in which maternal iron deficiency has led to a maladaptive placental response.

Transport of maternal iron to the fetus occurs across the syncytiotrophoblast, a fetal epithelial cell layer that lines the placenta and directly interfaces with maternal blood. In examining the molecular events regulating iron transport across these cells, it is useful to compare analogous events in the epithelial cell type responsible for extrauterine iron accrual, i.e., the duodenal enterocyte. There is the obvious difference in uptake, with transferrin receptor 1 (TFR1) playing this role in the syncytiotrophoblast, rather than divalent metal transporter 1 (DMT1) in the enterocyte. Sangkhae et al. identified additional important ways in which this and subsequent cellular events in the placenta differ from those reported in the duodenum, particularly in response to iron deficiency (Table 1) (9, 10, 11).

Limitations of the molecular response to iron deficiency

The Sangkhae study revealed several unexpected and striking findings (9). It is recognized that increased expression of syncytiotrophoblast TFR1 is an important mechanism by which the placenta compensates for maternal iron deficiency (12). However, the Sangkhae et al. study identified certain unappreciated constraints on such upregulation (9). In iron deficiency, increased binding of iron regulatory proteins (IRPs) to iron regulatory elements (IREs) in the mRNA 3′-UTR upregulates TFR1. Although Sangkhae and colleagues observed the anticipated increase in IRP1 in the iron-deficient placenta, TFR1 expression was only modestly affected. Moreover, comparison of TFR1 in iron-deficient IRP1-KO and WT mice showed no obvious differences. The authors attributed these findings to the low expression of the ribonuclease regnase 1, which degrades the TFR1 transcript under iron-sufficient conditions (13). This mechanism may explain the very high expression of placental TFR1 even under iron-replete conditions (9).

A second, even more notable, finding was the downregulation of placental ferroportin (FPN) in iron deficiency. Based on the enterocyte paradigm, the low-hepcidin state of the iron-deficient fetus would upregulate syncytiotrophoblast FPN and increase iron export. The consequent decreased cellular iron should then

▶ Related Article: p. 625

Conflict of interest: The authors have declared that no conflict of interest exists.

Reference information: *J Clin Invest*. 2020;130(2):590–592. https://doi.org/10.1172/JCI134272.

Table 1. Comparison of iron transport regulation between the duodenal enterocyte and the syncytiotrophoblast

	Molecule	Effect of iron deficiency	Major regulatory mechanisms	Comment
Apical iron uptake				
Duodenal enterocyte	DMT1	Robust upregulation	↑Transcription (HIF2α); ↑mRNA stabilization (IRP1)	Upregulated in pregnant mother
Syncytiotrophoblast	TFR1	Modest upregulation	(↑) mRNA stabilization (IRP1)	High basal TFR1 expression; low basal regnase 1
Iron storage				
Duodenal enterocyte	Ferritin	Downregulation	↓Translation (IRP1)	Substantial ferritin stores when iron replete
Syncytiotrophoblast	Ferritin	Downregulation	↓Translation (IRP1)	Minimal ferritin stores even when iron replete
Basolateral iron release				
Duodenal enterocyte	*Fpn1B* transcript	Upregulation	↑ Transcription (HIF2α); Protein degradation (↓hepcidin)	Primary determinant of maternal increased dietary iron absorption
Syncytiotrophoblast	*Fpn1A* transcript	Downregulation	↓Translation (IRP1); Negligible effect on protein degradation (hepcidin low)	Contributes to iron preservation by syncytiotrophoblast

Summarized, based on refs. 9–11.

increase apical iron uptake. However, in the setting of limited iron supply, downregulation of FPN became the only mechanism for preventing syncytiotrophoblast cellular dysfunction. The investigators attributed this self-protection to regulation via the IRE in the 5′-UTR (i.e., the transcript *Fpn1A*) that reduced expression of the FPN transcript to near exclusion. Increased IRP1 binding to this transcript represses *Fpn1A* translation (similar to translational repression of ferritin) in iron deficiency. By contrast, enterocytes and certain other cell types with significant iron efflux (including macrophages and erythroblasts) predominantly express the non-IRE *Fpn1B* transcript. The particular setting of placental iron deficiency reveals the value of the IRE-containing transcript. Despite its important role in iron efflux, the syncytiotrophoblast depends on mechanisms to retain iron when the supply becomes limiting for its own metabolic needs. Given that the syncytiotrophoblast is continuously exposed to a low-hepcidin state, it relies on internal mechanisms to decrease FPN expression to prevent limitations that would interfere with cellular function (9).

Another striking finding that arose from the Sangkhae et al. study was the lack of an obvious role for hepcidin in the placental response to iron deficiency (9). It appears that under iron-replete conditions, fetal hepcidin expression is sufficiently low, such that a further decrease is inconsequential. However, fetal hepcidin may still modulate syncytiotrophoblast FPN expression or fetal iron status under other circumstances. Such modulation is observed in transgenic mice overexpressing hepcidin, as well as in other murine models (14). Moreover, there are certain fetal conditions associated with hepatocellular iron loading (hemolytic anemias, atransferrinemia, gestational autoimmune liver disease), in which inadequate fetal hepcidin expression may contribute to iron accumulation (15).

Sangkhae et al. also investigated iron loading using mouse models and demonstrated the anticipated effects on maternal hepcidin expression but little effect on fetal or placental iron parameters (9). It is possible that the marked iron loading used in these studies altered maternal hematologic parameters by affecting copper metabolism (16). It will be informative to examine the Sangkhae et al. mouse system when iron replacement is administered at doses similar to those used in human pregnancies.

Looking at the combined effects of limited placental TFR1 upregulation, FPN downregulation, and the inability to affect iron efflux by further suppressing hepcidin, it is perhaps no surprise that the fetal iron status fared so poorly with maternal iron deficiency in the Sangkhae et al. studies. Indeed, in some regards, fetal iron status (reflected by differences in blood hemoglobin concentration or erythrocyte mean corpuscular volume) was more affected than the mother's iron status. Such findings have not been reported in human studies. It is likely that the marked fetal effects observed by Sangkhae and colleagues reflect the severity of iron deficiency these mice experienced. It will be informative to determine the consequences of less severe iron depletion in the mouse model (9).

Identifying a placental biological marker of fetal iron status has been challenging. Placental iron deficiency severe enough to result in compensatory FPN downregulation clearly identifies a process maladaptive for fetal iron accrual. Sangkhae and colleagues thus devised the FPN/TFR1 ratio as the "placental iron deficiency index" (PIDI). The PIDI values in the mouse, particularly in late gestation, diverged sufficiently, allowing a clear distinction of iron-replete and -depleted groups. Values from placental tissue supported the overall concept that this ratio likewise reflected placental iron status in humans. However, there was considerable overlap in values between the groups, even when using a low cutoff for maternal ferritin to identify iron deficiency (9). Additional studies are needed — particularly those using placental tissue from pregnancies with other complications. Nonetheless, the PIDI appears useful as a research tool.

Conclusions

The observations that Sangkhae et al. made in the mouse model systems underscore the importance of maternal iron supply in meeting the needs of the developing fetus (9). Among the limitations on placental adaptation are the iron needs of the placenta itself. The placenta has been ascribed some rather unflattering terms regarding its handling of iron transport. From the studies presented here we might be tempted to add "selfish to the fetus" on top of "parasite upon the mother (17)." However, both terms may be rather unfair. Because the placental transferrin receptors compete for maternal iron-transferrin, there is an "altruistic" maternal response to downregulate its own iron utilization and maximize iron absorption. Following this maternal response, iron release into the circulation provides iron-loaded transferrin for the fetus. The placenta normally "selflessly" retains little iron as ferritin but instead readily exports it to the fetus. However, when the placenta is severely iron depleted, FPN is downregulated to meet placental metabolic needs. Consequently, ferritin remains with the mother. In keeping with the anthropomorphisms, perhaps the placenta is practicing what we are admonished to do before every airline flight: "in the event of an emergency, put on your own mask before helping those around you." For the good of all.

Address correspondence to: Robert Fleming, St. Louis University School of Medicine, Department of Pediatrics, 1465 S. Grand Avenue, St. Louis, Missouri 63104, USA. Phone: 314.977.9315; Email: robert.fleming@health.slu.edu.

1. McArdle HJ, Gambling L, Kennedy C. Iron deficiency during pregnancy: the consequences for placental function and fetal outcome. *Proc Nutr Soc*. 2014;73(1):9–15.
2. Rao R, Georgieff MK. Iron in fetal and neonatal nutrition. *Semin Fetal Neonatal Med*. 2007;12(1):54–63.
3. Brannon PM, Taylor CL. Iron supplementation during pregnancy and infancy: uncertainties and implications for research and policy. *Nutrients*. 2017;9(12):E1327.
4. [No authors listed]. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1998;47(RR-3):1–29.
5. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95: anemia in pregnancy. *Obstet Gynecol*. 2008;112(1):201–207.
6. [No authors listed]. Final Update Summary: Iron Deficiency Anemia in Pregnant Women: Screening and Supplementation. U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/iron-deficiency-anemia-in-pregnant-women-screening-and-supplementation. Accessed November 25, 2019.
7. Pavord S, et al. UK guidelines on the management of iron deficiency in pregnancy [published online ahead of print October 2, 2019]. *Br J Haematol*. https://doi.org/10.1111/bjh.16221.
8. Cao C, Fleming MD. The placenta: the forgotten essential organ of iron transport. *Nutr Rev*. 2016;74(7):421–431.
9. Sangkhae V, et al. Effects of maternal iron status on placental and fetal iron homeostasis. *J Clin Invest*. 2020;130(2):625–640.
10. Knutson MD. Iron-sensing proteins that regulate hepcidin and enteric iron absorption. *Annu Rev Nutr*. 2010;30:149–171.
11. Ramakrishnan SK, Shah YM. Role of intestinal HIF-2α in health and disease. *Annu Rev Physiol*. 2016;78:301–325.
12. Young MF, et al. Impact of maternal and neonatal iron status on placental transferrin receptor expression in pregnant adolescents. *Placenta*. 2010;31(11):1010–1014.
13. Yoshinaga M, et al. Regnase-1 maintains iron homeostasis via the degradation of transferrin receptor 1 and prolyl-hydroxylase-domain-containing protein 3 mRNAs. *Cell Rep*. 2017;19(8):1614–1630.
14. Willemetz A, et al. Matriptase-2 is essential for hepcidin repression during fetal life and postnatal development in mice to maintain iron homeostasis. *Blood*. 2014;124(3):441–444.
15. Zoller H, Knisely AS. Control of iron metabolism--lessons from neonatal hemochromatosis. *J Hepatol*. 2012;56(6):1226–1229.
16. Wang T, et al. Copper supplementation reverses dietary iron overload-induced pathologies in mice. *J Nutr Biochem*. 2018;59:56–63.
17. Loke YW. *Life's Vital Link*. Oxford, UK: Oxford University Press; 2013.