Iron-deficiency anaemia in pregnancy: the role of hepcidin

See Articles page e1564

According to WHO, more than one in three pregnant women worldwide has iron-deficiency anaemia.[1] Because this disorder is associated with adverse maternal and neonatal outcomes if present at delivery, iron supplementation is recommended.[2] However, treating iron-deficiency anaemia in pregnancy is not straightforward. Patients' adherence to daily oral iron treatment regimens is low, most likely because of a high frequency of gastrointestinal side-effects,[3] and oral iron has a low rate of systematic absorption.[4] Moreover, the optimum regimen of oral iron treatment is unclear. Findings of a Cochrane review concluded that intermittent iron treatment could be as effective as daily iron supplementation for treatment of iron-deficiency anaemia in pregnancy.[5] Although suboptimum, a one-size-fits-all approach for treatment of iron-deficiency anaemia in pregnancy with daily oral iron supplementation remains the international standard.[6]

In *The Lancet Global Health*, Amat Bah and colleagues assessed whether the treatment of iron-deficiency anaemia in pregnancy could be optimised by incorporating a physiologically plausible biomarker, hepcidin, into treatment algorithms.[7] Amounts of hepcidin are suppressed by iron deficiency or iron-deficiency anaemia and are increased by high amounts in serum of iron or iron stores. This relationship is important because higher amounts of hepcidin decrease intestinal absorption of iron.[8] Bah and colleagues posited that incorporating the amount of hepcidin into iron-deficiency anaemia treatment algorithms would allow iron supplementation to be given only to those women who would more effectively absorb iron, ensuring that a treatment regimen with significant side-effects is restricted to those with the highest likelihood of receiving maximum benefit.

Bah and colleagues did a multicentre, three-arm, randomised controlled trial of nearly 500 pregnant women in The Gambia and analysed whether one or both of two distinct hepcidin-based screen-and-treat approaches exceeded the non-inferiority margin when compared with conventional daily oral iron treatment, according to WHO guidelines.[7] In both intervention groups, oral iron supplementation was given only to those women with amounts of hepcidin less than 2·5 µg/L; one group received WHO's recommended daily supplementation of 60 mg of iron daily and the other received 30 mg of iron daily. The primary outcome was amount of haemoglobin at day 84 of treatment, and the non-inferiority margin was set at –5·0 g/L.

Women in the intervention (screen-and-treat) groups received significantly less iron compared with women in the control (standard treatment) group, but the primary outcome did not exceed the preset non-inferiority margin for either screen-and-treat algorithm. However, persistent anaemia was more common in the intervention groups compared with the control group. Bah and colleagues concluded that the screen-and-treat algorithms incorporating hepcidin were less effective at treating iron-deficiency anaemia in pregnant women compared with standard care of daily iron supplementation, and they suggest their findings support current WHO guidelines regarding daily oral iron supplementation.[1,6,7]

Non-inferiority trials are becoming increasing common,[9] and their interpretation might require some clarification for those accustomed to superiority trials.[10] In this trial, the primary outcome fell within the prespecified non-inferiority threshold for both intervention groups compared with WHO's recommended regimen; in other words, both proposed screen-and-treat algorithms were non-inferior to the standard treatment for the primary outcome. However, Bah and colleagues have concluded that hepcidin-based algorithms are less effective compared with standard treatment,[7] which is not an appropriate conclusion for a non-inferiority trial.[9,10]

Why did the authors make this conclusion? Perhaps it is because the study's most clinically relevant secondary outcome (the proportion of haemoglobin <11 g/dL at day 84) occurred with greater frequency with both screen-and-treat algorithms. Although it seems reasonable to interpret these findings in secondary outcomes as inferior, it is important to note that secondary outcomes must be interpreted with caution in any trial. Moreover, the investigators did not specify non-inferiority margins for the secondary outcomes a priori.

Furthermore, women in either intervention group had an increased frequency of anaemia at 84 days compared with at randomisation. This potentially counterintuitive finding has some possible explanations. First, the assay

used for weekly hepcidin testing in the intervention groups did not include information about actual iron absorption, instead reporting a predetermined hepcidin threshold to diagnose iron deficiency. Second, hepcidin might not be useful clinically for monitoring iron status among women who are adherent to iron supplementation. Bah and colleagues note these limitations.[7] Finally, the iron supplementation used in this study might not have been administered in an ideal route. The rate of persistent anaemia in the control group approached 50% after 84 days of treatment, corresponding to only a 13% reduction in anaemia after nearly 3 months of daily iron supplementation. This important finding indicates that most patients failed treatment in a high-quality study in which participants were confirmed to adhere to recommended daily oral iron supplementation. Thus, the study inadvertently provides concerning evidence about the limited efficacy of oral iron treatment, however administered, for iron-deficiency anaemia in pregnancy.

Although increasing evidence suggests that intravenous iron could be a more effective treatment with a good side-effect profile, this route of administration was not tested in this study. In a meta-analysis of randomised trials, intravenous iron infusion had better haematological variables at delivery, improved perinatal outcomes, and fewer side-effects when compared with oral iron supplementation for women with iron-deficiency anaemia in pregnancy.[3] We agree with Bah and colleagues that cost-effectiveness analyses and infrastructure development to overcome implementation barriers are needed in low-income settings,[7] but it is possible that iron infusions could help decrease morbidity related to iron-deficiency anaemia in pregnancy in both low-income and high-income settings.

Although data from this trial do not support use of hepcidin-based approaches, Bah and colleagues should be commended for creating and testing novel treatment algorithms aimed at decreasing the side-effect burden of iron treatment without negatively affecting outcomes. Future studies should test other approaches and iron formulations to optimise treatment for iron-deficiency anaemia in pregnancy.

Adam K Lewkowitz, Methodius G Tuuli
Department of Obstetrics and Gynecology, Alpert Medical School, Brown University, Providence, RI 02912, USA (AKL); and Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN, USA (MGT)
alewkowitz@kentri.org

AKL and MGT declare no competing interests.

1 WHO. The Global Prevalence of Anaemia in 2011. Geneva: World Health Organization, 2015.
2 Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015; **7:** CD004736.
3 Lewkowitz AK, Gupta A, Simon L, et al. Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis. *J Perinatol* 2019; **39:** 519–32.
4 Lopez A, Cacoub P, Macdougall I, Peyrin-Biroulet L. Iron deficiency anemia. *Lancet* 2016; **387:** 907–16.
5 Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2012; **7:** CD009997.
6 WHO. Intermittent iron and folic acid supplementation during pregnancy. Feb 11, 2019. https://www.who.int/elena/titles/intermittent_iron_pregnancy/en/ (accessed Sept 18, 2019).
7 Bah A, Muhammed AK, Wegmuller R, et al. Hepcidin-guided screen-and-treat interventions against iron-deficiency anaemia in pregnancy: a randomised controlled trial in The Gambia. *Lancet Glob Health* 2019; **7:** e1564–74.
8 Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015; **126:** 1981–89.
9 Mauri L, D'Agostino RB. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med* 2017; **377:** 1357–67.
10 Riggs TW, Rouse DJ. Noninferiority complex. *Obstet Gynecol* 2018; **132:** 833–34.