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Overview of Iron Deficiency and Iron Deficiency Anemia in Women and Girls of Reproductive Age

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Abstract

Over 50% of pregnant women are anemic and the majority of these are iron deficient. Micronutrient deficiency, the symptom of heavy menstrual bleeding in nonpregnant individuals, and loss of blood associated with pregnancy and obstetric delivery contribute to iron deficiency (ID). Poor outcomes with low maternal iron can affect not only the pregnancy but can also have major bearings on the offspring. Correction of ID and iron deficiency anemia (IDA) in pregnant and prepregnant populations with single-dose intravenous iron supplementation may offer improved outcomes. A harmonization process that incorporates all major randomized controlled trials studying the use of single-dose IV iron compared with oral iron may suggest actions for changing the global trajectory of ID/IDA for women and girls of reproductive age.

KEYWORDS
anemia, heavy menstrual bleeding, hemorrhage, intravenous iron supplementation, iron deficiency, iron deficiency anemia

1 | INTRODUCTION

Pregnancy is considered to be the greatest stress test in a woman's life. In some circumstances, the body is severely taxed and fails to enlist sufficient protective mechanisms to assure survival. In India, history suggests that Mumtaz Mahal, the wife of Mughal Emperor, Shah Jahan, died from hemorrhage while giving birth to her 14th child (the Taj Mahal was built in her memory).[1] Although the risks of hemorrhage during childbirth have been well-known since the Middle Ages, the link between bleeding, iron, and the presence of anemia is more contemporary. Lemery and Goeffroy (1713) demonstrated that whole blood contained iron,[2] whereas Vincenzo Menghini (1704–1759) was the first to show its presence in red blood corpuscles.[3] Hemoglobin was accidentally discovered by Hunefelt in 1840 while observing and dissecting earthworms[4,5] and iron deficiency anemia (IDA) was first reported by Karl Vierordt and his student H. Welcher in 1852.[6] However, it was not until 2000 that Bothwell calculated a pregnant woman's total iron requirement.[7]

2 | EFFECT OF ANEMIA AND OTHER MICRONUTRIENT DEFICIENCIES ON WOMEN AND GIRLS OF REPRODUCTIVE AGE

The World Health Organization (WHO) definition of anemia (hemoglobin level of less than 12 g/dL in nonpregnant women and less than 11 g/dL in pregnant women) is uniformly recognized.[8] However, the definition of anemia by trimester of pregnancy differs according to the WHO and the Centers for Disease Control and Prevention (CDC). Both organizations agree that, in pregnant women, a hemoglobin level of less than 7 g/dL is considered severe anemia and 10–11 g/dL is mild anemia.[9,10] However, there is discordance in the cutoffs for the second trimester, where CDC defines a normal value as less than 10.5 g/dL, rather than 11 g/dL, to account for expanded red cell mass, hemodilution, and the needs of the growing fetoplacental unit.[9] In 2011, WHO estimated that 29% of nonpregnant women and 38% of pregnant women were anemic worldwide.[11] Globally, iron deficiency

(ID) underlies over 60% of anemia cases,[12] and the prevalence of prenatal ID has been reported at 19.2%.[13] Iron requirement rapidly increases as the duration of pregnancy progresses, with only 0.8 mg/day of iron necessary in the first trimester (given no menstrual blood loss), 4–5 mg/day in the second trimester and at the time of most rapid fetal growth, and more than 6 mg/day in the third trimester of pregnancy.[7] According to Bothman,[7] women must enter pregnancy with iron stores of greater than or equal to 300 mg to fully meet the iron requirements needed in pregnancy. Many women, especially in low- and middle-income countries (LMICs), enter pregnancy with far less iron.

Micronutrient deficiency is a global problem but is especially prevalent in countries within Sub-Saharan Africa and South Asia, where rates of IDA are also the highest.[14] While iron is the most important micronutrient, depleted levels of folate, zinc, iodine, calcium, and vitamins A, D, and B12 have also been associated with poor maternal outcomes.[15] The rates of ID and IDA vary by country and are confounded by concurrent illness, socioeconomic status, food choices, and type of diet.

Furthermore, women with short interpregnancy intervals generally have insufficient time to restore the required iron needs before entering a subsequent pregnancy.[16] More than 1000 published papers have linked low iron stores during pregnancy to adverse pregnancy outcomes in pregnant women and their offspring.[17–31] While many of these studies are small, most suggest specific and serious health risks associated with insufficient iron stores. The greater the degree of anemia, the greater the odds of maternal mortality and morbidity.[32] Furthermore, anemia diagnosed in the first trimester of pregnancy has the highest predictive value for a poor health outcome.[33] Although the complications attributed to low iron in pregnant women would appear sufficiently significant to warrant mandated screening and the development of updated treatment guidelines, the negative impact on the progeny of pregnant women, including nonreversible neurodevelopmental changes in the infant, may be even more compelling.[30,31]

Infants of iron-deficient mothers have a higher rate of low birth weight (<2500 g) and increased stunting, which in many LMICs may reach 30%–50%.[29] Perhaps most importantly, all-domain neurocognitive impairment is reported, especially in the offspring of women with moderate or severe IDA.[31] Thus, many children cannot attain their full genetically determined growth and optimal development. Recent articles have also linked low maternal iron stores to increases in autism spectrum disorders and schizophrenia.[34,35] A summary of the adverse outcomes in mothers and offspring associated with ID/IDA is given in Table 1.

TABLE 1 Summary of adverse outcomes in mothers and offspring associated with iron deficiency and iron deficiency anemia

	Adverse outcome
Mother	
	↓ life quality and cognition and ↑ fatigue [25]
	↑ postpartum hemorrhage [26]
	↑ overall maternal mortality [27]
	↑ cesarean deliveries [36]
	↑ need for blood transfusion [36]
Offspring	
	↑ Risk of neonatal and childhood anemia [21,22]
	↑ neonatal and infant mortality/morbidity [27]
	↑ preterm birth [28]
	↑ low birth weight [28]
	↓ neurocognitive development [30,31]

3 | CHALLENGES IN ADDRESSING IRON DEFICIENCY OUTSIDE PREGNANCY

The challenges in addressing ID do not end with pregnancy as the nadir for low maternal iron stores occurs in the postpartum period. Rates of postpartum anemia may approach 80% in some countries, which has seen a further increase, perhaps secondary to the rapid increase in cesarean delivery rates.[36–39] Women who suffer from ID also present with associated postpartum depression, complaints of fatigue, reduction in cognition, and an overall lowering of productivity and quality of life.[25] Supplemental oral iron, suggested by WHO, is often not provided at the time of delivery, and women generally do not return for their postpartum visits.[40,41] Those who do attend for follow up and take oral iron as prescribed often complain of adverse gastrointestinal effects, leading to poor adherence or early discontinuation.[42,43]

Anemia among prepregnant adolescent girls has not changed significantly over time despite a multitude of governmental and health agency programs attempting to address this high-priority issue.[44] An often overlooked and understudied cause of IDA in prepregnant girls and women is heavy menstrual bleeding (HMB), with rates reported as high as 50%.[45] Screening and treating the structural and nonstructural underlying causes of HMB (discussed further in other reviews in this Supplement) in advance of pregnancy can be considered an efficient and cost-effective approach, not only for under-resourced countries but as a priority globally. HMB has traditionally been defined as blood loss of 80 mL or more.[46,47] Since quantification of menstrual blood loss is impractical, the estimated prevalence is difficult to determine. In 2007, the UK's National Institute for Health and Care Excellence (NICE) defined HMB clinically as "… excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or material quality of life",[48] a definition also adopted by FIGO.[49] High-quality evidence reports that women who have symptoms meeting this definition have blood loss exceeding 100 mL per month.[50] HMB is highly associated with ID and IDA, but is often overlooked because of normalization by family, other members of society, and even healthcare practitioners. The subject of IDA does not often make medical headlines, as it rarely presents as an acute condition; however, an interest in this condition and its link to adverse clinical outcomes has seen a recent resurgence.[51]

Laboratory assessments are necessary to report the presence of anemia and to determine if the anemia is related to reduced iron stores.

In prepregnant women, the symptom of HMB and the subsequent iron loss may not be satisfactorily corrected with improved dietary intake of iron or even oral iron supplementation, and yet it is responsible for much of the ID and IDA in women and girls of reproductive age. While assessment and treatment of the many causes of HMB are beyond the scope of this paper and have been discussed in another review in this Supplement, screening should be considered a necessary component of any strategy designed to address the global problem of ID and its extreme, IDA. A major change to the implementation of such an approach will result in better societal acknowledgment of both HMB and ID.

In pregnant women, despite WHO recommendations on the importance of utilizing hemoglobin and ferritin for confirming IDA, only hemoglobin values are generally captured or available in the medical record, and the time during pregnancy reported for such testing varies widely. All too often, women do not undergo appropriate screening and are simply provided with supplemental oral iron. We now recognize that the adage "more is better" in the case of iron supplementation likely produces poorer results, as only a relatively small amount of oral iron, based on the trimester of pregnancy, will be absorbed.[52] It is reported that hepcidin, having a half-life of about 48 h, impairs further iron absorption when supplemental iron is provided or prescribed in large doses or at an interval greater than every other day—these recent findings have yet to be incorporated into clinical practice.[52,53]

4 | POTENTIAL WAY FORWARD

It is plausible that single-dose intravenous iron supplementation may offer improved outcomes. More than 100 published papers attest to the safety of intravenous iron, including its use in pregnancy,[54] and several studies have been published suggesting improved maternal outcomes.[55] Our research group, with funding from The Children's Investment Fund Foundation, is currently conducting the largest randomized controlled trial comparing two single-dose formulations of intravenous iron with the standard of care oral iron. The intravenous iron is provided in a single dose to women with moderate anemia between 14 and 17 weeks of pregnancy.

While several smaller studies are also ongoing in Africa and South Asia, the projected randomization of 4300 women in the Reducing Anemia in Pregnancy in India: RAPIDIRON (RAPIDIRON Trial),[56] comprising women from four geographically remote sites within two Indian states, will provide primary outcome data on both changes in blood indices and the rate of low birth weight. Before randomization, all women receive a dating ultrasound and laboratory testing at a centralized facility to obtain levels of hemoglobin, ferritin, transferrin saturation index, and reticulocyte hemoglobin. The cost-effectiveness of large-scale administration of intravenous iron supplementation may present as a concern in its implementation; however, this is still under investigation.

In conclusion, although poor pregnancy outcomes associated with low maternal iron stores have been recognized for some time, the knowledge that it can have major bearings on the offspring is a relatively new and critical concept. A harmonization process that incorporates all major randomized controlled trials studying the use of single-dose intravenous iron compared with oral iron will soon be initiated. The hope is that the emerging science will suggest actions for changing the global trajectory of ID and IDA for women and girls of reproductive age.

AUTHOR CONTRIBUTIONS

Richard J. Derman conceptualized and drafted the manuscript. Richard J. Derman and Anmol Patted edited, critically reviewed, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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