American Journal of Obstetrics and Gynecology (2005) **193**, 36–44

ELSEVIER

American Journal of OBSTETRICS and GYNECOLOGY

www.ajog.org

REVIEW ARTICLE

Have we forgotten the significance of postpartum iron deficiency?

Lisa M. Bodnar, PhD, MPH, RD,[a,*] Mary E. Cogswell, DrPH, RN,[b] Thad McDonald, MD[c]

Magee Women's Research Institute and Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA[a]; Maternal and Child Nutrition Branch, Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA[b]; and Department of Obstetrics and Gynecology, Wake Medical Center, Raleigh, NC[c]

Received for publication August 16, 2004; revised November 22, 2004; accepted December 6, 2004

KEY WORDS
Postpartum
Iron deficiency
Anemia
Mass screening
Hemoglobin

The postpartum period is conventionally thought to be the time of lowest iron deficiency risk because iron status is expected to improve dramatically after delivery. Nonetheless, recent studies have reported a high prevalence of postpartum iron deficiency and anemia among ethnically diverse low-income populations in the United States. In light of the recent emergence of this problem in the medical literature, we discuss updated findings on postpartum iron deficiency, including its prevalence, functional consequences, risk factors, and recommended primary and secondary prevention strategies. The productivity and cognitive gains made possible by improving iron nutriture support intervention. We therefore conclude that postpartum iron deficiency warrants greater attention and higher quality care.

Iron deficiency affects between 20% and 50% of the world's population,[1] and is associated with numerous adverse health outcomes. In developed countries, iron deficiency prevention efforts most often target infants and pregnant women because their high iron requirements make these groups most vulnerable to iron deficiency.[2] Specifically, pregnancy requires about 1000 mg of total body iron, most of which is used to supply oxygen to the fetus, increase maternal red cell mass, and allow for normal blood losses at delivery.[3] The increased iron requirements of pregnancy cannot be met by the typical US diet or the iron stores of most women.[4] Therefore, if women are left unsupplemented during pregnancy, they bear a considerable risk of developing iron deficiency.[3]

In contrast, the postpartum period is conventionally thought to be the time of lowest iron deficiency risk[3] because iron status is expected to dramatically improve after delivery. Maternal body iron stores are enhanced as the expanded red cell mass of pregnancy contracts at delivery.[5] Maternal iron requirements radically decline with the birth of the infant, whose iron needs take precedence over the mother's.[6] Iron losses are significantly reduced by postpartum amenorrhea and the relatively small amount of iron lost through breast milk.[7] Many studies have shown iron status recovering

Dr Bodnar was supported by the Magee-Womens Research Institute Fellowship.

* Reprint requests: Lisa M. Bodnar, PhD, MPH, RD, A742 Crabtree Hall, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA 15261.

E-mail: bodnar@edc.pitt.edu

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doi:10.1016/j.ajog.2004.12.009

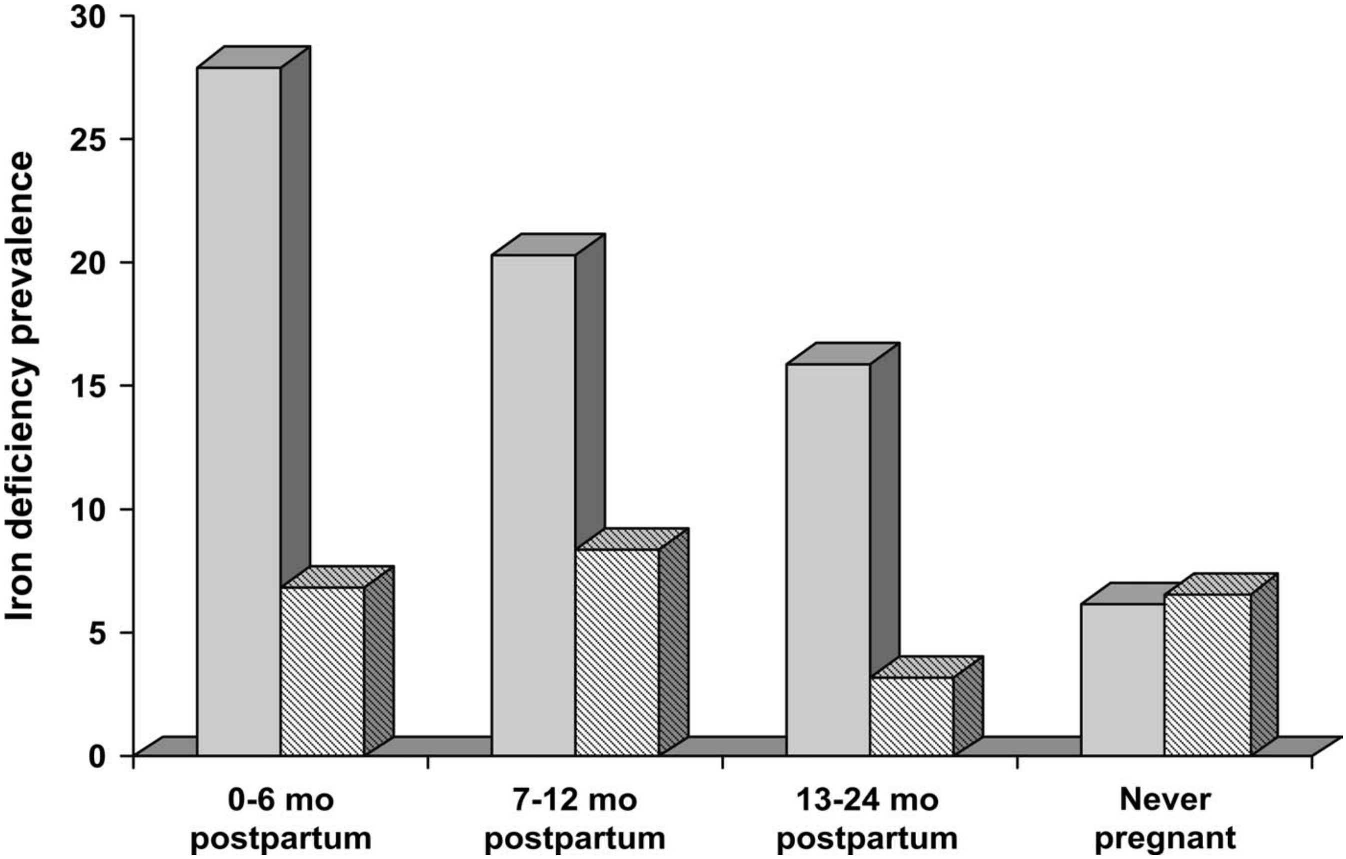

Figure Prevalence of iron deficiency by reproductive status and income among women aged 20 to 40 years, National Health and Nutrition Examination Survey, 1988–1994. Solid bars represent women who had an income ≤130% poverty index, and hatched bars represent women who had an income >130% poverty index. Adapted from reference 15.

and a concomitant low prevalence of postpartum anemia in samples of Caucasian women of mid- to high socioeconomic status.[8-14] Recent investigations of ethnically diverse low-income populations in the US, however, have reported that postpartum iron deficiency and anemia are far more common than previously thought,[15-18] signaling that poor postpartum iron status is a public health problem that warrants greater attention. Moreover, because existing policies for postpartum iron deficiency prevention were based on previous studies of low-risk women, a reexamination of recommendations to prevent postpartum iron deficiency may be necessary.

In light of the recent emergence of this problem in the medical literature, we sought to review the current knowledge on postpartum iron deficiency, including its prevalence, functional consequences, risk factors, and recommendations for prevention and treatment in order to increase clinicians' awareness of this disorder and improve women's postpartum health.

Prevalence

Data from the National Health and Nutrition Examination Survey (NHANES) 1988–1994 indicate that iron deficiency, anemia, and iron-deficiency anemia were prevalent in 12.7%, 10.3%, and 4.2%, respectively, of all US women aged 20 to 40 who were 0 to 6 months postpartum.[15] Iron deficiency was defined as abnormal results for at least 2 of 3 tests: serum ferritin <12 μg/L, free erythrocyte protoporphyrin >1.24 mmol/L, and transferrin saturation <15%. Iron deficiency anemia was defined as iron deficiency plus anemia, with anemia defined as hemoglobin <120 g/L after adjustment for smoking. After stratifying by income status, however, women who lived at ≤130% of poverty (the income threshold for many federal aid programs) were more than 4 times as likely to have iron deficiency (29.7% vs 6.9%; Figure) and iron-deficiency anemia (10.3% vs 2.1%), and 3 times as likely to have anemia (22.2% vs 6.3%) as women who lived at >130% of poverty.[15] This high prevalence of anemia was consistent with other recent studies of low-income populations 1 to 6 months postpartum.[16-18] Prevalence of postpartum anemia also differs substantially by ethnicity/race. In a recent cross-sectional study of 59,428 women participating in the Special Supplemental Program for Women, Infants, and Children (WIC),[16] the prevalence of anemia among non-Hispanic black women ranged from 38.3% to 48.0% from 4 to 26 weeks' postpartum and was roughly twice

Table I Functional consequences of iron deficiency among women of childbearing age

Impaired physical work capacity	
	Aerobic fitness
	Endurance capacity
	Work efficiency
	Fatigue
	Voluntary activity
Deficits in cognitive function and mood	
	Short-term memory
	Verbal learning
	Attention span/concentration
	Intelligence
	Depressive symptoms
Reduced immune function	

that of non-Hispanic white women at each week postpartum; prevalence of anemia among Hispanic women fell between that of black and white women. In each group, hemoglobin concentrations were relatively constant over time. These data also showed that, of the 9129 women who entered WIC with a normal hemoglobin concentration in the third trimester, 21.3% had anemia at their postpartum return visit.[16]

It is currently unknown whether iron status improves after 6 months' postpartum among low-income women. Cross-sectional data from NHANES indicate that iron deficiency prevalence decreases in low-income women from 29.7% at 0 to 6 months' postpartum to 20.3% from 7 to 12 months' postpartum and 15.9% from 13 to 24 months' postpartum (Figure).[15] Even at 13 to 24 months' postpartum, however, the prevalence of iron deficiency in low-income women is higher than for low- or high-income women who have never been pregnant (6.2% and 6.6%, respectively).[15]

Functional outcomes of iron deficiency in women of childbearing age

The functional outcomes of iron deficiency and iron deficiency anemia are well-documented among women of childbearing age (Table I). For this review, we searched MEDLINE on Ovid (1966 to July 2004) for citations in English with the following keywords: (iron, iron deficiency, iron-deficiency anemia, anemia, hemoglobin) and (oxygen consumption, physical endurance, physical fitness, efficiency, work, fatigue, "quality-of-life," immunity, cognition, verbal learning, memory, attention, intelligence, depression, depressive disorder, affect). We included studies where women of reproductive age made up the entire sample or a large proportion of the sample. If a sufficient review article was available, we cited this below and augmented the text with articles that were published subsequently.

Physical work performance

Iron is found in hemoglobin, myoglobin, oxidative enzymes, and respiratory chain proteins, and is therefore essential for oxidative energy production. All levels of iron deficiency adversely influence tissue oxidative capacity, and severe reductions in hemoglobin causing anemia disturb oxygen carrying capacity.[19] It is not surprising, then, that randomized double-blinded, placebo controlled trials have shown that iron deficiency with and without anemia impair aerobic fitness,[20,21] endurance capacity,[19,22] and work efficiency.[19]

For instance, Brownlie et al[20] randomized 41 physically untrained, iron depleted (serum ferritin <16 μg/L), nonanemic (hemoglobin >120 g/L) women aged 18 to 33 to either 100 mg iron or placebo daily for 6 weeks. After all women were physically trained for 4 weeks, the iron-treated group showed significantly greater improvements in 2 markers of aerobic fitness: maximum oxygen consumption (VO_2 max) and maximal respiratory exchange ratio. The results were driven by improvements in fitness levels among women with overt tissue-iron deficiency at baseline (ie, serum transferrin receptor concentrations >8.0 mg/L). These results suggest that marginal iron deficiency without anemia, in the presence of overt tissue-iron deficiency, impairs aerobic adaptation among previously untrained women. In another randomized placebo-controlled trial, Li et al[23,24] found that among 80 iron-deficient, nonanemic and iron-deficient and anemic female cotton workers in China, improvements in VO_2 max found were proportional to the severity of initial anemia. Brutsaert et al[22] reported that after randomizing 20 iron-depleted (serum ferritin <20 μg/L) nonanemic (hemoglobin >110 g/L) women to receive iron or placebo for 6 weeks, the iron-supplemented women showed significant improvements in muscle fatigability.

Iron supplementation of iron deficient women without anemia may also improve nonspecific symptoms, including fatigue. A randomized double-blind, placebo-controlled trial was conducted among 144 nonanemic (hemoglobin ≥ 117 g/L) women with unexplained fatigue, a majority of whom had low serum ferritin concentrations. After 4 weeks of treatment, the iron group reported a significantly lower level of fatigue than the placebo group.[25] These results are consistent with another randomized trial in iron-deficient women[26] and 2 observational studies relating iron status to fatigue.[27,28]

The impaired physical work capacity and fatigue associated with iron deficiency have serious social and economic consequences. Scholtz et al[29] observed that anemic female factory workers produced an average of 5.3% less in the factory, and performed an average of 6.5 hours less of housework per week, results consistent with another recent observational study.[30] Randomized double-blind, placebo controlled trials have indicated that improving iron status can increase work efficiency.

The aforementioned trial by Li et al[24] reported that the iron-treated group had a significant 17% increase in production efficiency (calculated as the ratio of productivity to energy expenditure) compared with the placebo group. Similar increases in work efficiency associated with iron supplementation were reported in a randomized trial of anemic female tea pickers in Sri Lanka.[31] We are unaware of any studies that examined work productivity or voluntary activity in women with iron deficiency without anemia.

Observational data also highlight an association between maternal anemia and depressive disorders. A recent study reported significantly higher depressive symptoms at postpartum day 28 among women who were anemic on postpartum day 7 compared with nonanemic women, and a negative correlation between hemoglobin concentrations and depressive symptoms.[46] Iron deficiency without anemia has also been associated with higher symptoms of depression and irritability among young women taking oral contraceptives.[44]

Cognitive function and mood

A majority of the research on the relation between iron deficiency and cognition has focused on infants and children, with strong evidence indicating that iron-deficient children are at risk of poor cognitive development in the present and future.[32] However, emerging data suggest that iron deficiency adversely impacts the adult brain as well. Distinct from a decrease in hemoglobin synthesis, iron deficiency impacts cognition through a decrease in activity of iron-containing enzymes in the brain.[33-35] In adults, depleted brain iron alters neurotransmitter function, cellular and oxidative processes,[36] and thyroid hormone metabolism.[37]

Several randomized double-blind, placebo-controlled trials of iron supplementation have been carried out among women of childbearing age. One such trial of 16- and 17-year-old girls reported that the iron group had significant improvements in lassitude, mood, and ability to concentrate in school.[38] A study of 25 pregnant teens at <16 weeks of gestation found that twice-daily 90-mg iron treatment for 4 weeks improved some measures of attention span and short-term memory.[39] Both studies had small samples of iron-deficient women. In the only randomized placebo-controlled trial of iron supplementation among nonanemic iron-deficient women, Bruner et al[40] reported a significant increase in verbal learning score in 37 iron-treated women compared with 36 receiving placebo. There were no differences between groups on attention or memory scores. Lynn and Harland[41] randomized an even sample of 413 boys and girls aged 12 to 16 to receive 17 mg elemental iron per day or placebo for 16 weeks. Among the 17% of students with serum ferritin ≤ 12 μg/L, iron-treated subjects showed a statistically significant gain of 6 IQ points compared with control subjects. There was no benefit to iron treatment in the remaining subjects with serum ferritin >12 μg/L.

Most observational studies have shown an association between iron status measures and cognitive performance,[42-44] while one reported no effect.[45] The inconsistent findings may be a result of lack of control of important confounders and relatively few iron-deficient and/or anemic women studied.

Immune function

Iron deficiency depresses lymphocyte, neutrophil, and macrophage function.[47,48] Thus, increased susceptibility to infection is a functional consequence of a deficiency of iron, rather than all-cause anemia. Like certain other trace elements, iron deficiency suppresses the immune system to a sufficient extent as to increase risk of morbidity due to viral, microbial, and parasitic infections.[48,49] Improving iron status with adequate intake restores immunocompetence.[49] Nonetheless, a delicate balance in iron requirement exists. Although iron is needed for effective immune response, if the supply of iron is higher than what is required for the host, the invading microbes can use the iron for growth, exacerbating infections.[47,48] However, the clinical and public health relevance of a high iron supply relative to requirements is not known.

Summary

Taken together, these data indicate that postpartum iron deficiency has subtle yet insidious effects on economic and social aspects of women's lives, including the ability to fully engage in childcare, household tasks, and social and leisure activities. Because iron deficiency alters aerobic capacity and endurance, as well as cognition and mood, it has the capacity to diminish productivity associated with both physical and intellectual work. While reduced endurance causes lower wages in physically demanding jobs, the economic losses associated with cognitive deficits are even more vast, particularly in a developed country such as the US.[50] In fact, the economic consequences of iron deficiency in the US are thought to be tremendous.[50]

Risk factors for postpartum iron deficiency

Many factors exacerbate postpartum iron status, including maternal characteristics at the start of pregnancy, and events occurring during pregnancy, labor and delivery, and the early postpartum period. One of the strongest known risk factors for postpartum anemia is high prepregnancy body mass index (BMI; kg/m^2). The risk of postpartum anemia sharply rises as prepregnancy BMI increases from 24 to 38.[51] Compared with a normal-weight woman with a BMI of 20, anemia risk is nearly twice as great in overweight women with a BMI of 28, and 3 times as great among obese women with a BMI of 38 even after controlling for confounders.[51] This elevated risk may partially result from the high incidence of postpartum hemorrhage, abdominal delivery, and macrosomia among obese women.[52-54] Such complications can result in blood losses up to 1000 mL, the equivalent of 400 mg of iron. In fact, a clinically recognized postpartum hemorrhage and infant macrosomia independently predict a 6.4-g/L and a 5.2-g/L lowering of postpartum hemoglobin concentration, respectively.[55] It is likely that there is a strong relationship between delivery blood loss and risk of postpartum iron deficiency and anemia, but blood loss is difficult to quantify and is therefore lacking in most large datasets.

Lack of prenatal iron supplementation may increase the risk of postpartum iron deficiency. Randomized trials indicate that without prenatal iron supplementation, iron stores, as measured by serum ferritin, remain at deficient levels through 6 months postpartum.[11,14,56] In contrast, hemoglobin concentration may to recover to first-trimester or prepregnancy concentrations by 12 weeks' postpartum without iron supplementation,[8-10,12-14] but nearly all such trials have had important limitations, most notably, their small sample sizes of Caucasian women who entered prenatal care with good iron status and their lack of data on adherence to iron treatment or use of iron supplements postdelivery. Future studies will be needed to determine the effect of iron supplementation on postpartum anemia and iron deficiency in higher risk groups.

Not surprisingly, women with anemia at 24 to 29 weeks' gestation or before delivery are at increased risk of postpartum anemia.[17] Clearly, compromised prenatal iron status would not only render women more vulnerable to the effects of blood loss at delivery, but would limit the amount of iron available to return to mothers' stores after delivery.

Postpartum iron deficiency risk is high among women who deliver multiple fetuses.[57] This increased risk is likely caused by iron demands that are greater than the already high requirements of a singleton pregnancy. In twin pregnancies, plasma volume and red cell mass are 120% that of singleton pregnancies, and multiple fetuses have a greater draw on maternal iron stores than single fetuses.[58] Additionally, women delivering multiple fetuses are more likely to have excessive blood loss at delivery compared with women delivering singletons.[52]

Anemia from 1 to 6 months postpartum occurs more frequently in women who do not exclusively breastfeed,[17] and in women who breastfeed for short durations.[16] One small study reported significantly higher serum ferritin concentrations at 6 months' postpartum in lactating women compared with nonlactating women, even after adjusting for postpartum iron supplement use.[59] The authors attributed the difference in iron stores between the 2 groups mostly to the return of menses, which occurred in 99% of the nonlactating women compared with 15% of lactating women. The lengthened period of amenorrhea associated with lactation[60] decreases the demand for iron, as the iron losses in breast milk are only about half the usual amount lost during menstruation.[61]

In the future, other potential risk factors for postpartum iron deficiency, such as inadequate postpartum iron intake via diet and/or supplements, long duration of lochia, and shortened amenorrhea should be studied and their effects on postpartum iron status quantified.

Guidelines for the prevention of postpartum iron deficiency

Iron deficiency affects more than 1 in 10 women 0 to 6 months' postpartum in the US[15] and, while it disproportionately burdens low-income populations, its common occurrence overall signals that iron deficiency is a problem that should concern all clinicians who care for postpartum women.

The Centers for Disease Control and Prevention (CDC),[57] the Institute of Medicine (IOM),[4] and American College of Obstetricians and Gynecologists (ACOG)[62] have published national recommendations for the prevention of iron deficiency during the postpartum period. The US Preventive Services Task Force does not specifically mention prevention of iron deficiency among postpartum women, but states there is insufficient evidence to recommend for or against routine screening for iron deficiency anemia in asymptomatic persons other than pregnant women and high-risk infants.[63] Prevention of iron deficiency includes ensuring an adequate intake of iron, as well as screening for, diagnosing, and treating iron deficiency. Anemia screening is a particularly important prevention method because the adverse effects of iron deficiency, although serious, may also be subtle and rarely would cause women to seek medical attention. This may be particularly true in the postpartum period, when fatigue, decreased productivity, and poor cognitive functioning could be mistaken for the consequences of lifestyle adjustment associated with a new baby's birth. Screening is necessary to identify which women need treatment. In Table II, we have summarized published prevention guidelines specific to the postpartum period.

For the prevention of iron deficiency in the postpartum period, ACOG recommends iron supplementation "only if the mother herself needs it," and anemia screening at the postpartum visit "when indicated,"[62]

Table II National recommendations for primary and secondary prevention of iron deficiency among postpartum women

	Centers for Disease Control and Prevention[57]	Institute of Medicine[4]	ACOG[62]
Primary prevention	If no risk factors are present (anemia through the third trimester, excessive delivery blood loss, and multiple birth), supplemental iron should be stopped at delivery.	Continue supplemental iron if any risk factor is present (anemia through the third trimester, excessive delivery blood loss, and multiple birth); otherwise, supplemental iron should be stopped at delivery.	"Iron should be administered only if the mother herself needs it."
Secondary prevention	Screening	Screening	Screening
	Anemia screening at the 4- to 6-week visit for women who have anemia continued through the third trimester, excessive blood loss during delivery, and a multiple birth.	Anemia screening at the 4- to 6-week visit for women who have anemia continued through the third trimester, excessive blood loss during delivery, and a multiple birth.	Anemia screening at the 4- to 6-week visit "when indicated." Iron supplements should be kept out of the reach of children.
	Treatment	Treatment	
	Start oral dose of 60 to 120 mg/day iron.	Start oral dose of 60 to 120 mg/day iron.	
	Counsel women about correcting iron deficiency through diet.	Counsel women about correcting iron deficiency through diet.	
	Repeat anemia screening in 4 weeks.	Repeat anemia screening in 4 to 6 weeks.	
	Iron-deficiency anemia is confirmed if repeat screen shows Hb concentration increase $\geq$10 g/L or Hct $\geq$3%.	If there has been no response (an increase $\geq$10 g/L or Hct $\geq$3%) and good compliance, determine serum ferritin concentration and consider other causes of anemia.	
	Treatment should continue for 2 to 3 months.	If there has been a response, treatment should continue for 2 to 4 months or until anemia resolves. After that time, the dosage of iron can be reduced to 30 mg/day for 6 months. Repeat serum ferritin concentration is suggested before termination of treatment to ensure repletion of iron stores.	

but indications are not further outlined. The CDC and IOM recommend that women who have had "anemia continued through the third trimester, excessive blood loss during delivery, and a multiple birth"[4,57] should be supplemented with iron from delivery to the 4- to 6-week postpartum visit and screened for anemia at the postpartum visit. The purpose of a selective supplementation and screening program such as this is to identify and treat nearly all diseased persons while supplementing the minimal number of individuals and carrying out the minimal number of screening tests.[64] An algorithm is used to identify individuals who are at high or low risk of the outcome and refer high-risk individuals for screening and treatment.

Recently, we conducted the first empirical evaluation of the performance of the CDC/IOM selective screening algorithm, and compared it with an algorithm developed in our population of low-income women who delivered singleton infants.[17] This analysis confirmed the importance of prenatal anemia in predicting postpartum anemia risk, and identified 3 risk markers of postpartum anemia (prepregnancy obesity, not exclusively breastfeeding, and multiparity) that were not included in the CDC/IOM algorithm. Postpartum hemorrhage, which had a low prevalence in our population (5%) and has a low prevalence nationally (4%-6%),[65] was not verified as a risk marker. This finding was not surprising because rare complications are unlikely to facilitate anemia prediction in most populations. Although we were not able to evaluate multiple births as a risk marker among our population, the low national incidence of multiple births (~3%)[66] suggests that this risk marker also would likely have little influence on risk assessment of postpartum anemia.

Selective screening with a risk assessment algorithm such as the CDC/IOM algorithm[4,57] or our algorithm[17] may provide a cost-saving option for public health clinics with budgetary constraints. Yet, because anemia screening for iron deficiency is inexpensive and poses few risks to women,[57] universal screening may yield a greater public health benefit than selective screening, particularly in settings where the anemia prevalence is high.[17]

Adequate dietary iron intake in the postnatal period may help to prevent iron deficiency. For women aged 19 to 30, the recommended dietary allowance (RDA) of iron for nonpregnant/nonlactating women, pregnant women, and lactating women is 18, 27, and 9 mg/day of iron, respectively.[7] The recommendation for lactating women is based on the assumption that menstruation will not resume for 6 months' postpartum. A unique recommendation has not been made for nonlactating postpartum women; their RDA is the same as that of nonpregnant/nonlactating women (18 mg/day). Given the high prevalence of iron deficiency, of particular concern is the low RDA for lactating women, a recommendation that has already been questioned.[67] This average requirement was based on iron needs estimated as the sum of iron secretion in human milk, assuming exclusive breastfeeding, and basal losses of iron.[7] As noted above, anemia at 1 to 6 months' postpartum occurs more often in nonlactating than lactating women,[16,17] but it has yet to be determined from such data whether the protective effect of lactation is caused by its lengthening of amenorrhea, which reduces iron loss, or its association with higher socioeconomic status,[68] other healthy behaviors,[69] or an uncomplicated pregnancy or delivery. At 6 months' postpartum, Caucasian lactating women have higher serum ferritin concentrations than their nonlactating counterparts, even after controlling for iron supplement use,[59] but these findings should be confirmed in higher-risk populations.

Clearly, there are major gaps in our knowledge of the best methods of preventing postpartum iron deficiency. Most notably, there are no published data to indicate the effectiveness of the current selective postnatal iron supplementation and anemia screening in preventing postpartum iron deficiency and, more importantly, its functional consequences. Selective supplementation and screening programs should be compared with alternative programs, such as universal screening, to determine which yields the most desirable cost-benefit ratio. Such investigations should be a research priority. More data are also needed on the acceptance of and adherence to iron supplements in postpartum women, and whether or not 9 mg/day of iron is adequate to account for iron losses and recovery of iron status postpartum among lactating women.

Additionally, data are lacking on current postpartum iron deficiency prevention strategies employed by clinicians in public and private settings, including if and when postpartum supplementation and/or anemia screening are used, and specifically if current guidelines are followed. Before national recommendations are modified, these critical gaps must be filled.

Conclusion

Although further research is needed to increase insight into the mechanisms, functional consequences, and risk factors of postpartum iron deficiency and the most effective methods of prevention, data suggest that postpartum iron deficiency is more prevalent than previously thought, and that the postpartum period should not be considered a time of low risk for iron deficiency, particularly among low-income women. Postpartum iron deficiency warrants greater attention and higher quality care. The productivity and cognitive gains made possible with improving iron nutriture in the postpartum period support intervention. Health professionals, researchers, and patients should, therefore, engage in a dialogue about postpartum iron deficiency to further understand prevention of this public health problem.

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