Maternal Iron Deficiency Anemia Affects Postpartum Emotions and Cognition[1]

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ABSTRACT The aim of this study was to determine whether iron deficiency anemia (IDA) in mothers alters their maternal cognitive and behavioral performance, the mother-infant interaction, and the infant's development. This article focuses on the relation between IDA and cognition as well as behavioral affect in the young mothers. This prospective, randomized, controlled, intervention trial was conducted in South Africa among 3 groups of mothers: nonanemic controls and anemic mothers receiving either placebo (10 μg folate and 25 mg vitamin C) or daily iron (125 mg $FeSO_4$, 10 μg folate, 25 mg vitamin C). Mothers of full-term normal birth weight babies were followed from 10 wk to 9 mo postpartum ($n = 81$). Maternal hematologic and iron status, socioeconomic, cognitive, and emotional status, mother-infant interaction, and the development of the infants were assessed at 10 wk and 9 mo postpartum. Behavioral and cognitive variables at baseline did not differ between iron-deficient anemic mothers and nonanemic mothers. However, iron treatment resulted in a 25% improvement ($P < 0.05$) in previously iron-deficient mothers' depression and stress scales as well as in the Raven's Progressive Matrices test. Anemic mothers administered placebo did not improve in behavioral measures. Multivariate analysis showed a strong association between iron status variables (hemoglobin, mean corpuscular volume, and transferrin saturation) and cognitive variables (Digit Symbol) as well as behavioral variables (anxiety, stress, depression). This study demonstrates that there is a strong relation between iron status and depression, stress, and cognitive functioning in poor African mothers during the postpartum period. There are likely ramifications of this poorer "functioning" on mother-child interactions and infant development, but the constraints around this relation will have to be defined in larger studies. J. Nutr. 135: 267–272, 2005.

KEY WORDS: • *iron* • *postpartum* • *maternal* • *cognition* • *behavior*

Iron deficiency is the most common single nutrient deficiency in the world with estimates of >50% of women of reproductive age being affected (1). Most research on infants and young children is consistent with a negative effect of iron deficiency anemia (IDA)[3] on cognitive and behavioral development (2–5). Less research has focused on the effects of iron deficiency in adolescents or young adults (6–9). Of particular interest to us is the effect of iron deficiency on behavior and cognitive functioning (10). Groner and colleagues (6) demonstrated a number of years ago that iron treatment of pregnant adolescents resulted in an improvement in the Digit Symbol cognitive test. More recently, hemoglobin (Hb) concentration was observed to be significantly related to postpartum depression and fatigue in mothers despite the fact that they were of high socioeconomic status (11). This observation is consistent with a general association between improved iron status and the ability to concentrate as well as a reduction in fatigue with iron therapy (7–9,12).

The mechanism(s) by which iron deficiency alters cognition and behavior in adults is largely unexplored despite the generally accepted observation that iron-deficient individuals suffer malaise, are lethargic, and may be less vigilant in performing tasks (10,11). Electrophysiologic recordings showed increased asymmetry related to serum ferritin in adults but no relation to anemia per se (12). Neurotransmitter metabolism was altered in 2 different studies of iron-deficient adult women but the relation to cognition and behavior was not explored (13,14). Animal studies with adult onset iron deficiency were not conclusive regarding neural functioning (15). There is no apparent requirement for "anemia" per se, because Bruner et al. (9) documented a relation between poor memory and low ferritin levels in nonanemic iron-deficient adolescents. Treatment trials showed an association between iron treatment and measures of lassitude (7) and memory (6), suggesting that cognitive and behavioral domains do respond directly to an improvement in iron status.

The overall aim of the study was to determine whether IDA

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[3] Abbreviations used: CN, control; CRP, C-reactive protein; EPDS, Edinburgh Postnatal Depression Scale; Ft, ferritin; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia; IDA-Fe, iron-deficient anemic receiving iron; IDA-PL, iron-deficient anemic receiving placebo; MCV, mean corpuscular volume; R, rand; STAI, state-trait anxiety inventory; TSAT, transferrin saturation.

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TABLE 1

Data collection scheme for mothers and infants[1]

Assessment	6 wk	10 wk	9 mo
Maternal variables	Hematology Sociodemographic Raven's Matrices	Digit Symbol Depression Anxiety Stress Mother-infant interaction	Hematology Sociodemographic Raven's Matrices Digit Symbol Depression Anxiety Stress Mother-infant interaction
Infant variables	Birth information	Physical exam Griffiths scale of development	Physical exam Griffiths scale of development

[1] In addition, home visits occurred every 2 wk to reinforce supplement use and to observe home environment variables.

in postpartum mothers is associated with behavioral changes consistent with negative effects on the mother's interaction with her infant and on the infant's development. This specific report will present the data collected in poor young South African women on the effect of maternal IDA on maternal emotions and cognition. A separate report describes the mother-child interactions and infant development outcomes that resulted from this blind, placebo-controlled, intervention trial (unpublished results).

SUBJECTS AND METHODS

Ethics. All methods were reviewed and approved by the Institutional Review Boards at The Pennsylvania State University and The University of Cape Town and were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Methodology. The study was done in Khayelitsha, South Africa, a periurban community located 40 km east of Cape Town, which is home to a black African population of ~300,000 people. This community has water and electricity but most homes have neither. Most of the population has become urbanized recently, is mobile, and has close ties to their families in the former Ciskei and Transkei in the Eastern Cape Province. The prevalence of IDA in women in 1991 was estimated at 20.8% in a previous survey of this community (16). As a settlement community, nearly all individuals migrated from the Eastern Cape tribal lands to this area in hopes of finding employment and a better quality of life.

Design. The study was a prospective randomized controlled double blind intervention trial involving 3 groups of mothers: iron-deficient anemic mothers provided a daily dose of vitamin C (25 mg) and 10 μg of folic acid (IDA-PL); anemic mothers provided a daily dose of 125 mg of $FeSO_4$, 25 mg of vitamin C, and 10 μg of folic acid (IDA-Fe); and nonanemic control mothers who received no supplementation (CN). Mothers were enrolled in the study at a well-baby clinic visit 6–8 wk after delivery of their infants. Clinic visits occurred at the Empilisweni clinic in Khayelitsha.

The inclusion criterion included the following: *1*) For identification of IDA: Hb between 90 and 115 g/L, and at least 2 of the following iron deficiency parameters: mean corpuscular volume (MCV) $<$ 80 fL, transferrin saturation (TSAT) $<$ 15%, serum ferritin (Ft) $<$ 12 μg/L. These clinical criteria were in accordance with diagnostic evaluations established by the Hematology Department at the Cape Town University Hospital. These definitions were chosen to clearly define IDA (17). We used C-reactive protein (CRP) as an indicator of immune system activation; when the values were $>$5.0 mg/L, ferritin was no longer used as a criterion of IDA because it can be falsely elevated in inflammation. *2*) For the identification of controls: Hb $>$ 135 g/L, MCV $>$ 80 fL, TSAT $>$ 15%, and Ft $>$ 12 μg/L. Any woman with a Hb $<$ 90 g/L was excluded from the study as being too anemic (Hb $<$ 90 g/L); she was referred to treatment and provided iron supplements. *3*) Other inclusion criterion: Mothers had to be between 18 and 30 y old, primary caregivers, breast-feeding for the duration of the study, have no chronic diseases, and be apparently healthy at the physical health screening.[4] The infants had to be $>$38 wk of gestational age, have a birth weight $>$ 2500 g, have no hospitalization during the neonatal period, and have Apgar scores consistent with normal intrauterine growth and development.

Subject enrollment. We employed an opportunistic sampling approach by reviewing the monthly birth statistics of women who delivered in the birthing clinics in the settlement community. On the basis of the reported type of delivery, Apgar scores, birth weight, and residence of the mothers, we then contacted the mothers as potential subjects and requested that they be screened for inclusion into the study. The first direct contact with the mothers was at 6 wk postpartum when they returned to the clinics for well-baby visits. At that time, mothers were provided the informed consent and were screened using a Hemocue. If the Hb value was between 90 and 119 g/L and the woman consented to participate, a venous blood sample was drawn; a Raven's test and a sociodemographic questionnaire were administered, and home and clinic visit follow-ups were scheduled.

Once the hematologic results were determined by the clinical laboratory and examined by the project hematologists, the mothers were allocated (randomly in the case of the anemic mothers) to their treatments and each mother was given a code. One person, who was aware of the code, did the allocation to groups. Control mothers were matched for age, parity, and level of maternal education to the mothers in the anemic intervention groups. The enrollment rate of control mothers was regulated to match the enrollment rate of anemic mothers. Placebo pills or iron supplements were administered in the Health Clinics by staff with detailed instructions regarding the need to keep the pills away from young children and infants, to take 1 pill each day, and to return to the clinic for more pills well before their supply of pills was exhausted. Home field visits were conducted at the scheduled times indicated, but also once every 2 wk as time permitted, to reaffirm the need for the mothers to take their supplements, to conduct dietary intake evaluations, and to maintain contact.

Dropouts. Seven mothers moved to other parts of the country during the course of the study and did not complete the intervention trial. Mothers who dropped out included 4 from the placebo group, 2 from the iron treatment group and 1 from the control group.

Measures. A number of variables were measured in both mothers and infants over the course of the study with the key behavioral variables measured at 10 wk and 9 mo postpartum (**Table 1**). Our evaluation of maternal psychology included the following: the Edinburgh Postnatal Depression Scale (EPDS) (18), the Raven's Colored Progressive Matrices test (19), and 2 Perceived Stress scales (included stress, locus of control) (20). We also collected 3-d food records twice over the course of the study. The EPDS was selected mainly because it was used successfully in a previous study on postnatal depression in this South African Khayelitsha community (21). In the latter study,

[4] HIV was not present in any mothers, although this testing was done as part of a government project and was not a part of our exclusion or inclusion criteria.

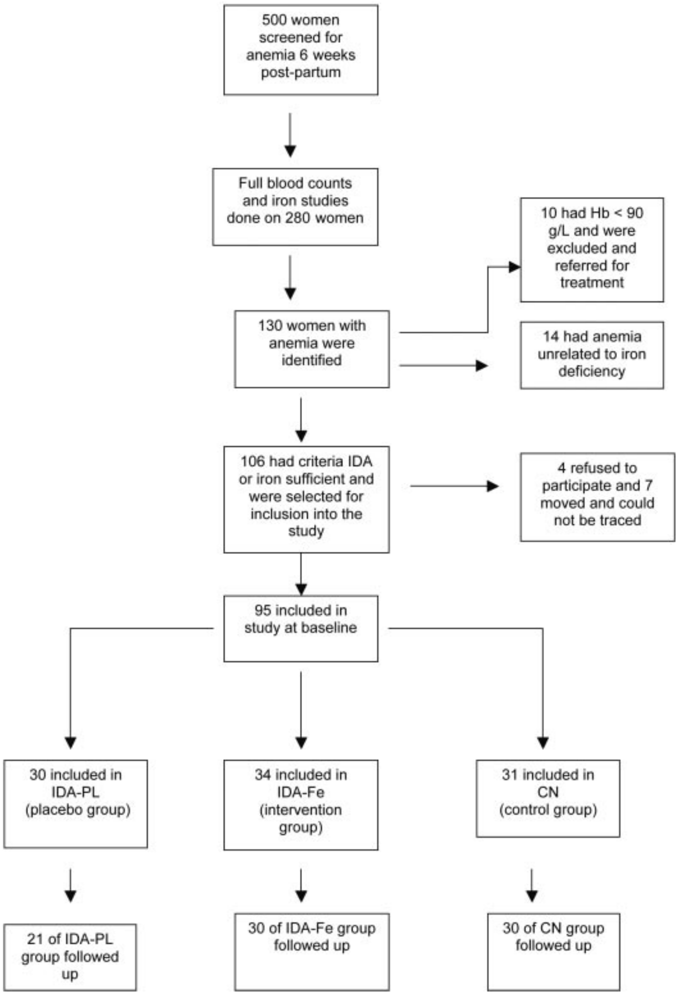

FIGURE 1 Flow chart of recruitment and participation in the study.

the instrument was able to identify a 34% prevalence of postnatal depression in these mothers, and a cutoff score of 10 provided good sensitivity and specificity of clinical depression. The Raven's Colored Progressive Matrices test was used in assessing the nonverbal intelligence of mothers. The cultural sensitivity of this task was recently examined by a WHO committee and others (22). The committee recognized that intercultural comparisons with this task are difficult; however, the 3 studies examined in southern Africa could be utilized within that part of Africa because they were within culture validity. Perceived Stress scales were used in migrant populations in the Cape for many years including studies of effects of both "migration" as well as maternal behaviors (23). Socioeconomic status was assessed by questionnaire with a focus on characteristics such as education, employment, or condition of the home. The questionnaire was used by the Child Health Unit staff in a number of studies in and around Cape Town.

Field workers were trained by Child Health Unit personnel, and interobserver reliability was established in a pilot testing with 10 mothers (Nolungile Clinic, Khayelitsha). The interobserver reliability exceeded 90% for all tests and scales administered. Attention was given to ensuring that the translations of questionnaires from English to Xhosa were culturally sensitive, valid, and appropriate. All depression and health questionnaires were translated and back translated by professional staff at the University of Cape Town.

Informed consent. All of the requirements for participation in the study were explained to the women in their native language, Xhosa. If they agreed to participate, they were asked to sign, or make a symbol of affirmation, in the appropriate place on the informed consent form.

Statistical analysis. All data were analyzed with SAS (version 8.1) software and are presented in tables and figures as means ± SEM. The general statistical approach was ANOVA with repeated measures; significant covariates were entered into the model statement if necessary to control for nonrandom distributions of baseline variables. Data were checked for normality of distribution and log transformed, if necessary, before ANOVA. Log transformation was necessary for ferritin as well as all of the cognitive and behavioral variables. Post hoc Tukey comparisons were considered significant at $P < 0.05$. Analyses at baseline for group differences were conducted both with and without the inclusion of subjects who later failed to return to the clinic for the final evaluation. We utilized the PROC-GLM program within SAS and stepwise linear regression to determine strengths of association.

RESULTS

Of the 500 women initially contacted at the clinics regarding participation, 280 mothers were screened on the basis of inclusion criterion; of these, 95 mothers were enrolled into the study (**Fig. 1**). Anemic subjects in the IDA-PL and IDA-Fe groups did not differ from each other or from nonanemic mothers (CN group) in age, BMI, income, or education after randomization to treatment group (**Table 2**). Anemic mothers differed significantly from nonanemic, CN mothers in hematological variables at baseline but the 2 anemic groups did not differ from one another (**Table 3**). A total of 81 mothers came to the last visit and thus completed the study: 21 in the IDA-PL group, 30 in the IDA-Fe group, and 30 in the CN group. Dietary 3-d food records were administered in duplicate between the 7.5 mo and 9 mo home and clinic visits to determine the adequacy of nutrient intakes (data not shown). There were no significant differences in dietary intake patterns between groups, but nearly all individuals consumed <75% of estimated daily requirements for calcium, iron, phosphorous, zinc, and most vitamins. The iron

TABLE 2

Demographic variables in nonanemic CN women and IDA women administered PL or Fe[1,2]

	n	Age	BMI	Income	Secondary level of education
		y	*kg/m²*	*R/mo*	%
Anemic (IDA-PL + IDA-Fe)	64	23.2 ± 4.0	26.8 ± 4.3	996 ± 774	86.8
Nonanemic (CN)	31	23.8 ± 3.7	28.4 ± 5.4	843 ± 623	75.7

1 Values are means ± SEM.
2 Anemic and nonanemic subjects did not differ significantly from each other in any of these variables, nor was there any difference between anemic mothers assigned to placebo compared with those assigned to iron.

TABLE 3

Maternal hematological and iron status variables at 10 wk and 9 mo postpartum in nonanemic CN women and IDA women administered PL or Fe[1,2]

Group	*n*	Hb		MCV		TSAT		Ft	
		10 wk	9 mo	10 wk	9 mo	10 wk	9 mo	10 wk	9 mo
		g/L		*fL*				*μg/L*	
IDA-PL	21	109 ± 7[b]	120 ± 8[b]*	84.4 ± 6.7	86.1 ± 5.6	0.089 ± 0.042[b]	0.129 ± 0.070[c]	11.9 ± 5.1[b]	17.1 ± 13.9[b]
IDA-Fe	30	108 ± 9[b]	129 ± 8[b]*	87.0 ± 7.6	89.3 ± 4.1	0.084 ± 0.043[b]	0.213 ± 0.085[b]*	10.6 ± 6.6[b]	33.8 ± 19.8[a]*
CN	30	136 ± 5[a]	134 ± 9[a]	90.7 ± 12.4	91.7 ± 4.4	0.274 ± 0.104[a]	0.286 ± 0.116[a]	56.0 ± 28.0[a]	48.4 ± 33.6[a]

[1] Values are means ± SEM. Means in a column with superscripts without a common letter differ, $P < 0.05$. * Different from baseline, $P < 0.05$.
[2] Data were log transformed to normalize the distribution before ANOVA but untransformed values are presented.

intake was 54% of the recommended South African intake for lactating mothers (16).

Iron treatment for 6 mo in the IDA-Fe mothers significantly improved Hb, TSAT, and Ft values, but was insufficient to completely normalize Ft concentrations in all mothers (Table 3). Anemic mothers provided with the placebo micronutrients (IDA-PL group) also had a significant increase in Hb over the 6 mo of the trial, reflecting a natural rate of restoration of iron status postpartum. The magnitude of the improvement in Hb, however, was substantially less than that in the IDA-Fe mothers. There were no changes in hematology of the CN mothers over the course of the intervention. The presence of nfection, as indicated by CRP levels, was similar in all groups. An alternative analysis of the effectiveness of iron treatment demonstrated that significantly more women in the IDA-PL group (25%) than in the IDA-Fe group (18%) were still anemic at the end of the study.

Behavioral and cognitive variables at baseline did not differ between iron-deficient anemic mothers and nonanemic mothers (**Table 4**). However, at the end of the iron intervention trial, a number of behavioral and cognitive variables differed significantly between treatment groups. Iron treatment resulted in a significant "improvement" in previously iron-deficient mothers' Raven's Progressive Matrices test scores as well as their Digit Symbol test scores. These iron-treated mothers had a 25% improvement in scores on the Raven's test; their scores were nearly identical to those of control nonanemic mothers at 9 mo. Anemic mothers who were not given iron had no change in performance on the cognitive tasks. Nearly all mothers experienced an increase in stress level over time, precluding an association with iron status. Covariance analysis for income, education, and baseline cognitive and behavioral levels did not change the main effects of iron treatment of anemic mothers.

To determine the strength of the association of cognitive and emotional state variables with iron status variables, we performed correlation and regression analysis (**Table 5**). At 10 wk, scores on the Raven's test were significantly correlated with Hb but not with other iron status variables. At 9 mo, scores on the Digit Symbol were significantly correlated with MCV, whereas scores on the Perceived Stress scale were significantly correlated with Hb, MCV, and TSAT. Scores on the EPDS and state-trait anxiety inventory (STAI) were significantly correlated with Hb and MCV. The EPDS depression scale, Perceived Stress, and STAI were significantly related to the amount of hunger reported by the mother, and her family income ($r = -0.31$, $r = -0.41$, $r = 0.44$, $P < 0.0001$, respectively) but not with iron status variables after these variables were entered into the prediction equation. We examined the influence of income, educational level of the mother, and relationship with partners in the household (evaluated on the basis of trust, reliability, and practical support) by stratification of mothers into 2 levels of income [rands (R)/mo] and 2 levels of education. Mothers with household incomes > R350/mo performed significantly better in the 3 emotional tests (1.6 vs. 6.1 in EPDS, 12.5 vs. 23 in Perceived Stress, and 24.7 vs. 36.5 in STAI) than mothers with incomes < R350/mo, whereas cognitive performance did not differ. Mothers with higher levels of education, >10 y, had significantly better cognitive performance as evidenced by scores on the Raven's Progressive Matrices (18.6 vs. 15.5) than mothers with <7 y of education, but there was no measurable difference in performance on the Digit Symbol test.

TABLE 4

Scores on cognitive and behavioral measures at 10 wk and 9 mo postpartum for nonanemic CN women and IDA women administered PL or Fe[1,2]

Group	*n*	Depression scale EPDS		Spielberger anxiety STAI		Perceived Stress		Raven's test		Digit Symbol	
		10 wk	9 mo	10 wk	9 mo	10 wk	9 mo	10 wk	9 mo	10 wk	9 mo
IDA-PL	21	2.4 ± 0.4	2.9 ± 0.5[a]	27.9 ± 1.0	27.6 ± 0.1	12.4 ± 0.7	17.2 ± 1.1[a]*	16.6 ± 0.6	16.7 ± 1.0[b]	7.0 ± 0.2	6.3 ± 0.5[c]
IDA-Fe	30	2.5 ± 0.3	2.1 ± 0.3[b]	27.5 ± 1.0	27.9 ± 0.1	16.5 ± 1.0	15.7 ± 1.2[b]	15.8 ± 0.6	20.4 ± 1.0[a]*	7.0 ± 1.3	6.1 ± 0.3[b]*
CN	30	3.1 ± 0.4	3.3 ± 0.5[a]	27.2 ± 0.9	28.6 ± 0.2	15.3 ± 0.8	19.1 ± 1.0[a]*	18.1 ± 0.7	20.3 ± 1.0[a]*	6.5 ± 0.2	6.8 ± 0.6[a]

[1] Values are means ± SEM. Means in a column with superscripts without a common letter differ, $P < 0.05$. * Different from baseline, $P < 0.05$.
[2] Data were log transformed to normalize the distribution before ANOVA but untransformed values are presented.

TABLE 5

Significant simple Pearson product moment correlations of cognitive and behavioral variables with iron status variables at 10 wk and 9 mo[1]

	Hb		MCV		TSAT	
	10 wk	9 mo	10 wk	9 mo	10 wk	9 mo
			r			
STAI	—	0.62*	—	0.58*	—	—
Perceived Stress	—	0.48*	—	0.33**	—	0.33**
Digit Symbol	—	—	—	0.34†	—	—
EPDS		−0.35**	—	−0.34**	—	—
Raven's	0.25‡	0.64*	—	0.42*	—	0.25‡

[1] Correlations were significant at * $P < 0.001$, ** $P < 0.005$, † $P < 0.01$, and ‡ $P < 0.05$.

DISCUSSION

Several important public health findings can be derived from this study: *1*) postpartum depression, stress, and cognitive impairment in poor women may be related to the existence of IDA; and *2*) this depression and stress respond to iron therapy.

The relation between maternal depression, anxiety, and iron status was more evident at 9 mo postpartum than at 10 wk postpartum. This was unexpected because postpartum depression is usually detected and related to mother-child interactions within the first few months after birth (11,24,25). Few of these cited studies, however, specifically examined IDA relative to postpartum depression. Several possible factors can lead to this greater association at 9 mo compared with 10 wk postpartum: *1*) poor iron status and anemia exerted a cumulative effect over time on maternal functioning. Some mothers continued to be iron deficient and anemic in the group that received placebo as dietary intake, and "recovery" during the postpartum period did not match iron requirements. The time frame for "replenishment" of body pools of iron, especially brain iron pools, after a period of iron deficiency is poorly defined. *2*) It is also possible that other factors within the immediate postpartum period may mask or overpower the relation between iron and postpartum depression. Our concept of "cumulative risk" includes both coexisting "environmental effects" as well as the accumulation of these effects, including poor iron status, over time. Our research design did not allow us to distinguish between concurrent effects and accumulated risks. For example, fatigue is a factor during the early postpartum period that has been related to anemia (11), but is likely not specifically dependent on anemia. In our previous work (11), depression symptoms were significantly correlated with the severity of anemia, but the duration of anemia was much shorter than that in the current study and the number of other "environmental risks" were far fewer than what is evident in the underprivileged mothers in the current investigation. For example, "hunger" is a very powerful predictor variable in the current study for maternal anxiety. However, the inclusion of income, spousal help in child rearing, and other items in multiple regression equations did not significantly alter the relation of iron status variables to depression and anxiety.

Mothers in the current study were very poor and remained poor throughout the study; this means that all behavioral and cognitive data should be considered within the context of poverty (21,25,26). Nonetheless, anemic mothers who continued to experience poverty and poor living conditions did show an improvement in depression, stress, and cognitive performance indicators with iron treatment. As noted previously, poverty and hunger were both significantly related to stress in the mothers; although we did not demonstrate correlations between nutritional status, social and economic variables, and behaviors, it would be premature to exclude an association between other social variables with iron status variables.

An "iron response" that connects an improvement in iron status to an improvement in cognition was presented previously in the literature, although not necessarily in the context of the present study (6,9). Iron-deficient adolescent inner city girls showed a significant improvement in verbal learning and memory after iron therapy (9). A placebo-controlled trial in young teen mothers also showed a positive response to iron therapy in cognitive performance variables, but variables of emotional status were not thoroughly studied (6). Other studies showed a relation between cognitive performance and iron status, but these were observational studies without an intervention component (27). A novel observation in the current study, however, is the association of IDA with emotional status and cognition in the postpartum period. Although this is generally a period of large positive changes in iron status if sufficient dietary iron is available, it may also be a period of little or no improvement while demands for maternal care giving continue to rise (28).

Depression, anxiety, and fatigue may well alter the developmental trajectory of the infants of these mothers, but the contributions of biological and environmental factors to a developmental delay/alteration are unresolved. That is, do depression and fatigue lead to altered mother-child interactions and altered infant development? Or does the existence of IDA in mothers several months postpartum indicate a high likelihood that the infants were iron deficient in utero and hence have delayed development because of the intrauterine period of iron deficiency (29–31)? The current investigation clearly cannot answer that set of questions but does demonstrate that further documentation regarding biological and nonbiological relations between maternal iron deficiency and infant growth and development is warranted.

In conclusion, this study demonstrated that there is a strong association of iron status with depression, stress, and cognitive functioning in poor African mothers during the postpartum period. There are likely ramifications of this poorer "functioning" on mother-child interactions and infant development, but the constraints around this relation have yet to be defined. These new data suggest that future studies should consider maternal nutritional status as a risk factor for maternal functioning during the postpartum period.

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