

## Effect of iron supplementation on the iron status of pregnant women: consequences for newborns<sup>1-3</sup>

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**ABSTRACT** We studied the effect of iron supplementation on the iron status of mothers and on biochemical iron status and clinical and anthropometric measures in their infants. The subjects were 197 pregnant women selected at 28 wk  $\pm$  21 d of gestation at a mother-and-child health center in Niamey, Niger. Ninety-nine women received 100 mg elemental Fe/d throughout the remainder of their pregnancies and 98 received placebo. The prevalence of anemia and iron deficiency decreased markedly during the last trimester of pregnancy in the iron-supplemented group but remained constant in the placebo group. Three months after delivery, the prevalence of anemia was significantly higher in the placebo group. At delivery, there were no differences between the two groups in cord blood iron variables. Three months after delivery, serum ferritin concentrations were significantly higher in infants of women in the iron-supplemented group. Mean length and Apgar scores were significantly higher in infants with mothers in the iron group than in those with mothers in the placebo group. *Am J Clin Nutr* 1997;66:1178-82.

**KEY WORDS** Anemia, iron deficiency, iron supplementation, pregnancy, women, newborns, Niger

### INTRODUCTION

In many developing countries, iron deficiency anemia in pregnancy is highly prevalent (1-6). This may be related to high iron requirements during gestation because iron is necessary to cover basal iron losses, the increase in maternal red cell mass, and development of the fetus and placenta (7). The risk of iron deficiency is particularly high in women who begin gestation with depleted or low body iron stores, a situation common in Africa and most Third World countries, where high parity and short intervals between children are often found (8). Also, iron requirements during pregnancy are not easily satisfied by dietary intakes, which generally provide poor iron bioavailability (9, 10).

In the past, the relation between maternal iron status and that in newborn infants was investigated by evaluating the biologic status of newborns according to the presence or absence of anemia in their mothers or by reporting on correlations between biochemical iron indicators in mothers and anthropometric, clinical, or biologic data in their newborns. However, most of these studies were cross-sectional, involving bivariate regression or, in some cases, multiple-regression analysis (11-16). This approach has limited usefulness because anthropometric, clinical, and biologic fac-

tors in newborns are related to numerous factors other than maternal iron status and correlation coefficients may be confounded by the effects of other correlated independent variables. In many studies linking maternal anemia to anemia in newborns, the cause of anemia was not necessarily related to iron status (14-16).

The most efficient way to evaluate the specific relative effect of iron deficiency on newborns is to use methods based on iron-supplementation trials that include a placebo group. Numerous studies showed beneficial effects of iron supplementation on hemoglobin concentrations and body iron stores in pregnant women (11, 17, 18). However, there is little information on the functional benefit of oral iron supplementation during pregnancy on the status of infants. The purpose of this study was to assess the effect of iron supplementation during the last trimester of pregnancy on the iron status of pregnant African women and their newborns. The study included evaluations of clinical and anthropometric outcomes.

### SUBJECTS AND METHODS

The sample was composed of 197 pregnant women aged 17-40 y. All women were selected at 28 wk  $\pm$  21 d of pregnancy during a prenatal consultation in a mother-and-child health center (MCH) in Niamey, the capital of Niger. This MCH center is located in a relatively isolated neighborhood that is socially organized as a village. Different ethnic groups live in this village but there is a predominance of Fulani. The population is equally divided into low- or middle-class civil servants and rural villagers. The entire community was informed of the study through traditional channels and talks with women visiting the MCH clinic.

None of the women had medical or obstetric problems. Informed consent was obtained from each subject. Iron or folate supplements were not given routinely to pregnant

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<sup>2</sup> Supported by a grant from the Nestlé Foundation.

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Received October 2, 1996.

Accepted for publication June 5, 1997.

women at Niger MCH centers at the time the study was conducted. At entry into the study, the women were randomly assigned a number that corresponded to either an oral iron-supplemented group (iron group) or a placebo group. Women in the iron group received 100 mg elemental Fe (ferrous betainate)/d (two tablets containing 50 mg elemental Fe) throughout the remainder of their pregnancies. The women's numbers corresponded to the number assigned by the manufacturer to the packages of tablets.

The double-blind design of this study was made possible by the absence of routine administration of iron or folic acid supplementation to pregnant women in Niamey MCH centers. Although supplementation is strongly recommended by the World Health Organization and UNICEF (19), iron and folic acid tablets were neither given nor prescribed routinely to pregnant women. Supplementation in this study was supervised by physicians, who recorded tablet consumption. The study protocol was approved by the local ethics committee, which was assembled by the dean of the Medical School of Niamey and composed of several faculty members and representatives of the community.

Four venous blood samples (10 mL) were obtained from each mother. The first was obtained on the day of study entry (at 6 mo of gestation), the second during the first stage of labor in the maternity ward in Niamey, and the third and the fourth at 3 and 6 mo postpartum, respectively. Cord blood samples were obtained immediately after clamping, before delivery of the placenta. In infants, blood (450  $\mu$ L) was collected by heel prick when they were 3 and 6 mo old.

For each sample, several assays were performed within 12 h after blood collection. Hemoglobin concentration and mean corpuscular volume were assayed by using a Coulter counter (Coultronic; Margency, France), packed-cell volume by using microcentrifugation (12 000  $\times$  g at room temperature for 5 min), and erythrocyte protoporphyrin values by using a hematofluorometer (Protofluor; Helena, St Leu-la-Forêt, France). Serum fractions were collected by centrifugation (1800  $\times$  g at 4 °C for 20 min), frozen at -20 °C, and sent to France packed in dry ice for other assays. Serum iron concentration was measured with a colorimetric method (20), transferrin was measured with an immunonephelometry assay (Behring, Rueil-Malmaison, France), and total-iron-binding capacity was calculated (21). Transferrin saturation was calculated by expressing serum iron values as a percentage of total-iron-binding capacity. Serum ferritin concentrations were determined in duplicate by an enzyme-linked immunosorbent assay (22). Serum ferritin was standardized according to international standards (National Institute for Biological Standards and Control, London).

Statistical analysis was carried out with Student's *t* and chi-square tests (SPSS software; SPSS Inc, Chicago). Because values for serum ferritin approached a log normal distribution, log transformation of this variable was used in all calculations.

## RESULTS

Ninety-nine pregnant women were included in the iron group and 98 in the placebo group. Mean ( $\pm$  SD) age (27.1  $\pm$  6.4 and 25.9  $\pm$  5.5 y, respectively, in the placebo and iron groups), parity (4.3  $\pm$  2.2 and 4.6  $\pm$  2.9 infants, respectively) and

uterine height (24.3  $\pm$  0.9 and 24.2  $\pm$  0.9 cm, respectively) were not significantly different in the two groups.

Changes in values of iron indicators (means and 5th and 95 percentiles) during pregnancy and 3 and 6 mo after delivery in the two groups of women are shown in **Figure 1**. Percentages of abnormal values for the main iron indicators are shown in **Table 1**. At study entry, the two groups were not different in any iron variables. The evolution of the prevalence of iron deficiency in the two groups is shown in **Figure 2**. Overall, 67.5% of pregnant women were anemic at 6 mo of gestation; 59.4% were iron deficient (two or more of the following abnormalities of independent indicators of iron status: transferrin saturation < 16%, erythrocyte protoporphyrin > 3  $\mu$ g/g hemoglobin, and serum ferritin concentration < 12  $\mu$ g/L). Anemia was associated with biochemical evidence of iron deficiency in 57% of women.

At delivery after 3 mo of iron supplementation, hemoglobin, packed-cell volume, mean corpuscular volume, serum iron, and serum ferritin values were significantly higher and erythrocyte protoporphyrin values were significantly lower (indicating a better iron status) in the iron group than in the placebo group. These differences persisted 3 mo after delivery. The prevalence of anemia and iron deficiency decreased markedly during the final trimester of pregnancy in the iron group but remained constant in the placebo group. Three months after delivery, the prevalence of anemia had decreased in both groups but was significantly higher in the placebo group. This trend persisted 6 mo after delivery but was not significant. The same observation was made about the prevalence of iron deficiency.

No differences between the placebo and iron-supplemented groups were found in any cord blood variables (**Table 2**). At 3 mo after delivery, serum ferritin concentrations were significantly higher in infants of women in the iron-supplemented group. This difference persisted at 6 mo: 42.9% of children with mothers in the iron group had serum ferritin concentrations < 12  $\mu$ g/L compared with 59.3% whose mothers were in the placebo group. Iron deficiency was less prevalent in the iron-supplemented group (48.1%) than in the placebo group (73.1%) but the difference was not significant. Newborn anthropometric data, Apgar scores (23), and placenta weight are shown in **Table 2**. Mean length and Apgar score were significantly higher in the iron group than in the placebo group. A difference in length was not observed at 3 and 6 mo after delivery. There were eight fetal or neonatal deaths—seven in the placebo group and one in the iron-supplemented group.

## DISCUSSION

In our study, the prevalence of anemia and iron deficiency anemia was very high in pregnant women at 6 mo of gestation in the whole population and at delivery in the placebo group. These results are in agreement with those of other studies in the Sahel and sub-Saharan Africa (1-4). Multiple factors affect hemoglobin concentration in Africa: eg, nutritional deficiencies, malaria, parasitemia, and sickle cell diseases. In our sample, anemia was associated with biochemical evidence of iron deficiency in nearly 60% of cases (9). Other etiologic factors may explain why 42% of

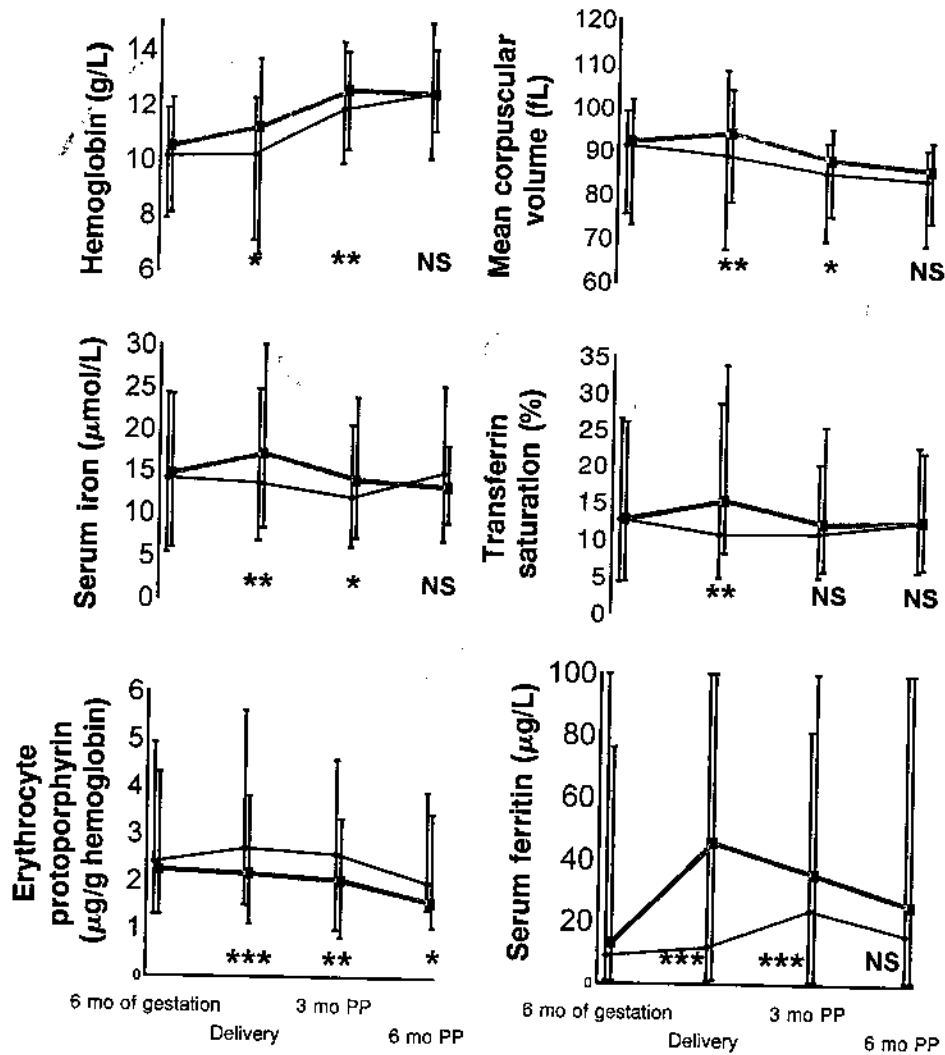


FIGURE 1. Mean values and 5th and 95 percentiles (vertical lines) at four evaluation times in mothers in the placebo (solid line) and iron-supplemented (hatched line) groups. PP, postpartum. Asterisks indicate significant differences between groups: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

cases of anemia in the iron-supplemented group persisted at delivery (compared with 70% in the placebo group). Iron supplementation during the final trimester of gestation had a significant effect on iron status during that trimester and in

the postpartum period. This beneficial effect persisted 3 mo after delivery.

We did not find any difference in iron status of newborns whose mothers had iron supplementation and those whose

TABLE 1

Abnormal values for iron variables in the iron-supplemented and placebo groups of mothers<sup>1</sup>

Iron variables	Placebo group (n = 98)				Iron-supplemented group (n = 99)			
	6 mo of gestation	Delivery	3 mo PP	6 mo PP	6 mo of gestation	Delivery	3 mo PP	6 mo PP
Anemia <sup>2</sup>	69.4	70.4	24.6	10.8	65.7	41.9 <sup>3</sup>	8.4 <sup>4</sup>	2.7
MCV < 80 fL	11.2	19.7	25.0	14.3	10.2	7.8 <sup>3</sup>	13.3 <sup>5</sup>	0
Serum iron < 10 μmol/L	24.5	31.7	37.5	25.9	23.2	10.8 <sup>5</sup>	22.0 <sup>5</sup>	21.4
Transferrin saturation < 16%	67.3	87.8	87.5	70.4	63.6	63.5 <sup>5</sup>	72.0	82.1
Erythrocyte protoporphyrin > 3 μg/g hemoglobin	14.3	25.0	30.1	11.1	12.1	14.7 <sup>5</sup>	7.1 <sup>5</sup>	5.4 <sup>4</sup>
Serum ferritin < 12 μg/L	54.1	51.2	33.9	40.7	48.0	17.6 <sup>3</sup>	12.0 <sup>5</sup>	25.0

<sup>1</sup> PP, postpartum; MCV, mean corpuscular volume.

<sup>2</sup> Hemoglobin concentration < 110 g/L during pregnancy and < 120 g/L after delivery.

<sup>3-5</sup> Significantly different from placebo group: <sup>3</sup> $P < 0.001$ , <sup>4</sup> $P < 0.05$ , <sup>5</sup> $P < 0.01$ .

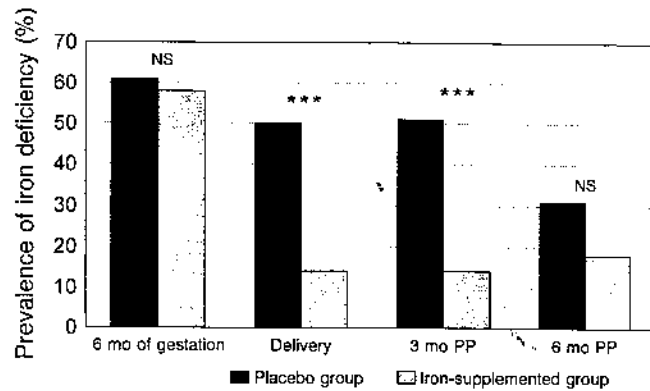


FIGURE 2. Prevalence of iron deficiency at four evaluation times in mothers in the placebo and iron-supplemented groups. PP, postpartum. Asterisks indicate significant differences between groups: \*\*\* $P < 0.001$ .

mothers took placebo; however, such differences began to appear at 3 mo and persisted 6 mo after delivery. The hypothesis that the fetus is able to obtain the iron it requires, even if the mother is iron deficient, is based essentially on early, careful studies of hemoglobin concentrations and hematocrit in mothers and infants. Studies of the relation between indicators of iron status in mothers and infants had somewhat conflicting results. Some authors found such a relation (1, 2, 4, 11, 24) whereas others did not (14, 16, 25). The discrepancies may be explained by different criteria used to define the iron status that did not permit valid classification of iron deficiency in mothers.

Moreover, most studies were cross-sectional and compared iron indicators in mothers during the delivery period with iron indicators in newborns. Evaluation of iron status alone at the end of pregnancy does not necessarily reflect the history of iron status during gestation. Many surveys showed an improvement in most iron indicators at the end of pregnancy (11, 17, 26). Thus, the best way to assess the effect of maternal iron deficiency on newborn iron status is to analyze results of trials of iron supplementation compared with placebo.

In a Dutch study of 30 pregnant women, half of whom were given 100 mg Fe/d beginning in the third month of pregnancy, Van Eijk et al (15) found, as we did, no difference in ferritin

concentrations of cord blood of infants whose mothers received iron supplements and those whose mothers did not. In that study, iron status of the mothers was adequate and none had subnormal serum ferritin concentrations at midpregnancy. In our study, iron deficiency and anemia were highly prevalent in the mothers but, like Van Eijk et al, we found no differences according to maternal iron supplementation in serum ferritin, hemoglobin, and other iron indicators in newborns. We did observe, however, that differences in serum ferritin concentrations appeared at 3 mo of age and persisted at 6 mo. These data are consistent with those of Mac Phail et al (27), who observed that infants of mothers who had not received adequate iron supplementation had very low serum ferritin concentrations at 6 mo of age, thus indicating an effect of maternal iron status on the offspring. The better iron status in infants aged 6 mo could have been due to greater iron contents in breast milk of mothers who received supplementation. This was not investigated in our study but is plausible because all women in the community we studied breast-fed until their infants are  $\geq 18$  mo of age.

One of the major objectives of our study was to assess the effect of iron supplementation on reproductive outcome. Because of the many sources of influence on pregnancy outcome, however, it is obvious that very large samples are needed to study its relation to iron nutrition. In-depth studies of the relation between pregnancy outcome and iron status have not been reported. Only the relation between pregnancy outcome and hemoglobin or hematocrit was studied carefully. Kaltreider and Johnson (28) reported that the incidence of delivery of low-birth-weight infants was significantly higher in women with hemoglobin values  $< 90$  g/L than in women with higher hemoglobin values. Beischer et al (29) and Singla et al (30) observed reduced birth weight in offspring of severely anemic mothers. Harrison and Ibeziako (31) found that maternal anemia was associated with retarded fetal growth. Kuizon et al (32), using multiple-regression analysis, did not find any correlation between birth weight and maternal hemoglobin concentrations; however, anemic mothers had placental hypertrophy.

More recently, one study of 12 718 singleton pregnancies found an association between maternal hematocrit just before delivery and premature birth ( $< 37$  wk of gestation), with

TABLE 2

Iron status and anthropometric and clinical variables in newborns of mothers in the iron-supplemented and placebo groups<sup>f</sup>

	Placebo group (n = 98)			Iron-supplemented group (n = 99)		
	Cord blood	3 mo PP	6 mo PP	Cord blood	3 mo PP	6 mo PP
Hemoglobin (g/L)	133 $\pm$ 20	105 $\pm$ 11	110 $\pm$ 17	136 $\pm$ 22	105 $\pm$ 12	105 $\pm$ 12
MCV (fL)	106 $\pm$ 10	78.9 $\pm$ 4.7	68.5 $\pm$ 3.5	107 $\pm$ 6.7	80.3 $\pm$ 5.4	74.7 $\pm$ 3.6
Serum iron ( $\mu$ mol/L)	18.5 $\pm$ 5.8	10.4 $\pm$ 3.0	9.7 $\pm$ 3.5	16.8 $\pm$ 5.1	13.2 $\pm$ 8.8	11.2 $\pm$ 8.1
Transferrin saturation (%)	34.8 $\pm$ 14.4	10.1 $\pm$ 3.8	8.8 $\pm$ 3.3	32.2 $\pm$ 12.3	13.2 $\pm$ 10.3	10.4 $\pm$ 7.7
Erythrocyte protoporphyrin ( $\mu$ g/g hemoglobin)	3.3 $\pm$ 1.0	2.8 $\pm$ 1.0	2.9 $\pm$ 1.1	3.2 $\pm$ 0.8	2.5 $\pm$ 0.6	2.7 $\pm$ 1.1
Serum ferritin ( $\mu$ g/L)	97 $\pm$ 51	80 $\pm$ 53	15 $\pm$ 20	107 $\pm$ 56	99 $\pm$ 63 <sup>2</sup>	26 $\pm$ 27 <sup>2</sup>
Weight (g)	3016 $\pm$ 450	5941 $\pm$ 836	7056 $\pm$ 748	3046 $\pm$ 408	5888 $\pm$ 672	6940 $\pm$ 850
Length (cm)	47.4 $\pm$ 2.5	60.8 $\pm$ 2.6	66.9 $\pm$ 2.8	48.1 $\pm$ 2.1 <sup>2</sup>	61.2 $\pm$ 2.7	67.0 $\pm$ 3.7
Placenta weight (g)	572 $\pm$ 127	—	—	568 $\pm$ 107	—	—
Apgar score	9.2 $\pm$ 2.0	—	—	9.6 $\pm$ 2.0 <sup>2</sup>	—	—

<sup>f</sup>  $\bar{x} \pm$  SD; PP, postpartum; MCV, mean corpuscular volume.

<sup>2</sup> Significantly different from placebo group,  $P < 0.05$ .

increases in premature births occurring with decreasing maternal hematocrit (33). However, use of the hematocrit value obtained right before birth may have distorted the results. Hemoglobin concentrations and hematocrit increase from the second to third trimester; therefore, women who give birth prematurely have lower hemoglobin concentrations than women who give birth after a full-term pregnancy. In a study of > 50 000 pregnancies, maternal values for hemoglobin and hematocrit were related to pregnancy outcome (34). A U-shaped relation was found among prematurity, low birth weight (< 2500 g), and fetal death. Higher risks were associated with the lowest and highest maternal hemoglobin concentrations. In both of these studies, the authors used a retrospective approach and maternal hematologic values were not examined in relation to iron status or iron supplementation. The studies suggested an association between mothers' iron status and pregnancy outcome but did not confirm that this association was a cause-and-effect relation. Only intervention trials can evaluate the relative effect of maternal iron deficiency on newborns.

Scholl et al (35), using an observational study design, found an association between iron deficiency anemia (serum ferritin concentration < 12 µg/L) and pregnancy outcome but not between iron deficiency without anemia and outcome. In their study, women with iron deficiency anemia had three times the risk of giving birth to an infant with low birth weight. In our study, we did not find a significant difference in birth weight according to maternal iron-supplementation status; however, differences existed in mean length at birth and Apgar score, which were higher in newborns whose mothers had received iron supplements. ■

We thank A Kaka and M Sournayla, Laboratoire de Biochimie, Faculté des Sciences de la Santé, Niamey, Niger, for their helpful assistance and the entire staff of the Centre de Protection Materno-Infantile Lamordé, Niamey.

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