Coffee consumption as a factor in iron deficiency anemia among pregnant women and their infants in Costa Rica[1-4]

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ABSTRACT The influence of coffee consumption on hematological and trace element status was studied in two groups of pregnant, low-income Costa Rican women: coffee drinkers (≥ 450 mL/d, n = 22) and coffee nondrinkers (0 mL/d, n = 26). Groups had similar income, education, prenatal care, age, parity, weight, height, pregnancy weight gain, prenatal iron supplementation, energy, protein, Fe, and vitamin C intake and infant sex and gestational age. Maternal hemoglobin (Hb) and hematocrit (Hct) at 8 mo gestation, cord blood Hb and Hct, infant birth weight and Hb and Hct at 1 mo of age, and breast-milk Fe concentration were significantly lower in the coffee group than in the noncoffee group. The association of coffee with infant Hb and Hct was independent of maternal Fe status and birth weight. These results are consistent with our previously reported data in rats and indicate that maternal coffee intake may contribute to maternal and infant anemia. *Am J Clin Nutr* 1988;48:645–51.

KEY WORDS Iron, coffee, pregnancy, lactation, anemia, human milk, drug-nutrient interactions

Introduction

The potential adverse effects of coffee and/or caffeine consumption on prenatal development is a controversial topic. Although recent epidemiological studies found little evidence for pronounced teratogenic effects of these substances in humans (1–3), in many cases important confounding variables, such as smoking and alcohol consumption, were not properly considered (4). Several indices of nutritional importance have been shown to be affected by coffee and/or caffeine intake. In humans, coffee intake was associated with an increased risk of low birth weight (5) as well as alterations in calcium metabolism (6). Thiamin status in humans was shown to be negatively affected by coffee consumption, apparently through an antithiamin action of tannins (7–9). Zinc and iron absorption can be significantly depressed by coffee intake (10, 11). In rats, offspring of mothers exposed to coffee have a greater risk of low birth weight (12–15) and delayed ossification (16, 17). Dietary caffeine was recently shown to increase Ca excretion in adult rats (18).

Recently, we found alterations in trace-mineral metabolism in offspring of rats consuming coffee during pregnancy (12). Hemoglobin (Hb) and hematocrit (Hct) values of pups of coffee-exposed rats were significantly lower whereas liver Fe concentrations were significantly higher than in pups of control rats. Because the rats were fed a diet with an adequate level of Fe, these findings suggested that coffee may interfere with the mobilization of Fe from the liver to sites of hematopoesis.

To investigate whether these patterns are also present in humans, we conducted a prospective study during late pregnancy and early lactation among low-income women in Costa Rica. Costa Rica was chosen because of widespread and frequent coffee consumption, a high incidence of breast-feeding, broad access to health care facilities, and a low incidence of smoking and alcohol consumption among pregnant women. In this study, variables known to affect pregnancy outcome were carefully considered to isolate as much as possible the influence of coffee on hematological indices.

Subjects and methods

Pregnant women of low socioeconomic status were contacted through the Prenatal Clinic of the Social Security System

[1] From the departments of Nutrition and Internal Medicine, University of California, Davis, CA.

[2] Presented in part at the Federation of American Societies for Experimental Biology meeting, Washington, DC, April 1, 1987.

[3] Supported in part by a grant from the National Institutes of Health, NIH P30 AM 35747, for a clinical nutrition research unit at the University of California, Davis.

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Received June 22, 1987.

Accepted for publication September 29, 1987.

in Cartago, Costa Rica (elevation: 1000 m), from September 1985 through October 1986. Of 378 women interviewed 301 were initially eligible for the study. The selection criteria were age, 17–30 y; parity, ≤ 3; initiation of prenatal care, by 6 mo of gestation; uncomplicated pregnancy and delivery; gestational age at delivery, 38–42 wk; non-smoking and no alcohol consumption; and breast-feeding. These criteria were chosen to reduce the likelihood of major differences between groups aside from coffee consumption that might affect pregnancy outcome. The protocol for this study was approved by the Human Subjects Review Committee at the University of California, Davis.

Based on habitual coffee consumption, these women were divided into coffee drinkers (≥ 450 mL/d and ≥ 10 g ground coffee/d) and coffee nondrinkers (0 mL/d). Women who drank 1–2 cups coffee/d were excluded from the study (n = 188) as were coffee nondrinkers who consumed tea (n = 3). Cola and hot chocolate were rarely consumed by women in this population.

Forty-eight women, including 26 coffee nondrinkers and 22 coffee drinkers, were included in the study. In general, the coffee nondrinkers avoided coffee because they did not like its taste and drank a beverage made out of raw sugar cane (*panela*) instead. The coffee consumed by the coffee group generally contained about the same amount of sugar as the panela (15 g/150 mL). The rest of the eligible subjects (n = 62) did not return for the scheduled visits either before giving birth or postpartum. The dropouts tended to have fewer years of education and a higher parity than did the study subjects. Other than that they were similar in age, income, and marital status.

A consent form signed by each participating subject explained the general nature of the study but did not specify our interest in coffee consumption. No women refused to participate. All women received prenatal supplements (0.5 mg/d folate and 200 mg/d ferric sulfate or 60 mg elemental Fe) by 6 mo of pregnancy and reported taking them regularly. On three occasions during the last trimester one of the authors (LM) obtained a 24-h dietary recall, noted the method of coffee preparation, and measured weight and height of each subject. Between 32 and 36 wk of gestation a midmorning venous blood sample was collected. At the last prenatal visit a food frequency questionnaire was completed. At delivery a cord blood sample was collected whenever possible. Gestational age was evaluated by the attending pediatrician by the modified Dubowitz criteria (19). Birth weight, length, and head circumference were recorded from the medical file.

At 1-wk and 1-mo postpartum mothers returned to the clinic between 0900 and 1000 with their infants. The same investigator as above measured weight (to the nearest 1 g on a beam-balance), length (to the nearest 0.5 cm on an infant measuring board), and head circumference (to the nearest 1 mm). Information was obtained from the mother regarding infant feeding habits and morbidity, and one more maternal 24-h dietary recall was obtained. In addition a venous infant blood sample and a midfeed breast-milk sample were obtained. All blood samples were collected in trace-element–free heparinized vacuum tubes (Vacutainer®, blue top, Becton-Dickinson, Orangeburg, NY) or microcuvettes (Sarstedt, Princeton, NJ). Hb, Hct, and red blood cell (RBC) count determinations (including mean corpuscular volume, MCV, and mean corpuscular hemoglobin, MCH were done the same day of collection. Plasma was stored frozen in acid-washed vials until further analysis. Women were asked not to breast-feed the baby for at least 1 h before the interview, at which time the infant was offered the breast; 3 min after the initiation of let-down reflex, a 10-mL sample of milk was expressed manually into acid-washed plastic vials. Milk samples were frozen until they were transported to the United States for analysis.

Hb was determined with a commercial cyanomethemoglobin kit (Hycel, Houston, TX). Hct values were obtained by centrifugation of blood samples in heparinized microcapillary tubes. RBC count was performed manually in a Hemocytometer after dilution in a Thomas pipet.

Total iron binding capacity (TIBC) was measured with a commercial enzymatic colorimetric assay (Iron and TIBC Assay #565, Sigma, St Louis, MO). Plasma ferritin was analyzed by radioimmunoassay (Rianen Ferritin RIA Kit, Dupont, Wilmington, DE). Because of the small amount of blood obtained from infants, TIBC was not measured in infant plasma and the number of samples for other indices varies.

Plasma and milk concentrations of Fe, Zn, and copper were determined by flame atomic absorption spectrophotometry (Perkin-Elmer 370, Norwalk, CT) after wet ashing in nitric acid (12 mol/L), concentration by evaporation, and dilution to volume with distilled deionized water (20). A delay in the processing of newly collected blood resulted in hemolysis of some samples. Trace mineral values for Fe and Zn were used only from plasma samples that showed no evidence of hemolysis. To adjust for widely different fat concentrations in the milk samples, they were defatted before trace-mineral analysis.

All statistical analyses were conducted with the Statistical Package for the Social Sciences (21). Multiple regression analysis using stepwise procedures was performed including as independent variables all variables in addition to coffee that could have potentially confounding effects. Forced regressions including all independent variables were also performed and the results did not differ from those obtained with the stepwise procedure. Analyses of residuals were performed for the final regression equations obtained to check for linearity and independence. No variables required transformation.

Results

Coffee consuming and nonconsuming subjects were similar in mean age, parity, income, education, initiation of prenatal care and vitamin and mineral supplement use, pregnancy weight gain, and prepregnancy weight and infant gestational age, sex, morbidity, and supplementation with fluids other than breast milk (**Table 1**). Energy, protein, vitamin C, and Fe intakes were also similar between groups, as was frequency of consumption of red meat and dark-green vegetables, which are important sources of dietary Fe (**Table 2**).

Birth weight was significantly lower for infants whose mothers consumed coffee than for infants of coffee nonconsumers ($\bar{x} \pm$ SD: 3189 ± 300 vs 3310 ± 343 g; $p < 0.001$ by multiple regression). In a stepwise regression including age, parity, income, education, duration of prenatal care and supplement use, protein and energy intake, pregnancy weight gain, pregravid weight and percent of ideal weight, coffee intake, and infant sex and gestational age, the variables included in the final equation were gestational age ($\beta = 0.68$), coffee intake ($\beta = -0.29$), and pregravid percent of ideal weight ($\beta = 0.22$). The

TABLE 1
Characteristics of subjects*

	Coffee nonconsumers (n = 26)	Coffee consumers (n = 22)
Age (y)	23.3 ± 3.9†	23.7 ± 3.4
Parity	0.92 ± 1.09	1.32 ± 0.95
Education (y)	7.96 ± 2.25	7.18 ± 1.97
Income (colones/mo)	7620 ± 3290	7350 ± 3390
Prenatal care (mo begun)	3.50 ± 1.39	3.73 ± 1.35
Prenatal vitamin-mineral supplement (mo begun)	3.77 ± 1.37	4.38 ± 1.12
Maternal height (m)	1.556 ± 0.051	1.553 ± 0.044
Maternal weight pregravid (kg)	54.5 ± 8.8	54.1 ± 7.3
Percent ideal weight‡	108.1 ± 13.7	106.8 ± 12.5
Pregnancy weight gain (kg)	11.6 ± 4.4	10.4 ± 3.1
Gestational age (wk)	39.8 ± 1.0	39.9 ± 0.9
Nursing frequency at 1 mo (h between feedings)	2.76 ± 1.09	2.86 ± 0.89
Sex of infants (n males/n females)	15/9	11/11
Infant morbidity: reported illness in first month		
n	8	8
%	31	36
Formula supplement given within first month		
n	7	8
%	27	36
Fluids other than breast milk given within first month		
n	15	13
%	58	59

* No significant differences found between groups ($p \geq 0.10$).
† $\bar{x} \pm$ SD.
‡ Determined from corrected Fogarty tables (22).

TABLE 2
Dietary intake of subjects*

	Coffee nonconsumers (n = 26)	Coffee consumers (n = 22)
Energy (% RDA)†	73.8 ± 27.2	68.3 ± 15.8
Protein (% RDA)†	95.8 ± 42.3	90.3 ± 27.0
Iron (% RDA)†	55.2 ± 23.4	50.8 ± 12.3
Vitamin C (% RDA)†	139.8 ± 50.1	158.0 ± 83.2
Red meat (servings/wk)‡	3.3 ± 1.0	3.3 ± 1.3
Dark green vegetables (servings/mo)‡	2.7 ± 1.3	3.1 ± 1.2

* Values shown are $\bar{x} \pm$ SD; intake from vitamin and mineral supplements not included. No significant difference found between groups ($p \geq 0.10$).
† Mean value from 24-h recalls; Recommended Dietary Allowances (RDA) from INCAP (23).
‡ From food-frequency questionnaire.

other infant anthropometric measurements were found to be similar between groups.

Maternal and cord Hb and Hct values were significantly lower in the coffee group than in the control group (**Fig 1**). Twenty-three percent of coffee consuming mothers had Hb levels < 110 g/L (a commonly used cutoff for anemia during pregnancy; 24) as compared with 0% of the coffee nonconsumer group. Multiple regression analysis indicated that coffee intake was significantly associated with Hb and Hct even when age, parity, income, education, duration of prenatal care and supplement use, pregnancy weight gain, pregravid weight and percent of ideal weight, and intake of energy, protein, Fe, vitamin C, red meat, and dark green vegetables were controlled for.

Maternal RBC count was significantly lower in the coffee consumer group than in the nonconsumer group (**Table 3**). Mean MCV was not significantly different between groups but 43% of coffee consumer group mothers had a value < 82 fL (considered a more sensitive indicator of underlying Fe deficiency during pregnancy than other erythrocyte indices; 25) as compared with 23% of coffee nonconsumer mothers. Mean MCH was not different between groups. Maternal TIBC was slightly higher for the coffee consumer group than for the nonconsumer group although the difference was not statistically significant. Maternal and infant plasma Fe, Cu, Zn, and ferritin values were similar for the two groups (Table 3). The number of mothers with ferritin values < 10 μg/L was similar in the coffee nonconsumer and consumer groups (6 vs 5, respectively). The slightly higher than normal values for Fe and Zn may be due to some degree of hemolysis.

At age 1 wk infant Hb was not different between groups but Hct levels were significantly lower for infants

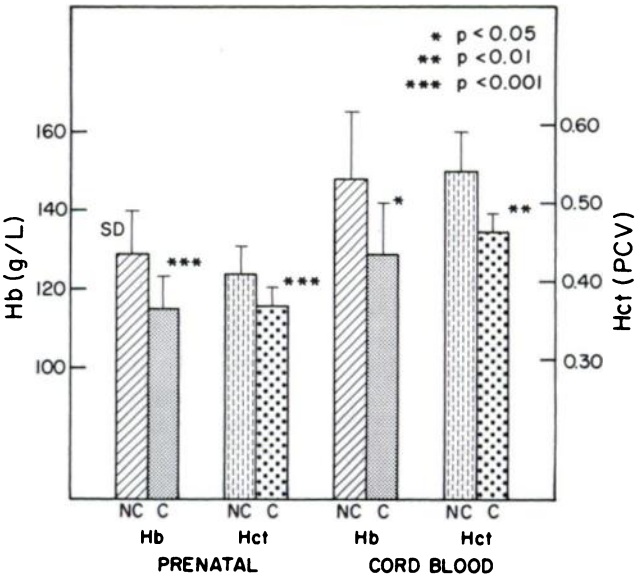

FIG 1. Prenatal and cord Hb and Hct values for the coffee nonconsumer (NC) and consumer (C) groups. Significance levels are based on multiple regression. Sample sizes: prenatal NC = 24, C = 22; cord NC = 8, C = 6. PCV, packed-cell volume.

TABLE 3
Maternal and infant hematological values*

	Coffee nonconsumers	Coffee consumers
Prenatal		
RBC (10^2/L)	4.7 ± 0.3 [26]†	4.4 ± 0.5 [22]‡
MCV (fL)	88 ± 8 [26]	85 ± 9 [22]
MCH (pg)	28 ± 3 [26]	27 ± 3 [22]
TIBC (μmol/L)	69 ± 20 [11]	77 ± 9 [11]
Ferritin (μg/L)	16 ± 14 [12]	14 ± 15 [12]
Fe (μmol/L)	35 ± 11 [10]	28 ± 11 [10]
Cu (μmol/L)	33.8 ± 4.8 [18]	34.5 ± 9.7 [16]
Zn (μmol/L)	15.4 ± 1.9 [11]	14.2 ± 1.7 [10]
Infant—1 wk		
Ferritin (μg/L)	173 ± 86 [13]	206 ± 76 [16]
Fe (μmol/L)	59 ± 21 [12]	67 ± 23 [10]
Cu (μmol/L)	16.1 ± 5.2 [13]	15.3 ± 3.3 [13]
Zn (μmol/L)	31.2 ± 13.8 [13]	26.3 ± 11.0 [13]
Infant—1 mo		
Ferritin (μg/L)	180 ± 71 [14]	198 ± 59 [12]
Fe (μmol/L)	45 ± 15 [13]	39 ± 14 [11]
Cu (μmol/L)	17.0 ± 4.6 [13]	16.7 ± 2.7 [11]
Zn (μmol/L)	25.9 ± 10.9 [13]	19.3 ± 6.9 [10]

* $\bar{x}$ ± SD.
† n = values in brackets.
‡ Significantly different between groups, $p < 0.05$.

of coffee consumer mothers than for infants in the nonconsumer group (**Fig 2**). At 1-mo postpartum both Hb and Hct values were significantly lower in the coffee consumer group than in the nonconsumer group. The influence of coffee consumption was significant even when birth weight was controlled for. Other variables included in the regression analysis were those listed above for the prenatal results plus infant sex, gestational age, morbidity within the first month, and whether the infant received any formula or fluids other than breast milk.

Within the coffee consumer group, multiple regressions were performed to determine whether a dose-response effect was evident. The level of coffee intake was inversely related to infant Hct at age 1 wk ($\beta = -0.54$; $p \leq 0.005$) but no dose-response effect was observed for any of the other outcome variables. The range of coffee intake was 10–48 g dry coffee/d but only three women had intakes > 25 g/d.

To determine whether the influence of maternal coffee intake on infant Hb and Hct was an indirect effect of the lower maternal Hb and Hct levels, the correlations between maternal and infant Hb and Hct values were examined. None of them was statistically significant. Nonetheless, multiple regressions were performed with prenatal Hb and Hct included as independent variables for each of the infant outcome variables. With these regressions coffee intake was no longer significantly associated with infant Hct at 1 wk but was still inversely related to infant Hb and Hct at 1 mo ($\beta = -0.44$ and -0.41, respectively; $p < 0.05$).

Concentrations of Cu and Zn in milk were similar in both groups but milk Fe levels at 1 mo averaged one-third lower in the coffee consumers (**Table 4**). Maternal prenatal Fe status, particularly MCV, was significantly associated with milk Fe concentrations ($r = 0.51$; $p < 0.01$). Although the natural log of ferritin was also positively related to breast milk Fe ($r = 0.38$), the correlation was not statistically significant because of small sample size. Dietary Fe had no effect on milk Fe in the regression analysis. In a multiple regression including both coffee intake and maternal MCV as independent variables, the influence of coffee consumption on milk Fe was marginally significant ($\beta = -0.35$; $p = 0.058$). Milk Fe was not related to infant Hb and Hct at age 1 mo ($r = -0.28$ and -0.04, respectively; $p > 0.20$).

Discussion

Our results indicate that maternal coffee consumption is associated with lower infant birth weight; lower levels of maternal, cord, and infant Hb and Hct; and decreased concentrations of Fe in breast milk in this population of low-income women. The influence of coffee on birth weight was independent of maternal energy intake or weight gain during pregnancy. Energy intake was slightly though not significantly lower in the coffee group and may reflect an appetite-depressant effect of coffee or the substitution of coffee in the diet for other foods of higher energy density. However, the multiple regression results

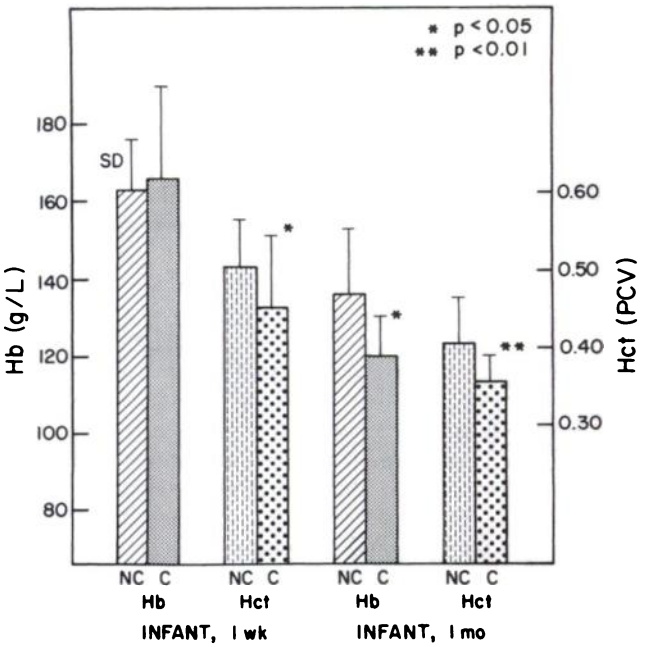

FIG 2. Infant Hb and Hct values at 1 wk and 1 mo of age for the coffee nonconsumer (NC) and consumer (C) groups. Significance levels are based on multiple regression. Sample sizes: 1 wk NC = 10 Hb and 15 Hct, C = 8 Hb and 15 Hct; 1 mo NC = 9 Hb and 19 Hct, C = 11 Hb and 14 Hct. PCV, packed-cell volume.

TABLE 4
Milk iron, zinc, and copper concentrations*

	1 wk		1 mo	
	Coffee nonconsumers	Coffee consumers	Coffee nonconsumers	Coffee consumers
Iron (μmol/L)	4.8 ± 2.3	3.6 ± 1.8	5.7 ± 2.0	3.8 ± 1.6†
n	11	10	13	13
Zinc (μmol/L)	40.1 ± 17.4	41.6 ± 14.4	28.2 ± 15.1	21.3 ± 9.5
n	11	12	14	14
Copper (μmol/L)	6.6 ± 1.7	7.4 ± 1.3	5.2 ± 1.7	5.2 ± 1.7
n	11	11	14	14

* $\bar{x} \pm$ SD.
† $p = 0.01$.

indicated that coffee was negatively associated with birth weight even when energy intake was controlled for. Consistent with these results, in our rat study (12) we found no difference in total food intake between coffee consumer and nonconsumer groups, yet birth weight was significantly lower in the former.

Fe deficiency anemia (Hb < 110 g/L) was observed in 23% of the coffee consumers as compared with none of the nonconsumers. All of the women in the study were living at a relatively high altitude and therefore an even higher cutoff point for defining anemia could be justified (24). Thus, the figure of 23% may actually be an underestimate of the percentage of coffee consumers who were anemic. The other hematological results (low RBC count and low MCV) suggest a microcytic normochromic type of anemia in the coffee consumers. Although the difference in maternal TIBC between groups was not statistically significant, the higher mean value in the consumer group is in accordance with an Fe deficiency state in these women. It is important to note that this high incidence of anemia occurred even though all of the women in the study reported taking supplemental Fe regularly. An interesting observation is that these supplements were usually taken during breakfast, which generally consisted of coffee (or panela for the no-coffee group); cereals, such as bread, tortilla, or rice; beans; and perhaps milk and/or eggs. Some of these foods, including coffee, are known to negatively affect Fe absorption (10, 26–28). On the other hand, it is possible that panela could have a positive effect on Fe absorption because of the enhancement of Fe absorption by carbohydrates (29). However, the amount of sugar added to coffee was similar to that in panela.

The association of coffee intake with infant Hb and Hct was independent of its relationship to birth weight as indicated by the significance of coffee intake in the regressions when birth weight was included. Likewise, coffee was negatively related to infant Hb and Hct independently of its association with maternal Hb and Hct.

The lower Fe content of milk of coffee consumer mothers was in part related to the association of coffee with maternal Fe status. To our knowledge the association between maternal MCV and milk Fe levels has not been reported (30). However, coffee was still marginally associated with milk Fe when maternal MCV was controlled for. These results suggest that there may be a direct relationship between coffee intake and milk Fe concentration. The lower milk Fe levels in the coffee consumer group were not causing the lower infant Hb and Hct levels at age 1 mo because there was no significant association between milk Fe and infant hematological values. Thus, maternal coffee consumption may affect the infant directly either prenatally during fetal development or postnatally via the transmission of constituents of coffee in breast milk.

The design of the present study does not allow us to identify the possible mechanisms for the effects of coffee on Fe status. The results are similar in some respects to those found in the previous rat study (12). In both cases coffee was negatively related to infant Fe metabolism as manifested by decreased Hb and Hct levels. In the rat study a cross-fostering design indicated a postnatal effect of coffee because pups of control mothers showed reduced Hb and Hct levels after only 3 d of being cross-fostered to coffee mothers. However, this does not rule out the possibility of a prenatal effect of coffee on fetal Fe metabolism as well. In addition to the coffee treatments, steam-decaffeinated coffee was given to another group with results very similar to those found in the regular coffee groups (unpublished data), suggesting that caffeine is not the causative factor for the observed effects. It should be noted that there are several other metabolically active compounds in coffee in addition to caffeine, including other methylxanthines, aromatic volatile and nonvolatile acids, piperidines, chlorogenic acid, tannins, trigonelline, and ketones (31). About 20% of the solids in coffee have not yet been identified (32).

In our rat study liver Fe stores were elevated in the coffee consumer group but the human results show no increase in plasma ferritin (considered to be reflective of Fe stores) in coffee consumers compared with nonconsumers. Plasma ferritin was not measured in our rat study. Note that the animals started pregnancy with adequate Fe reserves. Maternal prenatal Hb and Hct levels

of rats were normal, which was not the case for the human subjects, whose dietary Fe intake (exclusive of supplements) was only ~50% of recommended levels (23). Moreover, it is not known whether plasma ferritin is a good indicator of liver Fe stores under certain pathological states. It is possible that coffee disrupts the normal relationship between liver ferritin and plasma ferritin. Thus, the apparent impaired mobilization of liver Fe stores observed in the rat study is not necessarily inconsistent with the human results.

Although the Food and Drug Administration recommends that women avoid coffee consumption during pregnancy, no such recommendation exists for lactation. The use of drugs during lactation has been a topic of considerable research, including the transfer of caffeine into breast milk (33, 34). However, the other active compounds in coffee besides caffeine have generally been disregarded. The relationship between coffee and breast-milk Fe has potential health consequences because the Fe content of human milk is normally relatively low (although highly bioavailable). Given that the infants of coffee consumer mothers in this study were already at greater risk of anemia, the later consequences of low milk Fe may be serious.

In Central America indirect exposure to coffee prenatally and in early infancy may be compounded by direct feeding of coffee to older infants and young children. It has been estimated that children under age 3 y in Central America have a daily intake of ~2–3 g dry coffee (35, 36) and in Guatemala bread softened with coffee has been reported as one of the first foods fed to infants (37). Merhav et al (38) recently reported a much higher incidence of microcytic anemia among tea-drinking infants than among tea nondrinkers in Israel. Considering the high incidence of Fe deficiency anemia worldwide and its likely association with immunological function (39–43) and mental development (44, 45), these findings indicate that dietary habits such as coffee and tea consumption deserve more attention as potential causative factors. Further studies among women drinking < 3 cups coffee/d and in populations with a lower prevalence of Fe deficiency are necessary to evaluate the public health significance of our findings.

We gratefully acknowledge the access to facilities and general assistance provided by the Instituto Costarricense de Investigacion y Ensenanza en Nutricion y Salud (INCIENSA). Dr Charles Franti provided valuable statistical advice.

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