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## Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study<sup>1-3</sup>

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**ABSTRACT** Using criteria from the Centers for Disease Control, anemia and iron-deficiency anemia (anemia with serum ferritin concentrations  $< 12 \mu\text{g/L}$ ) were assessed in  $> 800$  inner-city gravidas at entry to prenatal care. Iron-deficiency anemia was associated with significantly lower energy and iron intakes early in pregnancy and a lower mean corpuscular volume. The odds of low birth weight were tripled and of preterm delivery more than doubled with iron deficiency, but were not increased with anemia from other causes. When vaginal bleeding at or before entry to care accompanied anemia, the odds of a preterm delivery were increased fivefold for iron-deficiency anemia and doubled for other anemias. Inadequate pregnancy weight gain was more prevalent among those with iron-deficiency anemia and in those with anemias of other etiologies. The prevalence of iron-deficiency anemia (3.5%), however, was lower than anticipated for an inner-city, minority population in whom most anemias had been attributed clinically to iron deficiency. *Am J Clin Nutr* 1992;55:985-8.

**KEY WORDS** Pregnancy, anemia, iron-deficiency anemia, preterm delivery, low birth weight, serum ferritin

### Introduction

Anemia is more common in women, especially if they are young, poor, pregnant, or members of an ethnic minority. Until recently it was assumed that maternal anemia, which is considered to be prevalent during pregnancy, had few untoward sequelae, particularly for the fetus (1). However, in the past few years the relationship between anemia and poor pregnancy outcome, specifically an increased risk of preterm delivery, has been supported by several (2-5) but not all (6, 7) studies of the problem. The role of maternal anemia, particularly iron-deficiency anemia, in the etiology of preterm delivery therefore remains a source of controversy. Thus, the purpose of this study was to examine the influence of iron-deficiency anemia on preterm delivery.

### Methods

A total of 826 women aged 12-29 y—patients at two prenatal clinics in Camden, NJ—were recruited into a prospective study of maternal growth and nutrition during pregnancy. Gravidas with a history of serious nonobstetric problems (eg, systemic lupus erythematosus, chronic hypertension, diabetes mellitus, seizure disorders, leukemia or drug or alcohol abuse) were ex-

cluded. Because the study focused on differences in growth and development between adolescents and adults, which potentially affected the outcome of pregnancy, the samples were balanced with respect to parity and included young ( $< 18$  y) and more mature ( $\geq 18$  y) groups of pregnant women. Because effects of maternal anemia on outcome were found to be consistent for age and parity groups, data on young and more mature women were pooled in the analyses that follow. The study was conducted according to the guidelines of the University of Medicine and Dentistry of New Jersey and Cooper Hospital/University Medical Center.

Social, demographic, anthropometric, and dietary data were obtained during pregnancy by interview. Dietary intakes were obtained as recalls of the previous day's diet by a registered dietitian experienced in working with this population. Intake was estimated by the average of two such recalls taken early in pregnancy. Use of supplemental iron was also obtained by interview at entry to care, and in the second and third trimesters of pregnancy.

Maternal weight was measured at each prenatal visit, maternal height was measured at entry to care, and prepregnancy weight was obtained by recall. Body mass index (BMI) was computed as prepregnancy weight-for-height<sup>2</sup> (in  $\text{kg/m}^2$ ). Timing of bleeding and spotting during pregnancy, if any, was obtained by interview as well as from the medical record. Information on current and past pregnancy outcomes and complications were abstracted from the prenatal record, the delivery record, delivery logbooks, and the infants' charts.

Blood samples were drawn at entry to prenatal care and a sample was assayed for a quantitative measurement of serum ferritin by radioimmunoassay, by using the kit produced by Micromedics Systems, Inc, Horsham, PA. Hemoglobin, hematocrit, and mean corpuscular volume (MCV) measurements, assayed by standard methods from blood samples obtained at the same

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draw as the sample for ferritin, were abstracted from the medical record.

A total of 49 patients who did not have their serum ferritin concentrations measured were excluded. A comparison of their background characteristics and pregnancy outcomes to the cohort as a whole indicated that these patients were more likely to be smokers (49.0% vs. 26.7%) and less likely to have inadequate weight gain for gestation (13.0% vs. 26.4%).

Anemia was defined according to criteria proposed by the Centers for Disease Control (CDC) (8) and refined by the National Academy of Sciences (NAS) panel on nutrition and pregnancy (9). For all anemias, these criteria include hemoglobin values below the 5th percentile of CDC standards for gestation. By trimester, the lowest values meeting this definition were 110 g/L (first trimester), 105 g/L (second trimester), and 110 g/L (third trimester). Anemia accompanied by a low serum ferritin concentration, that is,  $< 12 \mu\text{g/L}$ , was considered by the NAS panel to reflect iron-deficiency anemia (9).

Gestation was reckoned from the mother's last menstrual period (LMP) as well as from the obstetric estimate. The obstetric estimate is also based on the LMP but is confirmed by an early ultrasound (70%) or serial measurement of uterine fundal height. In the event of a size-for-dates discrepancy  $> 2$  completed weeks, the obstetric estimate was based solely on early sonography ( $< 26$  wk). In this, as well as in our other studies (10), consistent effects on outcome were obtained with both estimates of gestation so that only results for which the LMP was used are reported.

Outcomes of interest included adequacy of weight gain for the entire pregnancy, defined to within 2 completed weeks of delivery by using published criteria (11); low birth weight ( $< 2500$  g); preterm delivery ( $< 37$  wk completed gestation); and size: small-for-gestational-age (SGA) ( $< 10$ th percentile for standards). Brenner et al's standards (12), used to define SGA births, allow for birth weight to be adjusted for length of gestation, ethnicity, maternal parity, and fetal sex.

Confounding was assessed by comparing adjusted and crude odds ratios because the problem of relying on tests of statistical significance alone is well recognized. Separate models were fitted for each outcome containing the risk factor, potential confounding variables, and interaction terms by using forward inclusion and backwards deletion. Multiple logistic regression, with control for confounding, was used when low birth weight, preterm delivery, and SGA were the outcomes of interest. Adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were computed from the logistic-regression coefficients and the corresponding covariance matrix (13).

## Results

At entry to care, which was on average  $16.7 \pm 5.4$  completed weeks ( $\bar{x} \pm \text{SD}$ ), a number of background characteristics differentiated anemic from nonanemic women (Table 1). These included a lower prepregnancy BMI, multiparity, and black ethnicity. Cigarette smoking was more common among the anemic women as was a history of prior poor outcome, particularly preterm birth. Use of iron supplements at entry to care was also more common among women who were anemic. Over the course of pregnancy, 76.5% of those initially anemic and 62% of those who were nonanemic used supplemental iron in addition to the iron contained in their prenatal multivitamins.

TABLE 1  
Background characteristics of women with and without anemia at or before entry to prenatal care\*

	Anemia ( <i>n</i> = 217)	No anemia ( <i>n</i> = 562)
Age (y)	18.4 $\pm$ 3.7	18.4 $\pm$ 3.9
BMI†	21.7 $\pm$ 3.5	23.2 $\pm$ 4.6
Multiparous (%)	53.0	45.2
On Medicaid (%)	77.9	79.2
Black ethnicity (%)	77.4	55.7
Cigarettes smoked per day (%)		
None	60.6	79.9
1-10	30.0	19.8
11-20	8.9	2.7
$> 20$	0.5	0.6
Prior child with low birth weight (%)	8.3	5.2
Prior preterm delivery (%)	8.8	5.0
Vaginal bleeding at entry (%)	18.0	14.8
Iron supplementation at entry (%)	10.6	4.6
Iron supplementation during pregnancy (%)	76.5	61.9

\*  $\bar{x} \pm \text{SD}$ . CDC criteria for anemia during pregnancy were based on hemoglobin and hematocrit values alone.

† Body mass index (in  $\text{kg/m}^2$ ).

An examination of the unadjusted proportions for outcomes among the total group of women who were anemic at entry showed a significantly increased risk of preterm birth ( $\chi^2 = 5.62$ ,  $P < 0.02$ ). After confounding was controlled for, however, there remained little increase in risk of preterm delivery and only a modestly increased risk of LBW and SGA, which was not statistically significant (Table 2). But, in this group, the risk of inadequate weight gain over the whole of pregnancy was increased by 50%.

The group of anemic women was then subdivided into those who did and those who did not meet the criteria for iron-deficiency anemia. At entry,  $\approx 27.9\%$  of pregnant women met the CDC's definition for anemia, but, of these, only 12.5% also met the criteria for iron-deficiency anemia (anemia accompanied by a low serum ferritin concentration,  $< 12 \mu\text{g/L}$ ). A total of 67.9% of the anemias detected at entry to care had been attributed clinically (Fe/TIBC ratio) to iron deficiency, and the women clinically diagnosed with iron-deficiency anemia were supplemented with iron in the course of their pregnancies. In one instance, anemia was attributed to a hemoglobinopathy (0.5%); in the remaining cases no cause was determined.

The MCV of red blood cells usually is decreased when anemia is caused by iron deficiency, although MCV alone is not a good diagnostic criterion of iron-deficiency anemia during pregnancy. At entry to care the MCVs of both groups of anemic women were lower than those of the nonanemic women. However, the average MCV (81.5 fL) of anemic women with low serum ferritin concentrations was significantly less than that of women who were not anemic and that of anemic women with higher concentrations of serum ferritin ( $\geq 12 \mu\text{g/L}$ ) (Table 3).

Diets of anemic women with low serum ferritin concentrations were also significantly lower (one-tailed *t* test) in energy (7743  $\pm$  784 vs 9702  $\pm$  146 kJ;  $\bar{x} \pm \text{SE}$ ,  $P < 0.01$ ) and in iron (13.3 mg  $\pm$  2.6 vs 17.9 mg  $\pm$  0.5,  $P < 0.05$ ) than were the diets of nonanemic women when age, parity, gestation at entry to care,

TABLE 2

Anemia and iron-deficiency anemia: associations with inadequate weight gain and pregnancy outcome\*

Outcome	Anemia			No anemia
	Total	Iron deficiency	Causes other than iron deficiency	
Low birth weight				
Unadjusted (%)	17.1	25.9	15.9	12.2
AOR†	1.55	3.10	1.34	1.00
95% Confidence interval	0.96-2.51	1.16-4.39	0.80-2.22	—
Preterm delivery				
Unadjusted (%)	26.2	44.4	23.5	18.4
AOR†	1.30	2.66	1.16	1.00
95% Confidence interval	0.86-2.24	1.15-6.17	0.76-1.79	—
Small-for-gestational-age				
Unadjusted (%)	11.1	8.3	11.5	7.5
AOR‡	1.66	1.24	1.67	1.00
95% Confidence interval	0.90-3.04	0.29-6.94	0.90-3.41	—
Inadequate weight gain				
Unadjusted (%)	31.0	40.0	29.9	24.6
AOR§	1.62	2.67	1.51	1.00
95% Confidence interval	1.10-2.36	1.13-6.30	1.02-2.25	—

\* AOR, adjusted odds ratio.

† Adjusted for maternal age, parity, ethnicity, prior LBW or preterm delivery, bleeding at entry, gestation at initial blood draw (entry), number of cigarettes smoked per day, and prepregnancy BMI.

‡ Adjusted for maternal age, parity, ethnicity, prior LBW, bleeding at entry, gestation at initial blood draw (entry), number of cigarettes smoked per day, and prepregnancy BMI.

§ Adjusted for maternal age, parity, ethnicity, bleeding at entry, gestation at initial blood draw (entry), and prepregnancy BMI.

and low prepregnancy BMI were controlled for. Diets of anemic women with serum ferritin concentrations  $\geq 12 \mu\text{g/L}$  reflected energy ( $9970 \pm 561 \text{ kJ}$ ,  $\bar{x} \pm \text{SE}$ ) and iron ( $18.3 \pm 1.9 \text{ mg}$ ,  $\bar{x} \pm \text{SE}$ ) intakes that did not differ significantly from intakes of the nonanemic women.

When anemia specific to iron deficiency was used as the independent variable and after confounding was controlled for, there was a  $> 2.5$ -fold increase in risk of preterm delivery (Table 2). The AOR for LBW was tripled in the women with iron-deficiency anemia but the risk of SGA was not increased. Risk of preterm delivery, SGA, and LBW were not significantly increased in anemic women who were not iron deficient. The exclusion of preterm infants who were also SGA did not alter the AOR for SGA births and maternal anemia. However, risk of inadequate weight gain for pregnancy was increased in both iron-deficient and noniron-deficient anemic women.

Bleeding at or before entry to prenatal care also increased the risk for preterm delivery (AOR 1.87, 95% CI 1.19-2.93), but not for LBW (AOR 1.30, 95% CI 0.77-2.27) or SGA births (AOR 0.65, 95% CI 0.26-1.58). Effects of bleeding and anemia (with adjustment as given in Table 2) were additive. The AOR for preterm delivery among iron-deficient anemic women who bled was 4.98 (95% CI 2.92-8.48). Risk of preterm birth was doubled for anemic women who were not iron deficient but who had had bleeding at entry to care (AOR 2.17, 95% CI 1.19-3.94). For all anemic women with bleeding at entry, the AOR was more than doubled (AOR 2.48, 95% CI 1.37-4.48).

Low concentrations of circulating ferritin, per se, did not influence risk of preterm delivery. After the data for women with

iron-deficiency anemia were excluded, the AOR of preterm delivery for women with serum ferritin concentrations  $< 12 \mu\text{g/L}$  at entry to care was 1.04 (95% CI 0.49-2.23), after the variables shown in Table 2 were adjusted for.

## Discussion

Ferritin is considered the "gold standard" for the diagnosis of iron-deficiency anemia in pregnancy (9, 14). Anemia (low hemoglobin or hematocrit) accompanied by a low serum ferritin concentration reflects iron-deficiency anemia, the most severe stage of iron depletion. Apart from iron deficiency, other causes of anemia are not characterized by low ferritin concentrations ( $< 12 \mu\text{g/L}$ ) (9).

Iron-deficiency anemia is characterized by the presence of microcytic red cells manifesting as an MCV generally  $< 80 \text{ fL}$ . Consistent with this, at entry to prenatal care, the MCV of both groups of anemic women was lower than the MCV of the nonanemic women. However, the MCV of anemic women with iron deficiency was significantly less than the MCV of nonanemic women and of women with other causes of anemia. During pregnancy MCV increases by  $\approx 5\%$ ; therefore, the traditional cutpoint may underestimate microcytosis.

Iron-deficiency anemia is also considered to result from a poorer intake of iron-containing foods (15, 16), although we are aware of no data in developed countries, apart from our own, that have corroborated this. In keeping with this expected relationship, women with iron-deficiency anemia consumed less iron and less energy and had energy and iron intakes lower than those of the nonanemic women when confounding factors were controlled for. Anemic women who were not iron deficient had dietary intakes comparable to the nonanemic women.

In the absence of data from pregnancy, it has been presumed that the bulk of the anemias identified during pregnancy are due to iron deficiency and not to other causes, such as infection, chronic disease, or an effect of hemodilution. Our data do not support this presumption. In the present study, which focused almost entirely on women from a poor urban environment, the prevalence of iron-deficiency anemia at entry to prenatal care was much lower than anticipated (3.5%). Nevertheless, the low overall prevalence of iron-deficiency anemia in this cohort agreed well with results from the second National Health and Examination Survey of 1976-1980 (17).

In that survey, the prevalence of iron-deficiency anemia in nonpregnant women, when hemoglobin and two or three ab-

TABLE 3

Mean corpuscular volume (MCV) for anemic and nonanemic women at entry to care\*

Independent variables	MCV
	<i>f</i>
Iron deficiency anemia	$81.5 \pm 1.2^{\dagger\dagger}$
Noniron-deficiency anemia	$87.1 \pm 0.4^{\ddagger}$
No anemia	$89.1 \pm 0.3$

\* Values adjusted for maternal age, parity, ethnicity, bleeding at entry to care, prepregnancy BMI, and gestation at initial blood draw (entry).

† Significantly different from noniron-deficiency anemia,  $P < 0.001$ .‡ Significantly different from no anemia,  $P < 0.001$ .


normal measures of iron status were used to indicate iron-deficiency anemia, was estimated to be between 2.5 and 4%. Over the past few decades there also has been a decline in anemia during childhood (which, like pregnancy, is considered a time of high risk for iron deficiency), to a prevalence of  $\leq 3\%$  in low-income groups (18, 19). This decline has been attributed to increased iron fortification of flour and cereals and to the availability of iron-rich formulas and supplemental foodstuffs from programs such as the Special Supplemental Food Program for Women, Infants and Children (WIC).

As far as we are aware, no prior attempt has been made to separate the influence of iron deficiency on pregnancy outcome from other anemias. We found that the relationship between anemia and preterm delivery was specific to iron-deficiency anemia and risk was more than doubled. Many preterm infants also weigh  $< 2500$  g and have a threefold increase in LBW in association with iron-deficiency anemia. All anemia, and anemias stemming from causes other than iron deficiency, did not significantly increase risk of preterm delivery, LBW, or SGA birth, a finding consistent with most prior studies.

Bleeding, which often precedes a preterm delivery, may also cause anemia. Thus, anemia may appear to be a risk factor when it is the outcome of an underlying pathological process, which ultimately gives rise to the poor outcome. When maternal bleeding and anemia were present simultaneously at entry to care, there was a fivefold increase in the risk of preterm delivery associated with iron-deficiency anemia and a twofold increase associated with other anemias.

Reduced expansion of the red cell mass and, in some cases, reduced expansion of maternal plasma volume and tissue stores, are components of an inadequate weight gain. Consistent with this, iron-deficiency anemia and anemias of other etiologies, each ascertained at entry to care, temporally preceded the development of and increased the risk for inadequate gestational gain throughout the entire pregnancy. Similar to iron-deficiency anemia, inadequate gestational gain is associated with poor dietary intake (20) and with increased rates of LBW, preterm delivery, and SGA births (20–22). Thus, inadequate weight gain may be an intermediate outcome through which iron-deficiency anemia or some correlated factor (eg, gastrointestinal side effects associated with supplemental iron use) could influence the outcome of pregnancy.

The use of maternal hemoglobin or hematocrit as an indicator of anemia is complicated by differences in the rate of expansion of the red cell mass and maternal plasma volume during pregnancy. As Klebanoff et al (6) demonstrated, failure to define criteria for anemia by gestation at blood draw, or in retrospective studies by gestation at delivery, may and apparently has resulted in what appears to be a strong, positive, but spurious relationship between the lower hematocrit values, which are characteristic of an earlier point in gestation, and preterm delivery.

Finally, the attributable risk for preterm birth to iron-deficiency anemia was calculated as Levin's attributable risk (23) from the AOR and the prevalence of iron-deficiency anemia at entry to care. The risk amounted to 5.5% overall and 11.1% in blacks, reflecting the low prevalence of iron-deficiency anemia for the entire cohort. Therefore, although iron-deficiency anemia may be either a risk factor or a marker, it makes only a modest contribution to the etiology of preterm delivery in this group of poor, urban women. 

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