

Iron-Deficiency Anemia: Reexamining the Nature and Magnitude of the Public Health Problem

Is There a Causal Relationship between Iron Deficiency or Iron-Deficiency Anemia and Weight at Birth, Length of Gestation and Perinatal Mortality?^{1,2}

Kathleen M. Rasmussen

Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853.

ABSTRACT An extensive literature review was conducted to identify whether iron deficiency, iron-deficiency anemia and anemia from any cause are causally related to low birth weight, preterm birth or perinatal mortality. Strong evidence exists for an association between maternal hemoglobin concentration and birth weight as well as between maternal hemoglobin concentration and preterm birth. It was not possible to determine how much of this association is attributable to iron-deficiency anemia in particular. Minimal values for both low birth weight and preterm birth occurred at maternal hemoglobin concentrations below the current cut-off value for anemia during pregnancy (110 g/L) in a number of studies, particularly those in which maternal hemoglobin values were not controlled for the duration of gestation. Supplementation of anemic or nonanemic pregnant women with iron, folic acid or both does not appear to increase either birth weight or the duration of gestation. However, these studies must be interpreted cautiously because most are subject to a bias toward false-negative findings. Thus, although there may be other reasons to offer women supplemental iron during pregnancy, the currently available evidence from studies with designs appropriate to establish a causal relationship is insufficient to support or reject this practice for the specific purposes of raising birth weight or lowering the rate of preterm birth. *J. Nutr.* 131: 590S–603S, 2001.

KEY WORDS: • pregnancy • hemoglobin • iron • folic acid • anemia

As part of a critical review process to examine the importance of iron deficiency and iron-deficiency anemia and anemia in public health, this review was undertaken to determine whether these conditions in pregnant women cause low birth weight (LBW) or perinatal mortality. Because LBW (<2.5 kg at birth) infants include both those who are preterm (<37 wk gestational age) and those who are small for their gestational age, the distinction between preterm and fetal growth retardation was maintained where the data permitted. Additional objectives of this review were to determine whether the causal factor was mild, moderate or severe iron-deficiency anemia and to estimate the quantitative importance of this factor for the health of pregnant women.

Conceptual framework

The primary question addressed in this review is whether maternal anemia, assessed primarily as hemoglobin concentration, is causally related to weight at birth or duration of

gestation or both (Fig. 1). As it is used in this diagram, LBW refers to the weight of the fetus at delivery, which may be before term. Furthermore, a second question is whether maternal anemia is causally related to perinatal mortality, either directly or indirectly via weight at birth or duration of gestation.

A more detailed conceptual framework was prepared to guide interpretation of the results obtained from the literature (Fig. 2). In this diagram, the primary determinants of maternal hemoglobin concentration during pregnancy are shown as the woman's hemoglobin concentration before conception and her combined physiological responses to pregnancy, increased plasma volume and increased red cell mass. It is unknown to what extent maternal hemoglobin concentration at various stages of pregnancy influences fetal growth and the timing of birth; thus, this diagram shows multiple influences of maternal hemoglobin concentration on these outcomes. In addition, there are several possible routes through which maternal hemoglobin concentration could influence perinatal mortality (Fig. 2).

Approach

To identify studies for this review, *Index Medicus* was searched electronically using Medline for citations in English, French and Spanish from 1966 to 1999. Iron deficiency, iron-deficiency anemia, anemia and hemoglobin were used as search terms along with the following outcomes of interest:

¹ Presented at the Belmont Meeting on Iron Deficiency Anemia: Reexamining the Nature and Magnitude of the Public Health Problem, held May 21–24, 2000 in Belmont, MD. The proceedings of this conference are published as a supplement to *The Journal of Nutrition*. Supplement guest editors were John Beard, The Pennsylvania State University, University Park, PA and Rebecca Stoltzfus, Johns Hopkins School of Public Health, Baltimore, MD.

² This article was commissioned by the World Health Organization (WHO). The views expressed are those of the author alone and do not necessarily reflect those of WHO.

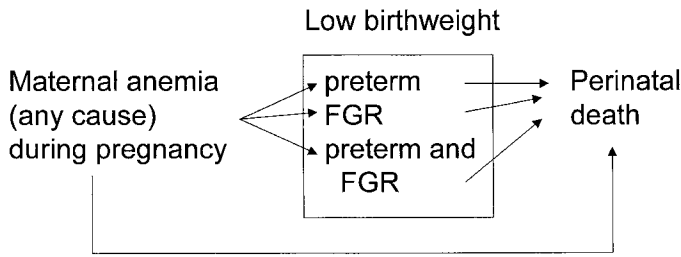


FIGURE 1 General approach to the review of the literature. FGR, fetal growth retardation.

LBW, prematurity, fetal growth and perinatal mortality. In addition, the Cochrane Reviews on routine iron (Mahomed 1998b) and folate (Mahomed 1998a) supplementation during pregnancy were consulted; the studies cited there, which date back to 1955, were also reviewed.

Despite the relatively comprehensive nature of this search strategy, some limitations are nonetheless present. It did not include a specific search for each possible cause of maternal anemia and the outcomes of interest. It was assumed that most of these would be picked up with the search terms “anemia” and “hemoglobin” and by the more specific attention to folate deficiency, the next most common nutritional cause of maternal anemia after iron deficiency.

The studies obtained were grouped into two broad categories, i.e., those studies suitable for establishing whether there is an association between maternal anemia and birth outcomes and those studies suitable for establishing whether this association is causal. The first group included observational studies as well as intervention trials that either did not meet usual criteria for causal inference (e.g., random assignment of subjects to treatment groups, blind assessment of outcomes) or were analyzed outside the framework of the intervention. The summaries of these studies are not included here. The second group consisted of interventions that were designed to eliminate maternal anemia, usually with the provision of iron or folic acid supplements or both and in which relevant birth outcomes were assessed (Table 1).

Limitations of the data reviewed: all studies

As is the case in nonpregnant adults, anemia in pregnant women does not result solely from lack of dietary iron. Other causes of anemia include the following: hookworm infection; malaria; schistosomiasis; recent or current infections; chronic inflammation; hereditary anemias; and other nutritional deficiencies, particularly of folic acid or vitamin B-12. The importance of these other causes of anemia varies from population to population. Some of these causes of anemia are also independently associated with birth outcomes.

The differential increases in plasma volume and red cell mass that are characteristic of pregnancy make interpretation of hemoglobin values challenging. The first problem is that plasma volume expansion, with its corresponding fall in hemoglobin concentration, obscures the usual relationship between iron deficiency and low hemoglobin values. It also makes it difficult to interpret the plasma-based indicators of iron deficiency (e.g., ferritin), which are also diluted by plasma volume expansion during pregnancy. The second problem is that plasma volume and red cell mass change throughout pregnancy. There is little consistency in the point at which maternal hemoglobin concentration was assessed during pregnancy; some investigators assessed this early in pregnancy, some later in pregnancy and others only at delivery. More confusing still are the papers that reported an association between the lowest maternal hemoglobin value and some outcome but did not reveal when this lowest value was obtained, making it impossible to correct for the gestational age at which the measurement was made.

The association between anemia and birth outcomes may be stronger if the anemia occurs at one time during pregnancy rather than at another time. This is because of differences in the rates of fetal growth and development during gestation. Similarly, the effectiveness of treatments may vary depending on when and for how long they are offered (G. H. Beaton and G. P. McCabe, unpublished, 2000). Finally, any effective treatment for anemia will reduce the association between preexisting anemia and birth outcomes in observational studies, and women probably received supplemental iron in many of these investigations.

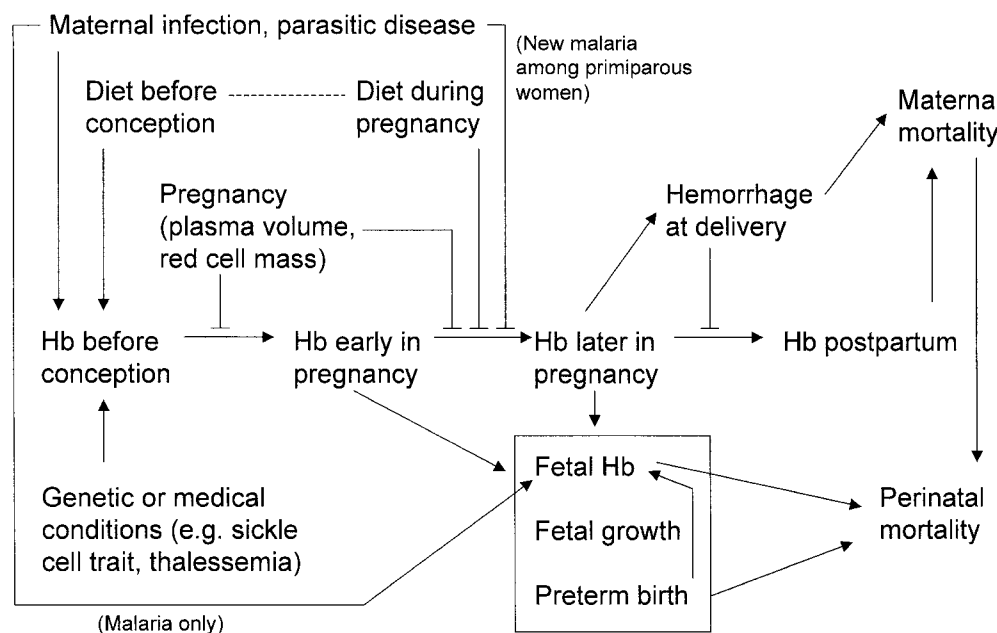


FIGURE 2 Detailed conceptual framework used to guide interpretation of the literature. Hb, hemoglobin concentration.

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TABLE 1

Effects of interventions to alleviate iron deficiency, iron deficiency anemia or folate deficiency on size at birth and duration of gestation¹

Study site; authors	Intervention	Subjects	Design concerns	Effect on size at birth	Effect on duration of gestation	Effect on perinatal mortality; fetal Hb concentration
Scotland (Aberdeen); (Paintin et al. 1966)	Iron, 12 or 115 mg/d from 20 to 36 wk of gestation or a placebo	$n = 173$; Hb >100 g/L at first visit	False negative (not anemic at outset, high mean BW)	No difference in BW among the treatment groups (mean BW about 3.3 kg)	n/a	n/a
Nigeria (Ibadan); (Fleming et al. 1968)	Folic acid, 5 mg/d or placebo (alternate assignment)	$n = 75$, but only 54 completed the study; PCV $\geq 27\%$ at 26 wk gestation	Confounding (non-random assignment), bias (high dropout rate), false negative (small sample size)	No effect of the treatment on BW (mean = 3.0 kg)	n/a	n/a
England (Liverpool); (Rae and Robb 1970)	Ferrous gluconate, 200 mg/d, or iron + folic acid, 5 mg/d	$n = 698$ randomized by day of clinic attendance, but all women seen in the 1st trimester were assigned for Fe + folic acid group	Confounding (non-random assignment); false negative (anemia not corrected by either treatment)	Women with megaloblastic (not normoblastic) anemia (Hb <109 g/L) tended to have babies with a lower BW than those who were never anemic (not significant)	n/a	n/a
South Africa; (Baumslag et al. 1970)	Iron, 200 mg/d; iron + folic acid, 5 mg/d; iron + folic acid + vitamin B-12 50 $\mu\text{g}/\text{d}$	$n = 183$ Bantu (after 28 wk gestation) and 172 whites (after 24 wk gestation); initial Hb not reported	Need for supplements as well as hematologic response to them were not reported	No difference in BW among the white subjects; excess of babies <5 lb among the Bantu given iron only but can't distinguish between term and preterm LBW	Preterm defined as BW <5 lb	n/a
England (London); (Fletcher et al. 1971)	Ferrous sulfate, 200 mg/d; iron + folic acid, 5 mg/d	$n = 643$, mean Hb at booking about 130 g/L	False negative (not anemic, high mean BW)	No difference between treatment groups (mean BW = 3.3 kg)	n/a	n/a
India (Hyderabad); (Iyengar 1971)	Iron, 60 mg/d; iron + folic acid, 100 or 200 or 300 $\mu\text{g}/\text{d}$	$n = 200$ at 20–24 wk gestation, but only 114 completed the trial; Hb >85 g/L	Bias (high dropout rate)	BW 200–300 g higher with 200 or 300 μg folic acid than none or 100 μg ($P < 0.05$)	No difference between treatment groups	No difference between treatment groups
Australia; (Fleming et al. 1974)	Ferrous sulfate, 60 mg/d; folic acid, 5 mg/d, both or placebo	$n = 146$ with Hb >10/dL at 20 wk gestation	False negative (not anemic; high mean BW and low statistical power)	Placebo, 3.476 kg ($n = 17$); Fe, 3.310 kg ($n = 21$); folic acid, 3.278 kg ($n = 15$); both, 3.395 kg ($n = 20$) (NS for main effects of Fe or folic acid)	Premature deliveries were excluded	n/a
India (Delhi and Vellore); (Sood et al. 1975)	Ferrous fumarate, none, 30, 60, 120 or 240 mg/d; with folic acid, 5 mg/d, and B-12, 100 μg every 2 wk	$n = 647$, stratified by initial Hb (all >50 g/L); treatment started at 22 wk gestation and continued for 10–12 wk	False negative [Fe doses of 120 mg/d or less did not eliminate anemia (but even 30 mg of Fe with folic acid and B-12 produced final Hb values >100 g/L) low statistical power]; bias (high dropout rate for BW)	No overall effect of hematinics on BW (data available for only 47% of subjects; low mean BW, 2.7 kg; $n = 33$ –56/group); 71 g difference in BW between 120 mg Fe and controls (not significant)	n/a	n/a

TABLE 1 (continued)

Effects of interventions to alleviate iron deficiency, iron deficiency anemia or folate deficiency on size at birth and duration of gestation¹

Study site; authors	Intervention	Subjects	Design concerns	Effect on size at birth	Effect on duration of gestation	Effect on perinatal mortality; fetal Hb concentration
India (Hyderabad); (Iyengar and Rajalakshmi 1975)	Ferrous fumarate, 60 mg/d alone or with folic acid, 0.5 mg/d (alternate assignment)	<i>n</i> = 282 with Hb >85 g/L at 20–28 wk gestation; subjects matched for height and parity	Confounding (non-random assignment); source of controls not specified	No treatment, 2.567 kg (30.8% LBW); Fe only, 2.650 kg (30.2% LBW); Fe + folic acid, 2.890 kg (15.5% LBW) (<i>P</i> < 0.001)	n/a	No effect of Fe or vitamins on infant Hb at 3 mo of age (<i>n</i> = 31–53/group)
England; (Trigg et al. 1976)	Ferrous sulfate, 50 mg/d or ferrous sulfate + folic acid, 0.05 mg/d	<i>n</i> = 76 Fe alone; <i>n</i> = 82 Fe + folic acid	False negative (not anemic; high mean BW)	No effect of folic acid on BW in Fe-supplemented women (mean BW = 3.4 kg)	n/a	n/a
England; (Taylor et al. 1982)	Ferrous sulphate, 350 mg/d + 350 µg/d folic acid or no supplement	<i>n</i> = 48 randomly assigned to receive either iron or no treatment	No placebo-controlled group, false negative (those randomly assigned were not anemic), excluded 3 subjects who had premature deliveries	No effect of Fe treatment with BW (mean = 3.5 kg)	No difference between Fe supplementation and no supplementation in duration of gestation, but excluded 3 subjects because of premature births	n/a
Finland; (Romslo et al. 1983)	Ferrous sulfate, 200 mg/d or placebo	<i>n</i> = 45 healthy women who delivered singleton infants at term	False negative (not anemic; high mean BW)	No effect of iron on BW (mean = 3.5 kg)	n/a	n/a
France; (Tchernia et al. 1983)	Iron or placebo (study 1); iron or iron + folic acid (study 3)	<i>n</i> = 203 for study 1 (<i>n</i> = 155 with Hb >110 g/L who were randomly assigned to treatment) and <i>n</i> = 200 for study 3	False negative (not anemic, low power); bias (assignment to treatment group not specified (study 3))	BW (<i>P</i> < 0.05) and birth length (<i>P</i> < 0.001) were higher in infants of mothers who received Fe + folic acid compared with those who received Fe alone	Serum folate values were lower (<i>P</i> < 0.01) among mothers of preterm (≤39 wk) infants; length of gestation was longer (<i>P</i> < 0.025) among women with higher (>200 µg/L) folate; length of gestation was longer (<i>P</i> < 0.001) among women treated with Fe + folic acid than with Fe alone	n/a
France; (Zittoun et al. 1983)	Fe sulfate, 105 mg elemental Fe/d + 500 mg ascorbic acid	<i>n</i> = 203 at 28 wk; if Hb <110 g/L, treated; otherwise randomly assigned to treatment or placebo	False negative (those randomly assigned were not anemic; high mean BW)	No association of Fe treatment with BW (mean = 3.3 ± 0.5 kg) or length of gestation or fetal Fe status	No association of Fe treatment with length of gestation	n/a
Nigeria (Zaria); (Fleming et al. 1986)	Clorquine + proguanil and either ferrous sulfate, 60 mg/d, folic acid, 1 mg/d, or both	<i>n</i> = 200, <24 wk gestation	False negative (not anemic)	No difference among the groups (mean BW = 2.85 kg)	n/a	No differences among the groups; 10.5% perinatal mortality among <i>n</i> = 152 with known outcome

TABLE 1 (continued)

Effects of interventions to alleviate of iron deficiency, iron deficiency anemia or folate deficiency on size at birth and duration of gestation¹

Study site; authors	Intervention	Subjects	Design concerns	Effect on size at birth	Effect on duration of gestation	Effect on perinatal mortality; fetal Hb concentration
France; (de Benaze et al. 1989)	Ferrous betainate, 45 mg elemental Fe/d in a divided dose, or placebo	<i>n</i> = 191 pregnant women beginning at 22 wk gestation and continuing until 2 mo postpartum; initial Hb = 125 g/L, serum ferritin = 60 μg/L	False negative (not anemic)	n/a	No difference between the groups in duration of gestation	n/a
Finland; (Hemminki and Rimpelä 1991)	Elemental Fe, 100 mg/d (routine); slow release ferrous sulfate, 50 mg 2 times/d (selective)	<i>n</i> = 1451 routine supplementation, <i>n</i> = 1461 selective supplementation; Hb >110 g/L	False negative (not anemic, high mean BW)	No difference between the 2 Fe supplementation regimens in BW (mean 3.6 kg)	No difference between the 2 Fe supplementation regimens in duration of gestation	Neonatal mortality was significantly higher in the routine (7.5/1000) than the selective (2.2/1000) groups
India (Varanasi); (Agarwal et al. 1991)	Ferrous sulfate, 60 mg/d + folate, 500 μg/d	<i>n</i> = 418 randomly assigned by subcenters (<i>n</i> = 6) to supplement or placebo; only 137 of 215 in the treated group and 123 of 203 in the control group completed the trial; initial Hb 10.1–109 g/L	Bias (high dropout rates) and false positive (randomization by subcenters with analysis by individuals)	BW was higher (2.88 kg) in the treatment than in the control (2.59 kg) group (<i>P</i> < 0.001); LBW reduced from 37.9% in the controls to 20.4% (<i>P</i> < 0.05); later start of supplementation (20–40 wk vs. 16–19 wk) associated with higher LBW (23.1 vs. 12.1%, respectively)	n/a	Reduced neonatal death rates in the Fe-supplemented group (<i>P</i> < 0.04)
Denmark; (Thomsen et al. 1993)	Ferrous iron, 100 mg/d + 18 mg/g	<i>n</i> = 52 randomly assigned as entered clinic to multivitamin containing either 100 mg (<i>n</i> = 22) or 18 mg (<i>n</i> = 21) ferrous iron	False negative (not anemic), no control group, excluded those with premature births	No difference between the 2 Fe supplementation regimens in BW (mean = 3.5 kg)	No difference between the 2 Fe supplementation regimens in duration of gestation, but excluded 3 subjects because of premature births	n/a
Gambia; (Menendez et al. 1994)	Ferrous sulfate, 200 mg/d (60 mg elemental Fe) or placebo; 5 mg folic acid weekly	<i>n</i> = 550 multigravidas with PCV >25% randomly assigned by compound of residence; double-blind; initial Hb 100–101 g/L	False negative (52% of treated group still anemic after delivery)	No statistically significant difference in BW (56 g) or %LBW between the treatment groups; 3.103 kg and 3% LBW for the supplemented and 3.047 kg and 5% LBW for the placebo group; among the women who took >80 Fe tablets, BW was 96 g higher in the supplemented group (<i>P</i> = 0.04)	n/a	n/a

TABLE 1 (continued)

Effects of interventions to alleviate iron deficiency, iron deficiency anemia or folate deficiency on size at birth and duration of gestation¹

Study site; authors	Intervention	Subjects	Design concerns	Effect on size at birth	Effect on duration of gestation	Effect on perinatal mortality; fetal Hb concentration
Denmark; (Milman et al. 1994)	Ferrous fumarate, 200 mg/d or placebo	<i>n</i> = 135 randomly assigned to receive placebo (<i>n</i> = 57) or ferrous fumarate (<i>n</i> = 63), double-blind	False negative (not anemic), bias (9% exclusion after randomization—primarily in placebo group)	No significant differences among the treated and control in total duration of gestation or mean birth weight	n/a	n/a
India (Tamil Nadu); (Srinivasan et al. 1995)	High risk (Fe + folic acid if not anemic, double dose if anemic, parenteral Fe if Hb <80 g/L), usual care (Tamil Nadu Government) (Fe + folic acid, 100 doses regardless of Hb value) or control (government program without services of midwives)	<i>n</i> = 12 subcenters, assigned randomly within 4 primary health centers; initial Hb 93–100 g/L at 34 wk of gestation	False negative (low statistical power)	No significant differences among the treatments in BW or %LBW (poor ascertainment of BW)	n/a	n/a
Niger; (Preziosi et al. 1997)	Ferrous betainate, 100 mg elemental Fe/d	<i>n</i> = 197 at 28 wk gestation; >65% anemic (Hb <110 g/L) at 6 mo gestation	False negative (42% of the treated group still anemic at delivery)	No difference between treatment groups in BW (mean = 3.0 kg); birth length was longer in Fe-supplemented group (<i>P</i> < 0.05)	n/a	n/a

¹ Abbreviations used: BW, birth weight; LBW, low birthweight; Hb, hemoglobin; n/a, not available; NS, not significant; OR, odds ratio; PCV, packed cell volume; RR, relative risk.

The relevant literature on this topic includes many older studies in which investigators did not distinguish between infants who were small for their gestational age and those who were born prematurely; both were included in the group labeled LBW. Some investigators solved this problem by restricting their sample to term births. This strategy removes preterm babies from the LBW group but also makes it impossible to evaluate the effect of treatment on the duration of gestation.

Limitations of the data reviewed: intervention studies

For the intervention studies to demonstrate a causal relationship between correction of maternal anemia and an increase in birth weight, a number of conditions must be met. For the purpose of this review, these factors fall into three broad categories, i.e., those that eliminate confounding and bias, those that permit one to attribute the effect observed to the elimination of anemia, iron deficiency or both, and those that eliminate false-negative findings. False-positive findings (such as those that come from analyzing the data by individual

subjects when the unit of randomization was, for example, the village and not the individual woman) were not often a problem in this literature and therefore are not considered in detail.

To eliminate confounding and bias, random assignment to treatment, double-blind assessment of outcomes and a placebo in the control group are normally used. Some of the older studies did not provide details on all of these procedures and may not have included them.

To be able to attribute the positive outcomes to the elimination of anemia, iron deficiency or both, these factors must, in fact, be eliminated. This requires that the subjects be offered an adequate dose of the target hematinic (e.g., iron, folic acid, vitamin B-12, blood transfusions) and that they take the dose assigned for a sufficient period. Unfortunately, sometimes the doses of iron (and other hematinics) used in these studies were ineffective in correcting maternal anemia, possibly because iron deficiency was not the sole or even the primary cause of the anemia. In some cases, the investigators acknowledged that the dose of iron

that they used was too low; in other cases, women did not take a sufficient number of the pills provided.

To eliminate false-negative findings, subjects must have the potential to respond to the treatment offered and there must be a statistically adequate sample size to be able to detect this response. First, this means that subjects had to have a cause of LBW that could be corrected by receipt of a hematinic such as iron or folic acid. Those experiments conducted in women whose anemia was not caused by, for example, iron or folic acid deficiency, cannot be expected to respond to supplementation with these substances with either a reduction in anemia or an increase in birth weight. Second, and similarly, the mean birth weight in the treated population had to be sufficiently low so that it could be expected to rise if the therapy were effective. Mean birth weight of populations (high end of the distribution: 3.5 kg) has long been known to be somewhat below the range of birth weights that are associated with minimal infant mortality (low end of the distribution: 3.5 kg) (Hyttén and Leitch 1971). The standard deviation around these means is usually ~ 0.5 kg. For this review, study populations in which the mean birth weights in the control group was ≥ 3.3 kg were not considered to have the potential to respond to treatment. Third, iron or folic acid deficiency must be the factor limiting birth weight so that correcting anemia caused by these deficiencies will permit birth weight to rise. There are numerous examples in which this condition probably was not met. It is especially likely to have been the case when the population's mean birth weight was low.

Finally, a statistically adequate sample size to ascertain whether iron or folic acid improved maternal hematologic status is much lower than that needed to ascertain whether birth weight or the duration of gestation has increased or perinatal mortality has decreased. For example, it is often possible to see a hematologic response to iron treatment with 50 women in each treatment group, but at least 250 women in each treatment group would be required to detect a 100-g difference in birth weight and even more subjects to detect an effect on mortality. Therefore, it is not surprising that many of the studies reviewed were able to detect an improvement in hematologic values but still lacked sufficient statistical power to detect an effect on these birth outcomes if such an effect had been present.

Overall, it is noteworthy that the effects of failing to treat anemia successfully or to eliminate the sources of false-negative results that are listed above is to bias findings toward the null. That is, investigations with one or more of these problems are likely to find that iron or folic acid did not improve birth outcomes when this might not have been true if a more adequate experimental design for this purpose had been used.

Evidence for an association between iron deficiency, iron-deficiency anemia, or anemia and birth outcomes

There is ample evidence from observational studies, both large and small, that there is an association between maternal anemia (as defined by hemoglobin concentration) and size at birth, duration of gestation, and neonatal or perinatal mortality.

In its broadest form, this association is U-shaped, i.e., the proportion of LBW infants rises (and the mean birth weight drops) when maternal hemoglobin values are either at the low or high end of the range. This association is most obvious in the three largest data sets examined, namely, the National Collaborative Perinatal Project from the United States (nearly 60,000 births) (Garn et al. 1981a), the Cardiff Births Survey from the United Kingdom ($\sim 55,000$ births) (Murphy et al.

1986) and data from the North West Thames region in the United Kingdom ($>150,000$ births) (Steer et al. 1995).

It is likely that the causes of small size at birth differ at the two ends of the range of maternal hemoglobin concentrations. High hemoglobin values may reflect poor plasma volume expansion, which is itself associated with impaired fetal growth (Duffus et al. 1971, Gibson 1973), or other pathological conditions (Yip 2000). Low (100–110 g/L) hemoglobin values in late pregnancy probably reflect changes in plasma volume (Whittaker et al. 1996). Only hemoglobin values <100 g/L are likely to reflect inadequate maternal nutritional status with respect to iron, folic acid and other nutrients. The specific cause of the low maternal hemoglobin values remains unknown in most available studies. It is noteworthy that the U-shaped relationship is more apparent in studies that use "lowest hemoglobin" than in those that control for the stage of gestation (Scanlon et al. 2000) or include data only from women very early in pregnancy, when changes in plasma volume are minimal (Zhou et al. 1998). Thus, it is possible that this shape is spurious.

The large studies permit assessment of the maternal hemoglobin values associated with the best birth outcomes. In the high risk population studied as part of the National Collaborative Perinatal Project (Garn et al. 1981a), the LBW rate was minimal at maternal hemoglobin values of 105–125 g/L in Caucasian women. In the Cardiff Births Survey (Murphy et al. 1986), LBW was minimal when the maternal hemoglobin value at booking was 104–132 g/L, regardless of whether booking was before 13 wk gestational age or 13–19 or 20–24 wk gestational age. In the recent data from the United Kingdom (Steer et al. 1995), birth weight was highest at maternal hemoglobin values of 86–95 g/L; LBW rates were lowest at maternal hemoglobin values of 96–105 g/L. Both of these hemoglobin values are below the cut-off value for anemia in pregnant women by current WHO criteria (i.e., 110 g/L). Interpreting the data in this report is not straightforward, however, because the hemoglobin values used were determined at various times during gestation. The only data available for African-American women come from the National Collaborative Perinatal Project and show a minimal rate of LBW at lowest maternal hemoglobin values of 85–95 g/L (Garn et al. 1981a). In a recent study of Chinese women (Zhou et al. 1998), the minimum risk of LBW occurred at hemoglobin values of 110–119 g/L, but these values were determined very early in pregnancy (4–8 wk of gestation), at a time of minimal expansion of plasma volume.

This same U-shaped pattern was also observed for the association between maternal hemoglobin concentration and duration of gestation as well as for the association between maternal hemoglobin and neonatal mortality. The group of studies from which this assessment can be made is much more limited than that for birth weight. Many of the latter studies either did not report the duration of gestation or restricted their sample specifically to mothers of term infants. Minimal rates of prematurity occurred at maternal hemoglobin values of 115–125 g/L in Caucasian women in the National Collaborative Perinatal Project (Garn et al. 1981a). In the recent data from the United Kingdom (Steer et al. 1995), the lowest rate of preterm birth occurred at maternal hemoglobin concentrations of 96–105 g/L, also below the current cut-off value for maternal anemia. Prematurity was minimal at the lowest maternal hemoglobin values of 105–115 g/L in African-American women in the National Collaborative Perinatal Project (Garn et al. 1981a). When the duration of gestation was controlled for, the minimum risk of preterm birth occurred above the cut-off value for anemia in a smaller cohort of Chinese women

TABLE 2

Relative and attributable risk of low birth weight according to severity and type of maternal anemia during pregnancy^{1,2}

Study site; authors	Relative risk (attributable risk) of LBW compared to mild or no anemia		
	Moderate anemia	Severe anemia (usually ≤ 80 g/L)	Iron deficiency anemia
Kashmir; (Verma and Dhar 1976)	2.13 (53%)	6.33 (84%)	—
United States; (Garn et al. 1981b)	—	1.55 (36%) for whites, 1.0 for blacks (lowest Hb midpoint of 80 g/L compared with 110 g/L)	—
Nigeria (Zaria); (Lister et al. 1985)	1.71 (42%)	—	—
Papua New Guinea; (Brabin et al. 1990)	—	At booking: 5.91 (83%) for primiparas, 1.42 (42%) for multiparas; at delivery: 2.38 (57%) for primiparas, 1.94 (48%) for multiparas	6.0 (OR) for primiparas early in pregnancy; not significant for multiparas or iron deficiency late in pregnancy
United States; (Scholl et al. 1992)	—	—	3.10 (adjusted OR)
India (Pune); (Hirve and Ganatra 1994)	—	1.53 (34.5%)	—
India (Varanasi); (Swain et al. 1994)	2.22 (55%)	—	—
Italy; (Spinillo et al. 1994)	—	5.05 (adjusted OR for SGA specifically)	—
Brazil; (Rondo et al. 1995)	0.76	—	—
England; (Steer et al. 1995)	0.76 (lowest Hb ≤ 105 g/L compared with 106–125 g/L)	2.44 [lowest Hb ≤ 85 g/L compared with Hb 96–105 g/L (lowest LBW rate)] (59%)	—
Ghana; (Onadoko et al. 1996)	1.07 (6.3%)	—	—
Papua New Guinea; (Brabin and Piper 1997)	Goroka (non-malarious): 1.35 primiparas, 1.15 multiparas; Madang (malarious): 1.54 primiparas, 1.14 multiparas	Goroka (nonmalarious): 1.65 primiparas, 5.0 multiparas; Madang (malarious), 1.59 primiparas, 1.74 multiparas	—
China; (Zhou et al. 1998)	2.96 (but only 0.99 for SGA)	—	—

¹ Relative risk calculated as LBW rate in anemic women/LBW rate in nonanemic women; attributable risk: (LBW rate in anemic women – LBW rate in nonanemic women)/LBW rate in anemic women.

² Abbreviations used: Hb, hemoglobin; LBW, low birth weight; OR, odds ratio; SGA, small-for-gestational age.

(hemoglobin values of 110–119 g/L at 4–8 wk of pregnancy) (Zhou et al. 1998) and also in a very large cohort of American women (Scanlon et al. 2000).

Data from the National Collaborative Perinatal Project showed that fetal death was minimal at maternal hemoglobin values of 95–105 g/L for Caucasians and 85–95 g/L for African-Americans (Garn et al. 1981a). Perinatal mortality rate was minimal at maternal hemoglobin values of 104–132 g/L in the data from the Cardiff Births Survey (Murphy et al. 1986). As was the case for birth weight and duration of gestation, some of these values are below the current cut-off value for anemia.

An association between maternal hemoglobin concentration and birth weight was most likely to be detected in studies, usually with a small sample size, that were conducted in populations with lower maternal hemoglobin concentrations and lower birth weight. Even when birth weights were higher, a specific association between iron-deficiency anemia (i.e., low hemoglobin combined with low serum ferritin concentration) and birth weight, preterm birth or both could be detected (Német et al. 1986, Scholl et al. 1992, Singla et al. 1997).

The effect of the severity of anemia on birth outcomes could be examined only in studies that did not eliminate women with severe anemia (usually defined as hemoglobin values <80 g/L). These studies (Bhargava et al. 1989, Duthie et al. 1991, Msolla and Kinabo 1997, Singla et al. 1997, Verma and Dhar 1976) all report either a strong statistical association between the lowest maternal hemoglobin values and low birth weight or a difference between 200 and 400 g in birth weight between women with hemoglobin values <80 g/L and those with higher values (>100 g/L). None of these investigations

eliminated any alternative explanations for this association, which is an important failing because confounding might be expected.

The relative risk of delivering a LBW baby when the mother has moderate or severe anemia or iron-deficiency anemia is provided in a few of the studies reviewed and was calculated, where possible, from data included in others (Table 2). It is difficult to compare these results across studies because the reference group was defined in various ways. Compared with no or mild anemia, moderate anemia had a relative risk of LBW of 0.76–2.96 and severe anemia had a relative risk of LBW of 1–6.33 in the studies reviewed. Only two studies were identified in which the authors considered iron-deficiency anemia specifically. In the United States, the adjusted odds ratio for LBW was 3.10 (Scholl et al. 1992). In Papua New Guinea, the odds ratio for LBW was 6.0 for primiparas when iron-deficiency anemia was recorded early in pregnancy; there was no excess probability for multiparas or for anemia late in pregnancy (Brabin et al. 1990). These data also were used to calculate the attributable risk (Table 2). For moderate anemia, the attributable risk was 42–55%; for severe anemia, it was 34.5–83%. One group calculated the proportion of LBW that could be attributed to maternal anemia (the population-attributable risk). With data from Papua New Guinea, Brabin and Piper (1997) calculated that, if the relationship were causal, severe (<70 g/L) maternal anemia was responsible for $<10\%$ of the LBW; in comparison, malaria was responsible for 40% of the LBW.

The relative risk of delivering a preterm baby when the mother has moderate or severe anemia or iron-deficiency ane-

TABLE 3

Relative and attributable risk of preterm birth according to severity and type of maternal anemia during pregnancy^{1,2}

Study site; authors	Relative risk (attributable risk) of preterm birth compared to mild or no anemia		
	Moderate anemia	Severe anemia (usually Hb \leq 80 g/L)	Iron deficiency anemia
United States (various locations); (Garn et al. 1981b)	—	1.43 (30%) for whites, 1.10 (9%) for blacks (lowest Hb midpoint of 80 g/L compared with 110 g/L)	—
Germany; (Goepel et al. 1988)	1.30 (23%)	—	—
United States (Boston); (Lieberman et al. 1988)	1.90 (47%) (hematocrit \leq 34% compared to all higher values)	—	—
United States (various locations); (Klebanoff et al. 1989)	0.6–1.6 for black women and 0.7–2.1 for white women depending on the duration of pregnancy (higher earlier and lower later in pregnancy)	—	—
Papua New Guinea; (Brabin et al. 1990)	—	“Not significantly increased” (at booking: 1.89 for primiparas and 0.55 for multiparas; at delivery: 1.08 for primiparas and 0.43 for multiparas) (Hb $<$ 80 g/L compared to all higher values)	—
Japan; (Fukushima and Wantabe 1991)	3.19 (67%)	—	—
United States; (Scholl et al. 1992)	—	—	2.66 (adjusted OR)
England; (Steer et al. 1995)	0.84 (lowest Hb \leq 105 g/L compared with 106–125 g/L)	2.46 [lowest Hb \leq 85 g/L compared with Hb 96–105 g/L (lowest LBW rate)] (59%)	—
Wales (Cardiff Births Survey); (Meis et al. 1995)	1.23 (adjusted OR of Hb $<$ 104 g/L compared with Hb 118–132 g/L)	—	—
China; (Zhou et al. 1998)	2.07	—	—
Egypt; (Afrafa et al. 1998)	2.63 (adjusted OR) in early pregnancy, 2.03 (adjusted OR) in the 3rd trimester	4.01 (adjusted OR) in early pregnancy ($<$ 90 g/L)	—
Papua New Guinea; (Allen et al. 1998)	0.64 (OR)	—	—
United States (Los Angeles); (Siega-Riz et al. 1998)	1.83 (adjusted OR for anemia at 28–32 wk gestational age)	—	—

¹ Relative risk calculated as preterm rate in anemic women/preterm rate in nonanemic women; attributable risk: (preterm rate in anemic women) – preterm rate in nonanemic women/preterm rate in anemic women).

² Abbreviations used: Hb, hemoglobin; OR, odds ratio.

mia is also provided in a few of the studies reviewed and was calculated from data included in others (Table 3). These data have the same limitations as described above for LBW. On the whole, the relative risks of preterm birth were lower than those for LBW. Compared with no or mild anemia, moderate anemia had a relative risk of preterm birth of 0.6–3.2 and severe anemia had a relative risk of preterm of 0.55–4.01 in the studies reviewed. The adjusted odds ratio of preterm birth was 2.66 for iron-deficiency anemia in the one study in which this was determined (Scholl et al. 1992). These data also were used to calculate the attributable risk (Table 3). For moderate anemia, the attributable risk was 23–67%; for severe anemia it was 9–30%.

Evidence that iron deficiency, iron-deficiency anemia, or anemia causes poor birth outcomes

Controlled experiments are necessary to examine whether there is a causal relationship between maternal anemia and poor birth outcomes; there are many fewer such experiments

than there are observational studies that report associations between these factors. Although for the most part, the trials listed in Table 1 were randomized and blind, often they did not meet the other criteria described above for demonstrating an effect of iron or folic acid supplementation on birth weight or duration of gestation. The possibility of false-negative results was particularly high because most studies were conducted in populations with adequate values for initial hemoglobin and birth weight. Therefore, these subjects had little potential to respond to supplementation with increases in birth weight or duration of gestation. Paintin and coworkers (1966) even commented that “the range of hemoglobin concentrations at the 20th week was mainly due to factors other than iron deficiency.” Some of these studies provided information on iron deficiency late in pregnancy. In general, fewer than half of the subjects were iron deficient even if their hemoglobin concentrations had dropped into the anemic range by this time.

The research trials in which women have been supplemented with iron or folic acid have been reviewed several

times in recent years (Mahomed 1998a and 1998b, Scholl and Reilly 2000, U.S. Preventive Services Task Force 1993). The U.S. Task Force review concluded: "Although iron supplementation can improve maternal hematologic indexes, controlled clinical trials . . . have failed to demonstrate that iron supplementation or changes in hematologic indexes actually improve clinical outcomes for the mother or newborn." The results of the two recent Cochrane Reviews were similar. For iron supplementation, the author said: ". . . There is very little information regarding the effect if any on any substantive measures of either maternal or fetal outcome . . ." (Mahomed 1998b). For folate supplementation, the other major nutritional cause of anemia during pregnancy, the author said: ". . . No advantage of routine folate supplementation was detected in terms of . . . preterm delivery. There is a nonsignificant reduction in the incidence of low birth weight associated with folate supplementation" (Mahomed 1998a). No additional studies were identified for the present review that would change these conclusions.

However, caution is warranted in interpreting these results because, relative to ascertaining an effect on birth outcomes, the design problems characteristic of these studies tend to bias them toward null findings. Furthermore, these null findings contrast strongly with the expectation of a causal relationship, albeit a complicated one, derived from the large body of observational data on this subject. Although the 23 studies listed in Table 1 include many that are randomized, placebo controlled, and double blind, none was free of possible bias. Some trials had multiple problems with design and interpretation. Among these 23 intervention trials, there was 1 with false-positive bias, 19 with false-negative bias and 6 with possible bias of unknown direction; confounding was a problem in 3 studies, and 1 had insufficient information to evaluate the possibility of bias and confounding.

It is perhaps instructive to examine in more detail those few experimental studies that were conducted in populations in which anemia was common and iron deficiency was a likely cause of this anemia (Agarwal et al. 1991, Menendez et al. 1994, Preziosi et al. 1997, Sood et al. 1975, Srinivasan et al. 1995). There was a wide range in the size of the effect of iron supplementation on birth weight reported in these investigations, i.e., from 0 to 290 g. The study with the largest effect (Agarwal et al. 1991) was the only one reviewed with the possibility of false-positive findings. In addition, the results of this study may be biased because information on birth weight was available only for a limited number of the subjects. The observed effect (71 g, nonsignificant) may have been underestimated in an older study (Sood et al. 1975) in which the dose of iron given also was insufficient to cure the subjects' anemia. However, bias is also a possibility in this investigation because such a small proportion of the subjects provided data on birth weight. In a study with a superior design (Menendez et al. 1994), the overall effect (56 g) was not statistically significant, but the effect of iron supplementation on birth weight in a subgroup of women who took more of the iron pills was greater (96 g) and statistically significant. This finding and the fact that supplementation did not correct the subjects' anemia suggest that the overall effect on birth weight may have been underestimated. The remaining studies showed no difference in birth weight between the treatment groups and suffered from low statistical power (Srinivasan et al. 1995) and failure to eliminate anemia (Preziosi et al. 1997), both causes of false-negative results. These results suggest that adequate iron supplementation could increase birth weight by 100 g at the most, an effect that would not be inconsequential if it could be substantiated.

In summary, only one intervention trial was identified that was without major design defects and provided evidence of a statistically significant positive effect of iron supplementation on birth weight, and that evidence was provided only for a subgroup of the subjects. No such positive findings were identified in trials conducted in nonanemic populations. Importantly, no intervention trials were identified that provided evidence of a negative effect of iron supplementation on birth weight.

Summary and conclusions

In populations in which the rate of iron or folate deficiency is low among nonpregnant women, the primary cause of anemia during pregnancy is likely to be plasma volume expansion, and this anemia is not associated with negative birth outcomes.

Maternal hemoglobin values during pregnancy are associated with birth weight and preterm birth in a U-shaped relationship with high rates of babies who are small, early or both, at low and high concentrations of maternal hemoglobin. However, some of this association may result from using "lowest hemoglobin" rather than a hemoglobin value controlled for the stage of pregnancy. A similar U-shaped relationship is likely to be present between maternal hemoglobin concentration and neonatal or perinatal mortality, but the data to establish this association remain insufficient.

The relative risk of LBW that results from moderate or severe anemia is inconsistent; nonetheless, it is generally higher than the also inconsistent relative risk of preterm birth that results from these conditions.

Severe maternal anemia (<80 g/L) is associated with birth weight values that are 200–400 g lower than in women with higher (>100 g/L) hemoglobin values, but researchers generally have not excluded other factors that might also have contributed to both LBW and the severity of the anemia.

Supplementation of anemic or nonanemic pregnant women with iron, folic acid or both does not appear to increase birth weight or the duration of gestation, but the intervention trials on which this conclusion is based generally suffered from design problems that would tend to produce false-negative findings.

In a number of studies, maximal values for birth weight and minimal values for preterm birth occurred at maternal hemoglobin values (all uncontrolled for the stage of gestation) below current cut-off values for anemia during pregnancy.

Implications for research

Effort should be directed toward using the available observational data to estimate the risk of LBW and preterm birth that is attributable to iron-deficiency anemia as distinct from anemia from other causes. This requires studies in which iron deficiency was ascertained by some method in addition to maternal hemoglobin concentration. Because data in many of the published papers were not presented in a way that would permit this calculation to be made, access to the original data, which was not possible for the present review, will be required to estimate this risk.

Priority should be given to conducting studies of iron and folate supplementation during pregnancy that meet the criteria for demonstrating a positive effect of supplementation on birth outcomes, should such an effect exist. In particular, this means studying a population in which the mean birth weight is <3.3 kg, treating all women to eliminate other causes of LBW or preterm birth, selecting women with iron-deficiency

anemia for iron supplementation (or folate deficiency for folic acid supplementation), and including a sufficient number of subjects for adequate statistical power.

Implications for public health

Consideration should be given to lowering the hemoglobin cut-off value for anemia during pregnancy because optimal birth outcomes may be achieved at hemoglobin values in the range currently designated as anemic.

Although there may be other reasons to offer women supplemental iron during pregnancy, the currently available evidence from studies with designs appropriate to establish a causal relationship is insufficient to support or reject this practice for the specific purposes of raising birth weight or lowering the rate of preterm birth.

ACKNOWLEDGMENTS

The author thanks Jean Pierre Habicht and, especially, Mary E. Cogswell, for their thoughtful and helpful comments on this paper before, during and after its presentation. A number of their ideas are included here. In addition, the constructive criticism provided by Laurence Grummer-Strawn is gratefully acknowledged.

LITERATURE CITED

- Afrifa, M., Abou-Zied, H., Attia, A. F. & Youssof, M. (1998) Maternal hemoglobin and premature child delivery. *Rev. Santé Méditerran. Orient.* 4: 480–486.
- Agarwal, K. N., Agarwal, D. K. & Mishra, K. P. (1991) Impact of anaemia prophylaxis in pregnancy on maternal haemoglobin, serum ferritin & birth weight. *Indian J. Med. Res.* 94: 277–280.
- Allen, S. J., Raiko, A., O'Donnell, A., Alexander, N.D.E. & Clegg, J. B. (1998) Causes of preterm delivery and intrauterine growth retardation in a malaria endemic region of Papua New Guinea. *Arch. Dis. Child.* 79: F135–F140.
- Baumslag, N., Edelstein, T. & Metz, J. (1970) Reduction of incidence of prematurity by folic acid supplementation in pregnancy. *Br. Med. J.* 1: 16–17.
- Bhargava, M., Kuman, R., Iyer, P. U., Ramji, S., Kapani, V. & Rhargava, S. K. (1989) Effect of maternal anaemia and iron depletion on foetal iron stores, birthweight and gestation. *Acta Paediatr. Scand.* 78: 321–322.
- Brabin, B., Ginny, M., Sapau, J., Galme, K. & Paino, J. (1990) Consequences of maternal anaemia on outcome of pregnancy in a malaria endemic area in Papua New Guinea. *Ann. Trop. Med. Parasitol.* 84: 11–24.
- Brabin, B. & Piper, C. (1997) Anaemia- and malaria-attributable low birthweight in two populations in Papua New Guinea. *Ann. Hum. Biol.* 24: 547–555.
- de Benaze, C., Galan, P., Wainer, R. & Hercberg, S. (1989) Prévention de l'anémie ferripreuve au cours de la grossesse par une supplémentation martiale précoce: un essai contrôlé. *Rev. Epidemiol. Sante Publique* 37: 109–118.
- Duffus, G. M., MacGillivray, I. & Dennis, K. J. (1971) The relationship between baby weight and changes in maternal weight, total body water, plasma volume, electrolytes and proteins and urinary oestriol excretion. *J. Obstet. Gynaecol. Br. Commonw.* 78: 97–104.
- Duthie, S. J., King, P. A., To, W. K., Lopes, A. & Ma, H. K. (1991) A case controlled study of pregnancy complicated by severe maternal anemia. *Aust. N. Z. J. Obstet. Gynaecol.* 31: 125–127.
- Fleming, A. F., Chatoura, G.B.S., Harrison, K. A., Briggs, N. D. & Dunn, D. T. (1986) The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Ann. Trop. Med. Parasitol.* 80: 211–233.
- Fleming, A. F., Henrickse, J. P. d. V. & Allan, N. C. (1968) The prevention of megaloblastic anaemia in pregnancy in Nigeria. *J. Obstet. Gynaecol. Br. Commonw.* 75: 425–432.
- Fleming, A. F., Martin, J. D., Hahnel, R. & Westlake, A. J. (1974) Effects of iron and folic acid antenatal supplements on maternal haematology and fetal wellbeing. *Med. J. Aust.* 2: 429–436.
- Fletcher, J., Gurr, A., Fellingham, F. R., Pranker, T.A.J., Brant, H. A. & Menzies, D. N. (1971) The value of folic acid supplements in pregnancy. *J. Obstet. Gynaecol. Br. Commonw.* 78: 781–785.
- Fukushima, M. & Wantabe, H. (1991) An observation on pregnancy outcomes in relation to haemoglobin levels. *Fukushima J. Med. Sci.* 37: 23–27.
- Garn, S. M., Keating, M. T. & Falkner, F. (1981a) Hematologic status and pregnancy outcomes. *Am. J. Clin. Nutr.* 34: 115–117.
- Garn, S. M., Ridella, S. A., Petzold, A. S. & Falkner, F. (1981b) Maternal hematologic levels and pregnancy outcomes. *Semin. Perinatol.* 5: 155–162.
- Gibson, H. M. (1973) Plasma volume and glomerular filtration rate in pregnancy and their relation to differences in fetal growth. *J. Obstet. Gynaecol. Br. Commonw.* 80: 1067–1074.
- Goepel, E., Ulmer, H. U. & Neth, R. D. (1988) Premature labor contractions and the value of serum ferritin during pregnancy. *Gynecol. Obstet. Investig.* 26: 265–273.
- Hemminki, E. & Rimpelä, U. (1991) A randomized comparison of routine versus selective iron supplementation during pregnancy. *J. Am. Coll. Nutr.* 10: 3–10.
- Hirve, S. S. & Ganatra, B. R. (1994) Determinants of low birth weight: a community based prospective cohort study. *Indian Pediatr.* 31: 1221–1225.
- Hytten, F. & Leitch, I. (1971) *The Physiology of Human Pregnancy*, vol. 2. Blackwell Scientific Publications, Oxford, UK.
- Iyengar, L. (1971) Folic acid requirements of Indian pregnant women. *Am. J. Obstet. Gynecol.* 111: 13–16.
- Iyengar, L. & Rajalakshmi, K. (1975) Effect of folic acid supplement on birth weights of infants. *Am. J. Obstet. Gynecol.* 122: 332–336.
- Klebanoff, M. A., Shiono, P. H., Berendes, H. W. & Rhoads, G. G. (1989) Facts and artifacts about anemia and preterm delivery. *J. Am. Med. Assoc.* 262: 511–515.
- Lieberman, E., Ryan, K. J., Monson, R. R. & Schoenbaum, S. C. (1988) Association of maternal hematocrit with premature labor. *Am. J. Obstet. Gynecol.* 159: 107–114.
- Lister, U. G., Rossiter, C. E. & Chong, H. (1985) 11. Perinatal mortality. *Br. J. Obstet. Gynaecol. (suppl.)* 5: 86–99.
- Mahomed K. (1998a) Routine folate supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library Update Software*, Oxford, UK.
- Mahomed K. (1998b) Routine iron supplementation during pregnancy (Cochrane Review). In: *The Cochrane Review Update Software*, Oxford, UK.
- Meis, P. J., Michielutte, R., Peters, T. J., Wells, H. B., Sands, R. E., Coles, E. C. & Johns, K. A. (1995) Factors associated with preterm birth in Cardiff, Wales I. Univariable and multivariable analysis. *Am. J. Obstet. Gynecol.* 173: 590–596.
- Menendez, C., Todd, J., Alonso, P. L., Francis, N., Lulat, S., Ceesay, S., M'Boge, B. & Greenwood, B. M. (1994) The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Trans. R. Soc. Trop. Med. Hyg.* 88: 590–593.
- Milman, N., Agger, A. O. & Nielsen, O. J. (1994) Iron status markers and serum erythropoietin in 120 mothers and newborn infants: effect of iron supplementation in normal pregnancy. *Acta Obstet. Gynecol. Scand.* 73: 200–204.
- Msolle, M. J. & Kinabo, J. L. (1997) Prevalence of anaemia in pregnant women during the last trimester. *Int. J. Food Sci. Nutr.* 48: 265–270.
- Murphy, J. F., O'Riordan, J., Newcombe, R. G., Coles, E. C. & Pearson, J. F. (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet* i: 992–994.
- Német, K., Andrassy, K., Bognár, K., Czappán, P., Stuber, A. & Simonovits, I. (1986) Relationship between maternal and infant iron stores: 1. Full term infants. *Haematologia* 19: 197–205.
- Onadeko, M. O., Avokey, F. & Lawoyin, T. O. (1996) Observations on stillbirths, birthweight and maternal haemoglobin in teenage pregnancy in Ibadan, Nigeria. *Afr. J. Med. Sci.* 25: 81–86.
- Paintin, D. B., Thomson, A. M. & Hytten, F. E. (1966) Iron and the haemoglobin level in pregnancy. *J. Obstet. Gynaecol. Br. Commonw.* 73: 181–190.
- Preziosi, P., Prual, A., Galan, P., Daouda, H., Boureima, H. & Hercberg, S. (1997) Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. *Am. J. Clin. Nutr.* 66: 1178–1182.
- Rae, P. G. & Robb, P. M. (1970) Megaloblastic anemia of pregnancy: a clinical and laboratory study with particular reference to the total and labile serum folate levels. *J. Clin. Pathol.* 23: 379–391.
- Romslo, I., Haram, K., Sagen, N. & Augensen, K. (1983) Iron requirement in normal pregnancy as assessed by serum ferritin, serum transferrin saturation and erythrocyte protoporphyrin determinations. *Br. J. Obstet. Gynaecol.* 90: 101–107.
- Rondo, P.H.C., Abbott, R., Rodrigues, L. C. & Tompkins, A. M. (1995) Vitamin A, folate, and iron concentrations in cord and maternal blood of intra-uterine growth retarded and appropriate birth weight babies. *Eur. J. Clin. Nutr.* 49: 391–399.
- Scanlon, K. S., Yip, R., Schieve, L. A. & Cogswell, M. E. (2000) High and low hemoglobin levels during pregnancy: differential risks for preterm birth and small for gestational age. *Obstet. Gynecol.* 96: 741–748.
- Scholl, T. O., Hediger, M. L., Fischer, R. L. & Shearer, J. W. (1992) Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *Am. J. Clin. Nutr.* 55: 985–988.
- Scholl, T. O. & Reilly, T. (2000) Anemia, iron and pregnancy outcome. *J. Nutr.* 130: 443S–447S.
- Siega-Riz, A. M., Adair, L. S. & Hobel, C. J. (1998) Maternal hematologic changes during pregnancy and the effect of iron status on preterm delivery in a West Los Angeles population. *Am. J. Perinatol.* 15: 515–522.
- Singla, P. N., Tyagi, M., Kumar, A., Dash, D. & Shankar, R. (1997) Fetal growth in maternal anemia. *J. Trop. Pediatr.* 43: 89–92.
- Sood, S. K., Ramachandran, K., Mathur, M., Gupta, K., Ramalingaswamy, V., Swarnabai, C., Ponniah, J., Mathan, V. I. & Baker, S. J. (1975) WHO sponsored collaborative studies on nutritional anaemia in India. 1. The effect of supplemental oral iron administration to pregnant women. *Q. J. Med.* 174: 251–258.
- Spinillo, A., Capuzzo, E., Piazzzi, G., Nicola, S., Colonna, L. & Iasci, A. (1994) Maternal high-risk factors and severity of growth deficit in small for gestational age infants. *Early Hum. Dev.* 38: 35–43.
- Srinivasan, V., Radhakrishna, S., Sudha, R., Malathi, M. V., Jabbar, S., Ramakrishnan, R. & Venkata Rao, T. (1995) Randomized controlled field trial

- of two antenatal care packages in rural south India. *Indian J. Med. Res.* 102: 86–94.
- Steer, P., Alam, M. A., Wadsworth, J. & Welch, A. (1995) Relation between maternal haemoglobin concentration and birth weight in different ethnic groups. *Br. Med. J.* 310: 489–491.
- Swain, S., Singh, S., Bhatia, B. D., Pandley, S. & Krishna, M. (1994) Maternal hemoglobin and serum albumin and fetal growth. *Indian Pediatr.* 31: 777–782.
- Taylor, D. J., Mallen, C., McDougall, N. & Lind, T. (1982) Effect of iron supplementation on serum ferritin levels during and after pregnancy. *Br. J. Obstet. Gynaecol.* 89: 1017.
- Tchernia, G., Blot, I., Rey, A. & Papiernik, E. (1983) Carences maternelles en fer et folates: répercussions sur le nouveau-né. *Sem. Hôp. Paris* 59: 416–420.
- Thomses, J. K., Prien-Larsen, J. C., Devandier, A. & Fogh-Andersen, N. (1993) Low dose iron supplementation does not cover the need for iron during pregnancy. *Acta Obstet. Gynecol. Scand.* 72: 93–98.
- Trigg, K. H., Rendall, E. J. C., Johnson, A., Fellingham, F. R. & Prankerd, T.A.J. (1976) Folate supplements during pregnancy. *J. R. Coll. Gen. Pract.* 26: 228–230.
- U.S. Preventive Services Task Force (1993) Routine iron supplementation during pregnancy: policy statement. *J. Am. Med. Assoc.* 270: 2846–2854.
- Verma, K. C. & Dhar, G. (1976) Relationship of maternal anaemia, birth weight and perinatal mortality in low birth weight neonates: (a hospital study). *Indian Pediatr.* 13: 439–441.
- Whittaker, P. G., Macphail, S. & Lind, T. (1996) Serial hematologic changes and pregnancy outcome. *Obstet. Gynecol.* 88: 33–39.
- Yip, R. (2000) Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. *Am. J. Clin. Nutr.* 72 (suppl): 272S–279S.
- Zhou, L.-M., Yang, W.-W., Hua, J.-Z., Deng, C.-Q., Tao, X. & Stoltzfus, R. J. (1998) Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. *Am. J. Epidemiol.* 148: 998–1006.
- Zittoun, J., Blot, I., Hill, C., Papiernik, E. & Tchernia, G. (1983) Iron supplements versus placebo during pregnancy: its effects on iron and folate status on mothers and newborns. *Ann. Nutr. Metab.* 27: 320–327.

DISCUSSION

Participants: Cogswell, Sazawal, Haas, Rasmussen, Beard, Habicht, Lynch, Stoltzfus, Schultink, Tielsch, Allen, Horton, Lozoff

Dr. Cogswell: I have four points. First, I agree with Rasmussen that there is an association between hemoglobin levels and birth weight and preterm delivery, but the U-shaped relationship between hemoglobin and low birth weight is due to two separate associations between low hemoglobin and preterm delivery and high hemoglobin and small-for-gestational age. In 173,000 pregnant women who attended publicly funded health programs in 10 states, we found that the high hemoglobin during the first and second trimester was not associated with preterm birth but low hemoglobin was. On the other hand, we found that very high hemoglobin, that is, >140 g/L, was associated with small-for-gestational age delivery. An elevated hemoglobin level is an indicator of possible pregnancy complications associated with poor plasma volume expansion and should not be mistaken for good iron status.

Second, I disagree that the lowest proportion of low birth weight occurs at maternal hemoglobin values below the current cutoffs for anemia. The use of lowest hemoglobin value in several large studies biases the relationship between hemoglobin and birth outcomes. As shown in a study by Zhou and colleagues, using the lowest value of hemoglobin artificially shifts the relationship between hemoglobin and low birth weight towards a lower distribution of hemoglobin. When random hemoglobin values are used and stratified by trimester, as in a few recent studies, the lowest proportion of low birth weight is found among women with hemoglobin values above the current cutoffs for anemia.

Third, few studies have contrasted the associations between low hemoglobin and preterm delivery in black and white women. In our data we found similar associations between low hemoglobin and preterm delivery in black and white women. If anything, the odds for preterm birth in black women with moderate to severe anemia during the second trimester was

stronger than in white women. These data do not support the use of different hemoglobin cutoffs by ethnic group.

Finally, I disagree that the currently available evidence does not support the practice of offering women supplemental iron during pregnancy. Observational studies are biased by the lack of ability to control for unknown factors related to iron deficiency and birth outcomes. However, after controlling for known factors that would influence this association, several observational studies show a strong association between low hemoglobin, and in one study, iron-deficiency anemia, and adverse birth outcomes. As Rasmussen pointed out, the results of the intervention trials to date were biased toward false-negative findings. These biases include small sample sizes; the inability of the population to respond because of inadequate duration, dose, or late start of iron supplementation; or a small proportion of women with iron deficiency. Results from poorly designed intervention trials do not outweigh the evidence from well-designed observational studies. Until well-designed intervention trials give evidence that it is not beneficial, the practice of iron supplementation during pregnancy is warranted by the strong association between anemia and adverse birth outcomes.

Dr. Haas: About the U-shape relationship that you are finding with hemoglobin and either intrauterine growth retardation or preterm, you have identified what appear to be two curves that were superimposed to create one curve. One curve that might be related to iron deficiency or all the pathology associated with that—which includes anemia—shows the high risk at low values; the other curve that is superimposed shows that as you decrease plasma volume expansion you have an increase in hemoglobin and also get an increase in pathology. Has anybody tried to look at the two curves separately and say what is happening with the relationship between hemoglobin and these outcomes when you have eliminated the plasma volume problem or when you look at the plasma volume, when you have eliminated hemoglobin problems? The nadir for hemoglobin when there is just anemia may hit near the cutoff that we have been using all along but may be obscured by the pathology associated with plasma volume at the higher end of the hemoglobin distribution.

Dr. Rasmussen: I agree with you, except that the number of plasma volume estimates we have in the literature is very small and most are from healthy Scottish women. So, we are not going to be able to use those to answer the question that you had in mind. It certainly is something that is worth doing.

Dr. Beard: Maybe another variation on that is to ask whether you can drive hemoglobin values up in the second and third trimester with iron supplementation?

Dr. Rasmussen: Yes. Yes, clearly.

Dr. Beard: Can you give iron supplements to subjects who are following the normal dilution patterns of hemoglobin and drive hemoglobin up into the pathological range?

Dr. Rasmussen: You can drive the hemoglobin up. The pathological range is open to question. You would have to define the pathological range quite a bit better.

Dr. Habicht: It is true that you can drive hemoglobin up by iron overload—if you raise saturation levels. If you look at the saturation levels, you see that hemoglobin goes up very slightly, but that is in nonpregnant women. You can drive it up somewhat, but nowhere near to these levels. If we extrapolate from that finding to pregnant women, the answer is, no, you cannot drive it up that high. It is almost certain, as far as I can see, that those high levels are not due to iron overload. Those levels are due to inadequate plasma expansion. In which case, it is irrelevant relative to recommendations about iron or for trying to estimate what we are after.

Dr. Beard: That is what I was trying to get at—whether the right half of that pregnancy hemoglobin distribution is iron responsive. If it is not an iron-responsive portion, then we are looking at a different pathology from what we are looking at in the left half.

Dr. Lynch: Is there any evidence that inducing iron deficiency is an effective way of treating inadequate plasma volume expansion?

Dr. Sazawal: I was not sure whether the negative results that we are seeing in pregnancy trials is related to the lack of sample size. From the trials that were presented, three trials had a positive point estimate and three trials had a negative point estimate, which suggests that if you were doing random effects analysis, you would end up with null: unrelated to the sample size issue. I thought that actually the data are inconclusive and there is a need for more studies. Whether those can be done is another question.

Dr. Stoltzfus: Then how do we get the evidence we need? Do we have to do smarter observational research or do we have to make a strong statement that randomized trials are needed and that it is ethical to do that in certain circumstances?

I want to offer two ideas. One thing that has intrigued me is why more people are not looking at erythrocyte protoporphyrin in pregnancy as an indicator of iron deficiency. It seems ideal because it is very physiologically defined as opposed to some other measures. It is also independent of plasma volume expansion. One way to do smarter observational studies would be to do some of the same things that we have already been doing but not use hemoglobin as the sole risk factor. We cannot interpret it very well. Make the primary potential risk factor erythrocyte protoporphyrin.

Another idea is the timing, because if you go back to Allen's paper, I was impressed by some of the outcomes being linked to things that are happening at 16–20 wk gestation. Is this working through development of the placenta? We know that the placenta is changed in anemia. The placenta develops earlier than the fetus and if we want to change placental development as the route to changing fetal development, we have to get in there faster because the placenta is growing rapidly in the first half of pregnancy. The fetus grows rapidly in the second half of pregnancy. So, the timing issue may be very important, and most of our data are coming from the second half of pregnancy and most of our supplementation trials get started in the second half of pregnancy.

Dr. Lynch: There may be advantage in using transferrin receptor as well. Theoretically, the transferrin receptor might actually be more attractive. The problem with the ratio of erythrocyte protoporphyrin to heme is that it depends on the time when the cell was made. So, it does persist beyond the time of the iron deficiency, whereas the transferrin receptor is going to be more sensitive to rapid changes. It is too early to know whether that is true, but it might be. Certainly, transferrin receptor does increase in pregnancy, but it does seem to be sensitive to iron deficiency.

Dr. Sazawal: Even if you ended up using some of these measures to do “smart observational studies,” you would be sitting at this table 4 years down the line again advocating need for a clinical trial. Maybe we need smarter designs of clinical trials. For example, you could look at different doses. You do not have to have a placebo control but you can have other control groups that are meaningful. Ultimately the issue is going to be resolved by good, well-done clinical trials, which this area does not have.

Dr. Schultink: If we want to argue that we need to do placebo-controlled trials, meaning you give one group no iron and you give the other group iron, this is going to be really

difficult. We have seen the long list of issues that influence low birth weight and birth outcome. There is no way that you can really expect to get a universal answer where you do a study in Bangladesh or somewhere in Africa or some other place and you give one group no iron and the other group iron. There is no way you could translate the outcome of one country to the other country because all the different factors influencing low birth weight vary enormously between regions. So, I am really wondering—do we need to do this? I would not be able to justify this from a programmatic point of view.

Dr. Tielsch: To turn the question around, there is serious doubt about whether the programs are justified and it clearly makes a difference. You would think programmatically very differently if 60% of the population of pregnant women need to be supplemented vs. 8% of the population. So, if there is little evidence—or certainly unconvincing evidence—for women with mild-to-moderate anemia measured at some appropriate time early in their pregnancy that supplementation does not affect reproductive outcomes, then why we are shipping containers full of iron supplements?

Dr. Allen: From a public health point of view, pregnancy is a window of opportunity when you have a woman coming for care. If you can get her to take iron supplements, there is not much doubt that this improves iron stores postpartum. There is also not much doubt in my mind that it improves infant iron status postpartum.

Folate is a big confounder in these studies. If one nutrient will reduce preterm delivery, I am quite convinced that it is folate, working through different mechanisms. You have to remove the effects of folate if you are going to look at the effects or iron supplements.

Dr. Habicht: Two points. The first one comes from Allen's. If you are going to give iron, you are always going to give folate. So, from a purely public health point of view, I actually would prefer to see an iron-folate study than an iron study. It will not satisfy our intellectual curiosity relative to iron, but I would prefer to see a package that makes some sense.

The other thing that bothered me is that Rasmussen excluded all studies that were not randomized intervention studies. It is so nice and neat to say there are the randomized trials here, and all the other goats are here. It seems to me that actually those goats all are not the same. We need to think a little bit more carefully how we think about looking at trials where there is some greater plausibility and trials where there is much less. I have actually made a claim that for program evaluation, you basically depend upon plausibility most of the time. You cannot do it through probability trials.

Dr. Brabin: We have been looking at a prospective cohort study of pregnant women and, first, half of the babies born have hemoglobins < 125 g/L—and normal is ~165 g/L. So, one third of their hemoglobin mass is missing. Second, there was a highly significant association between the seasonal pattern of iron deficiency and the pattern of future anemia in infants, which is fairly suggestive that this is iron deficiency. Third, the pattern of infant anemia is associated with the birth weight. Perhaps more importantly in terms of outcomes, after the 1st mo of life, infants were more at risk of dying if they had low birth weight plus fetal anemia than low birth weight alone. We have to think beyond birth weight. Despite their limitations, observational studies can be very important.

Dr. Lynch: I was going to make the same point. It is awfully important to look at the whole picture. One of the figures Rasmussen showed includes the study by Preziosi et al., with very little effect on birth weight. Now, that study showed very clearly that children at 3 and 6 mo whose mothers received placebo were much more iron deficient. In fact, although not

commented on by the authors, the neonatal death rate was much higher than in the supplemented individuals. If you put it altogether, as you are pointing out, this is a major effect.

Dr. Sazawal: We do not realize when we discuss these issues as research priorities how they affect what happens in the field. Saying, well, this is a good time to get the woman and why not give her iron assumes unlimited resources. I was sitting in the Ministry of Health with the UNICEF officer and discussed what can be done—what interventions you can do in pregnancy. The Secretary of Health said that we do not have enough money for iron. Give me some iron and forget about the rest. So, iron may be good, but it is an issue of what it displaces and what effect would be lost.

Dr. Tielsch: This is why understanding the magnitude of the effect in solid, qualitative terms is absolutely critical. You have got to provide program planners with some information that they can use to make rational decisions. Now, do they make rational decisions all the time? Of course not. We all do not make rational prioritization decisions all the time. At least we have to give them some tools they can use to rationalize their resource allocations.

Dr. Lynch: That is particularly why you must look at the whole effect.

Dr. Tielsch: Absolutely. You are absolutely correct.

Dr. Horton: Are we using birth weights because we know they are related to other things in infancy, when really what

we want to have is some indicator of the infant's status at birth? There are not many studies that have that. Studies are focusing on birth weight, using a proxy that is not really very good.

Dr. Lozoff: I do not think so. Some investigators have shown cognitive differences across the entire birth weight continuum up into the normal range. Now, people did not ask whether that is an iron effect or birth weight effect, but studies are considering birth weight in relation to child development across the birth weight range, not just in this low end.

Dr. Horton: Birth weight is of interest in its own right?

Dr. Tielsch: Birth weight is the compelling reproductive outcome of interest because it has such strong association with both development and early mortality.

Dr. Sazawal: It is the single strongest predictor in its own right for survival, for anything you see. In fact, it is the greatest single predictor in any study we have done, including the effect of intensive feeding in the 1st y of life or the growth at 1 y.

Dr. Horton: What if in addition to having birth weight, you also have some information about iron status?

Dr. Tielsch: You are absolutely right. Not every intervention that affects early infant mortality operates through birth weight. There are lots of interventions that do not operate through birth weight. Neonatal tetanus immunization, for example, operates independently.