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DOES IRON SUPPLEMENTATION MAKE A DIFFERENCE?

WORKING PAPER: 15

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DOES IRON SUPPLEMENTATION MAKE A DIFFERENCE?

Nancy L. Sloan, Elizabeth A. Jordan and Beverly Winikoff

ABSTRACT

This report presents data from randomized trials in developed and developing countries published between 1966 and 1989 in refereed journals. References were identified by computer search. All studies drew their samples from women attending prenatal clinics.

This review demonstrates that iron supplementation is efficacious, and is associated with initial hematologic status, dose, and duration of supplementation. The effects of iron supplementation on improving maternal hematologic status are improved in the presence of folate or vitamin C supplementation. No consistent effects on birthweight were observed.

The effectiveness of iron supplementation programs, however, has been equivocal, with the prevalence of global maternal anemia virtually unchanged in the past thirty years, even in the presence of iron supplementation programs. Innovative approaches, including prolonged iron supplementation, investment in fortification, promotion and education of iron supplements, and resolution of logistical problems that hinder availability of iron supplements at the community level, need to be tested through both clinic- and community-based research to find effective answers to this worldwide problem.

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I. INTRODUCTION

Anemia is the most common nutritional deficiency in the world (1,2). It is most prevalent in pregnant women, infants and children and is caused by inadequate diet, (mostly iron, but also deficiencies of dietary folate and vitamin B12), impaired absorption, blood loss (menstruation, childbirth, hemorrhage) or (in women) repeated pregnancies (2,3,4). Chronic infection (malaria, helminths) (5,6) genetic defects (sickle cell, thalassemia) and metabolic disorders are also major contributors (1,7,8,9,10,11,12,13,14,15). Other causes of red blood cell loss, such as drug and autoimmune reactions, are rare.

The adverse effects of anemia are multiple. Several studies have found anemia is associated with reduced work capacity, and its correction leads to an improvement in work tolerance (16). This has particular relevance to pregnant and lactating women for household and economic related productivity and child care in developing countries.

Anemia also reduces the capacity of the body to withstand sudden blood loss, either in trauma, surgery, or blood loss associated with childbirth. In developing countries, anemia may contribute to maternal mortality (13,17,18). Anemia during pregnancy also has adverse effects on the fetus. Severely anemic women are theorized to have higher rates of spontaneous abortion, preterm delivery and low birth weight infants (16). Although still controversial, much evidence suggests that anemia in pregnancy does not have an adverse effect on the hematological or iron status of the infant[1] (19). Anemia in preschool children, however, has been associated with behavioral abnormalities (20) and impaired scholastic achievement (21).

The prevalence of anemia in pregnancy has been widely investigated (17,22,23). **In developing countries, the highest prevalence of anemia is found in South Asia and Africa, where it is estimated that almost two-thirds of pregnant women and one-half of non-pregnant women are anemic** (7). Hemoglobin and hematocrit levels are the most commonly assessed measurements of anemia (although they do not distinguish among iron deficiency and other causes of anemia)(38,39). Serum ferritin is thought to be the single measurement most indicative of iron stores and thus iron deficiency.

Recent increased understanding of the physiology of pregnancy indicates that hemodilution in pregnancy occurs as a result of two distinct processes, plasma volume expansion (which increases an average of 50% in pregnancy), and a rise in red cell mass (which averages about 18% during pregnancy to facilitate a necessary increase in oxygen uptake) (24). The combination of these processes results in a decline of normal hemoglobin levels from the 20th to the 35th week of pregnancy, with about a 5% reduction in the first trimester, a 10-15% reduction in the second trimester, and a 5% increase after the 35th week of pregnancy when plasma volume stabilizes. Normal hemoglobin levels vary between 12.0 g/dl and 13.4 g/dl in pregnancy (1,8,25). Hemoglobin levels <11.0 g/dl are indicative of anemia in pregnancy, with levels <6.5 g/dl comprising a value below which maternal survival is threatened, and levels of around 9 g/dl representing the safety threshold (7,8).

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[1] Infants born to anemic women are thought to be more prone to iron deficiency later in life because their iron stores at birth are theoretically lower than those of infants born to non-anemic women.

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Increase in dietary iron is unlikely to meet iron requirements during pregnancy. The daily food intake requirement for iron in pregnancy ranges between 16.5 mg and 35 mg. Daily consumption in a national sample of poor women in the United States was estimated around 14.4 mg, and is probably higher than the daily iron intake of pregnant women from developing countries. It is estimated that 14.6% of dietary iron intake is absorbed by otherwise well nourished pregnant women. Absorption rates are probably lower in developing countries where parasitic diseases and malaria are prevalent, although utilization of iron may be more efficient in response to the greater needs created by these diseases. Supplemental iron is generally recommended during pregnancy in both developed and developing countries in order to correct baseline iron deficiencies and prevent iron deficiency from developing or worsening.

Interventions to reduce iron deficiency anemia in developing countries have included oral and parenteral supplementation of pregnant women, food fortification (including food additives), and simultaneous malaria prophylaxis. While food fortification provides a potentially long-term method to improve the iron status and has been relatively successful in the United States, its requirements render it an unlikely short or medium term strategy for reduction of anemia in developing countries. Identification of acceptable and commonly consumed foods produced at a limited number of sites, appropriate and locally available technology and equipment, long-term funding sources or affordable and acceptable mechanisms to pass the increased price to the consumer, and a long-term commitment by the government, producer, distributors, etc. are necessary components of successful fortification programs. Although it is possible to give iron in large doses intramuscularly and intravenously, these approaches are not viable public health strategies because of their serious and potentially fatal side effects, such as anaphylaxis (26), and the potential for transmission of HIV infection and hepatitis through re-use of needles.

The physiological decrease in iron stores and in hemoglobin levels have been shown to be partially ameliorated in controlled studies of otherwise relatively well-nourished pregnant women receiving iron supplementation (27,28,29,30,31,32,33). Recent supplementation studies of pregnant women have shown substantial reductions in anemia (up to 50%) and improved hemoglobin levels (up to 10-15% increase in mean values or approximately 1 g/dl) associated with daily supplements of 120-240 mg iron (either ferrous sulphate or iron aminuates) and sometimes supplemented with 5 mg folic acid during the final trimester of pregnancy (27,28,29,33). This is almost equivalent to one-half or one-third of the estimated daily iron cost of a normal pregnancy (Table 1) given the low absorption of dietary iron. **These changes have been observed, however, with supplemental doses that are considerably higher than that available though consumption of multi-vitamins (18 mg/day) or prenatal supplements (60 mg/day).**

Fewer studies report categorical outcome data (i.e., the effects of oral iron supplementation on maternal anemia in pregnancy). Studies with available data show that routine prenatal supplementation decreases the risk of low hemoglobin levels (Hb <10 or 10.5 g/dl)[2] approximately 8 fold, and low serum ferritins (<10 ug/l)[2] by 20 fold in controlled trials of pregnant women at 36-40 weeks gestation (24).

Dietary inadequacies constitute only part of the etiology of iron deficiency anemia in most countries; their effect is compounded by reduced absorption and utilization associated with

[2] Note: These levels represent that cited in the reference, and do not reflect the WHO criteria of <11.0 g/dl for maternal anemia.

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intestinal parasites and malaria (5,6). Thus, it is theoretically difficult to predict if supplementation under these conditions will produce larger effects due to increased absorption in states of deficiency, or smaller results due to concomitant factors that hinder absorption[3].

The physiologic availability of iron begins with the ingestion of dietary iron or supplements. **It is estimated that approximately 10% of dietary iron is absorbed, influenced by the quantity and chemistry of iron in the ingested food sources, and the concommittant consumption of foods which inhibit or enhance the availability of iron for absorption** (34,35,36). Small amounts (~1 mg) of iron are lost daily from the cells, shed from the skin or epithelial linings of the gastrointestinal or urinary tract. Pregnancy, menstruation, or lactation are large contributors to daily loss of iron (1.0-2.5 and 0.6-0.9, respectively).

The amount of iron absorbed from the gastrointestinal tract varies with time over pregnancy reflecting the relative needs of the woman. In iron sufficient women, iron absorption is low at about 1.2% during the first trimester; the daily needs are somewhat less since menstrual losses are not contributing. During the second trimester, iron absorption increases and reaches a maximum of about 15% during the third trimester, when fetal needs are greatest (29). Even with intestinal iron absorption at 15%, few women will be able to ingest enough iron in their diet to allow for 1-2.5 mg/day absorption. Women with less than 200 mg of storage iron who are not receiving extra iron from a fortified diet or from oral iron supplements will inevitably become iron deficient during pregnancy (37).

Table 1: Iron Cost of a Normal Pregnancy

Iron contributed to fetus	200-370 mg
In placenta and cord	30-170 mg
In blood loss at delivery	90-310 mg
In milk, lactation 6 months	100-180 mg
Total	420-1030 mg
Average per day (pregnancy 9 mo., lactation 6 mo.)	1-2.5 mg

Source: Buetler, E. "Iron" in Shils M.E. and Young V.R.: Modern Nutrition in Health and Disease, Sixth Edition, Lea & Febiger, Philadelphia, 1980.

[3] Dietary inhibitors may also account for a small portion of reduced iron availability, but do not play a major role in deficiency.

II. METHODS

There have been many iron supplementation trials in pregnant women in developed and developing countries over the past 30 years. Recently, Mahomed & Hytten (24) have summarized findings from trials of oral iron supplementation on a variety of outcome measures. Few of the reviewed studies were from developing countries, however, and results were interpreted based on meta analysis (see Appendix 1). Due to differences in data availability, methodologic variability, combinations of interventions, baseline status and interactive factors (synergistic or antagonistic), this review interprets the findings of studies published between 1966 and 1989 using standard epidemiologic criteria to describe the effects of oral iron tablet supplementation on maternal hematologic status under a wide array of conditions.

The present report presents data available from developed and developing countries published between 1966 and 1989 in refereed journals. References were identified by computer search. Approximately 60 iron supplementation trials in pregnant women were reviewed; two thirds of these involved intervention trials in developing countries where anemia is highly prevalent, and one third were done in developed countries where iron deficiency has a low prevalence (see Appendix 2 for an abstract of each study). Only twenty-four of these studies, all randomized controlled trials, had sufficient data presented for analysis of the effects of iron supplementation on maternal hematologic change in pregnancy. Factors considered include initial sample size, baseline Hb concentrations, daily dose of elemental iron, duration of therapy, proportion and reasons for loss to follow up, and additional nutritional supplementation or medical therapy. All studies drew their samples from women attending prenatal clinics.

Tables 2a-f present these factors and the results of these studies by region. Hemoglobin levels were calculated as hematocrit levels divided by three for studies reporting hematocrit only. Results of the studies are reflected in the last three columns of these tables, and present the difference in the absolute change in hemoglobin levels between initial and final mean Hb in the treatment group minus the absolute change in hemoglobin levels between initial and final hemoglobin measures in the comparison groups. Comparison groups are represented by a star (*) in these columns, and the effect of the treatment compared to that group is located directly beneath the star. The measure of treatment effect consistently referred to in this document is:

$$\text{TREATMENT EFFECT} = \frac{\text{Treatment Group Final Hb - Initial Hb}}{\text{Comparison Group Final Hb - Initial Hb.}}$$

Although the most meaningful analysis reflects the reduction in the proportion of anemic women associated with intervention, these data are sparse, and thus are limited to summarization presented here. Still, it is noteworthy that the mean hemoglobin levels of women in eleven of the fifteen randomized controlled trials conducted in developing countries reviewed in this article were below the World Health Organization definition for anemia during pregnancy (Hb <11 g/dl[4], compared to Hb <12 g/dl in non-pregnant women; WHO, 1968), indicating that approximately fifty percent or more women in these studies were anemic at baseline assessment.

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[4] It has been estimated that 80% of women with Hb <11.0 g/dl in pregnancy truly have anemia (INACG, 1981).

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III. RESULTS

Sample Size

Most of the studies reviewed had very small sample sizes (≤30 women per group) and thus minimal statistical power[5] to detect significant differences between groups or to presume comparability of the study groups. Of the 15 studies conducted in developing countries, 4 (27%; 11,39,40,44) had fewer than 31 women allocated to any individual treatment, 8 (53%; 6,11,41,43,47) had between 31 and 60 women per study group, and 2 (13%; 38,42) had more than 60 women per study group; one study (45) had between 31 and 60 women at follow-up but did not report number of women initially enrolled. Of the 9 studies conducted in developed countries, 5 (56%; 30,33,46,48,51) had fewer than 31 women allocated to each study group and 2 (22%; 50,27) had more than 60 women per study group; one study (49) had fewer than 30 enrolled but did not report the number followed.

Acceptability/Adherence with Therapeutic Regimen

Acceptability of or adherence with oral iron supplements is problematic, and has been theorized to reduce iron intake and therefore the dose and effectiveness of the supplementation. Many factors, both biological and cultural, may affect the acceptability and adherence with iron supplementation. Higher doses of oral iron are argued to be associated with higher rates of side effects including constipation, diarrhea, vomiting or epigastric pain.

Many studies noted problems with regular adherence with therapy. Three studies (11,39,42) had treatment groups in which the consumption of the tablet was supervised by study workers. The studies conducted by Charoenlarp et al. in Burma and Thailand, were the only studies measuring the effects between supervised and nonsupervised groups. In Thailand, there was no additional effect of supervision, but in Burma the high iron dose unsupervised group had less Hb increase compared to the supervised group receiving the same dose. This study hypothesized that the unsupervised women were less adherent due to side effects from the high dose iron.

The follow-up rates from studies with <100% follow-up (i.e., those that did not exclude women whose acceptance of the supplements was low) are the best indicator of the acceptability of the regimen. These studies indicate a wide variability in acceptance with about a 50% average.

Follow-up in three studies (33,29,27), all conducted in Europe, was very high (≥80%, but not universal), although 2 of these studies (33,29) had very small sample sizes.

Some studies had poor follow-up rates (41,15,50), reducing the validity of this article's measure of effect, change (i.e., difference) in mean hemoglobin from baseline to final measurement, because many women included in the reported initial mean hemoglobin were not included in the reported final mean hemoglobin.

The results from these studies, however, do not take into account the presumed lack of effect

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[5] Generally estimated between 50% and 70%. In this case, statistical power means the probability (here 50%-70%) that the hypothesis that no difference is attributable to the intervention, will be rejected if this is indeed false.

or small effect associated with short duration of supplementation in those not followed up (and missing) in the measure of final group mean hemoglobin. The effectiveness of iron supplementation, that is how well it works under real conditions where women reject supplementation for one reason or another, is therefore overestimated by the results of these studies.

Effectiveness vs. Efficacy

Most studies (11,30,38,39,40,42,43,46,47,48,51,52) reported 100% follow-up of women. In fact, women not followed through the end of pregnancy were actually excluded (as opposed to lost to follow-up) from these studies and from both initial and final hemoglobin levels reported. These studies thus measure the efficacy of iron supplementation, that is the effects of supplementation under controlled "ideal" conditions. As discussed above, the magnitude of efficacy is always greater than that of effectiveness.

The measurement of efficacy ignores the initial hemoglobin level for excluded (or lost) women and produces comparable groups (internal consistency) for those who completed the trial. This reduces the generalizability (external consistency) of the study so that the results are not generalizable to the obstetrical population as a whole.

Exclusion of women who delivered prematurely or who developed anemia (and were then treated), were problems in most studies. Women who deliver prematurely are more likely to be anemic, therefore their exclusion may artificially raise the final mean hemoglobin levels in the respective remaining groups of women. When women in placebo or control groups are removed from the trial because they develop anemia and are treated with iron, the final mean hemoglobin levels (which do not contain values from these women who developed anemia) are thus artificially higher than would be expected if these women had remained in the placebo or control group untreated. If the final hemoglobin levels for these women before treatment are included, then there is the problem that the final hemoglobin levels are obtained at different gestational ages and are not really comparable since the hemoglobin level falls over pregnancy, and then rises in the last few weeks of gestation (at 35-37 weeks).

Studies that did not exclude women with premature deliveries suffer different problems of "follow-up". If lower follow-up rates occurred in one group because more women in that group gave birth prematurely (and were not found for scheduled follow-up), the final mean hemoglobin levels of that group may be artificially high as: 1) there is a direct association between premature delivery and anemia, and 2) hemoglobin levels begin to rise in the last few weeks of pregnancy, possibly a reflection of late pregnancy changes in plasma volume. Therefore, larger loss to follow-up due to premature delivery will result in an underestimation of the differential changes of Hb levels to an unknown extent. Better follow-up rates may be expected in the experimental groups if iron corrects or prevents anemia (and therefore prematurity).

Initial Hemoglobin Status

Initial hematologic status needs to be considered when interpreting results of the trials as iron metabolism, the rate of iron absorption unlike other trace elements, depends on iron status and is not regulated through variation in excretion[6]. Iron absorption increases 2-3 fold above

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[6] Only 0.1 mg estimated is lost in daily excretion.

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normal in iron deficient individuals (WHO, 1974).

Most women in two (42,43) of the fifteen studies conducted in developing countries had initial mean hemoglobin levels below 10 g/dl; the majority reported levels between 10 and 10.9 g/dl (11,39,40,41,44), and the remainder (6,38,41,45,47) levels between 11 and 11.9 g/dl. Most women in the developed countries studies (29,30,46,48,49,51) had pre-intervention mean hemoglobin levels greater than or equal to 12 g/dl; the remainder (27,33,50) had levels between 11 and 11.9 g/dl.

In developing countries, some increase in effect was observed with lower initial hemoglobin levels following iron supplementation. Women with low initial hemoglobin values (<11 g/dl) showed differentials in hematologic change ranging from -0.3 g/dl to 2.5 g/dl with an estimated average effect of 1.2 g/dl above controls. Women with intermediate (between 11 g/dl and 12 g/dl) initial hemoglobin levels in studies in developing countries had differential hemoglobin change between -1.2 g/dl to 1.2 g/dl, with an average improvement of about 0.5 g/dl above controls.

Studies of women with intermediate hemoglobin levels (initial mean hemoglobin levels around 11.5 g/dl) in developed countries had better differential hemoglobin changes, ranging from 0.3 g/dl to 2.2 g/dl, and averaging about 1.0 g/dl above controls, than did studies of women in developing countries.

The difference in benefit of supplementation in women with intermediate initial hemoglobin levels may be attributable to the higher burden of parasitic loads, other infections and malnutrition in developing countries which interact with and reduce the efficiency of women's utilization of iron supplementation. **Combining studies of women from developed and developing countries with intermediate initial Hb levels reflects an average improvement in hemoglobin change of about 0.8 g/dl compared to controls.**

Data for women with initial mean hemoglobin levels equal to or above 12 g/dl was available only from developed countries, probably reflecting real differences in women's hematologic status between developed and developing countries. These studies found improved effects of supplementation ranging from 0.1 g/dl to 1.5 g/dl, with an average benefit of about 0.8 g/dl compared to controls.

TABLE 3: EFFECTS OF INITIAL HB STATUS IN PREGNANT WOMEN

INITIAL HB g/dl	DEVELOPING COUNTRIES		DEVELOPED COUNTRIES	
	Range of Effect g/dl	Average Effect g/dl	Range of Effect g/dl	Average Effect g/dl
≤10	0.2, 1.7	1.0	NA	NA
>10,<11	-0.3, 2.5	1.3	NA	NA
>11,<12	-1.2, 1.2	0.5	0.3, 2.2	1.0
≥12	NA	NA	0.1, 1.5	0.8

General Effects of Unaccompanied Iron Supplementation

Studies comparing hematologic change in women receiving iron supplementation alone with women receiving no supplements (except placebos) or other treatments (11,27,29,30,33,40,41,42,46,47 and 51) **found supplementation consistently resulted in better hemoglobin change over pregnancy, with differential changes ranging from 0.3 to 2.5 g/dl, averaging a difference of about 1.2 g/dl (median value=1.0).** Nine of the thirteen studies falling in this category showed effects between 0.8 g/dl and 1.3 g/dl. The smallest observed effect was associated with extremely low dose (12 mg) iron supplementation, and the largest effect may be partially attributable to differences in follow-up (which was very poor) and possibly initial hematologic status.

Two studies had only control groups that received low (60 mg) levels of iron supplementation (38,43). The average effects of higher iron supplementation was 0.6 (38) and 0.7 (43), respectively.

Dose Effects of Iron Supplementation: A positive dose-response relationship was evident between iron dose and Hb level change.

TABLE 4: DOSE-RESPONSE TO IRON SUPPLEMENTATION IN PREGNANT WOMEN

TREATMENT GROUP SUPPLEMENT DOSE (mg)	UNSUPPLEMENTED CONTROL GROUP		SUPPLEMENTED CONTROL GROUP	
	Range of Effect g/dl	Average Effect g/dl	Range of Effect g/dl	Average Effect g/dl
≤60	-1.7, 1.1	0.2	NA	NA
61-90	0.6, 1.5	1.0	NA	NA
91-120	0.6, 2.2	1.2	0, 0.2	0.1
>120	0.9, 2.6	1.6	-0.3, 1.0	0.3

Studies comparing supplemented to nonsupplemented women that provided less than or equal to 60 mg daily iron dose supplementation (27,42,46)[7], showed differential hematologic change ranging from -1.7 to 1.1 g/dl, with an average improvement of about 0.2 g/dl in studies including those providing antimalarials to experimental and control groups. The effects of supplementation ranged from 0.3 to 1.1 g/dl averaging about a 0.6 g/dl improvement in studies excluding those providing antimalarials compared to unsupplemented controls. Studies providing between 61 and 90 mg daily iron supplementation (41,47,48,49) had effects ranging between 0.6 g/dl and 1.5 g/dl, with an average increase of about 1.0 g/dl above unsupplemented control values. Women in studies providing between 91 and 120 mg daily iron supplementation (11,27,29,30,40,42,45,50,) had Hb changes ranging from 0.6 g/dl to 2.2 g/dl better than unsupplemented controls, averaging about 1.2 g/dl better. Those receiving greater than 120 mg daily iron supplementation (11,33,41,42,51) showed the largest benefit,

[7] Five study groups were provided 60 mg per day, three were provided 30 mg per day and another 12 mg per day.

ranging from 0.9 to 2.6 g/dl improvement, with an average improvement of about 1.6 g/dl compared to unsupplemented controls.

Studies comparing supplemented women to unsupplemented controls demonstrated a greater dose-response than did studies comparing women receiving higher vs. lower iron supplementation. Because studies comparing women receiving higher to lower supplementation provided lower level supplementation to their comparison groups, these studies do not include very low or low level dose treatment groups. These studies showed about a 0.1 g/dl improvement in hematologic change with a range of 0 to 0.2 g/dl improvement with doses between 91 and 120 mg iron supplementation. With supplementation higher than 120 mg, differential hematologic change ranged between -0.3 g/dl and 1.0 g/dl averaging about 0.3 g/dl improvement including studies providing antimalarials, and ranging between 0 and 1.0 g/dl averaging about 0.4 g/dl improvement in studies excluding those providing antimalarials.

Effects of Duration of Therapy: Three studies (42,44,47) provided less than or equal to 10 weeks of iron supplementation, and found associated benefits ranging between -1.7 g/dl and 1.7 g/dl, with an average benefit of about 0.6 g/dl compared to controls. Most studies (11,38,39,41,43,50) provided iron supplementation covering one trimester, or twelve weeks. Effects ranged between -0.3 g/dl and 2.6 g/dl, with an average hemoglobin differential of about 0.6 g/dl. Many studies (6,11,40,45,49) provided between 14 and 19 weeks of iron supplementation and found hemoglobin change was -1.2 g/dl to 1.5 g/dl different than controls, with an average improvement of 0.9 g/dl. Some studies (27,29,30,46,48,51), all in developed countries, provided iron supplementation for 20 to 27 weeks and found hemoglobin improvement ranging between 0.3 and 2.2 g/dl, with an average improvement 1.0 g/dl greater change than controls.

TABLE 5: EFFECTS OF DURATION OF IRON SUPPLEMENTATION IN PREGNANT WOMEN

DURATION OF THERAPY	Range of Effect g/dl	Average Effect g/dl
≤10 weeks	-1.7, 1.7	0.6
11-13 weeks	-0.3, 3.6	0.6
14-19 weeks	-1.2, 1.5	0.9
≥20 weeks	0.3, 2.2	1.0

Interactions of Dose and Duration: Of course, total dose of iron supplementation is influenced by dose and duration of iron supplementation.

Studies comparing supplemented groups to controls not receiving iron supplementation showed a clear dose-response pattern. Studies providing ≤7,000 mg over pregnancy (27,41,42,46,47,53,44,) showed a differential change in hemoglobin ranging from -1.7 to 1.1 g/dl with an average increment of 0.2 g/dl compared to unsupplemented controls. Studies providing 7,001 to 10,500 mg iron showed better hemoglobin changes ranging from 0.6 to 1.5 g/dl with an average benefit of 1.2 g/dl compared to unsupplemented controls. Studies providing between 10,501 and 17,500 mg iron showed similar hematologic change ranging from 0.6 to 2.2 g/dl with and average of 1.2 g/dl compared to unsupplemented controls. Studies providing >17,500 mg improved hemoglobin change between 0.9 g/dl and 2.6 g/dl

with an average of 1.5 g/dl, compared to unsupplemented controls.

The results of studies including comparisons of higher and lower iron supplementation were less clear, possibly because there were fewer studies with these types of comparisons. There were no such studies with treatment groups receiving ≤7,000 mg over pregnancy. Two studies provided between 7,001 and ≤10,500 mg with effects of iron supplementation ranging between 0 and 0.2 g/dl with and average of 0.1 g/dl improved hematologic change compared to controls receiving lower level supplementation. Two studies provided between 14,001 and ≤17,500 mg iron over pregnancy and found benefits ranging from 0.2 g/dl to 1.0 g/dl with and average of 0.6 g/dl better hemoglobin change compared to controls receiving lower level supplementation. Three studies provided >17,500 mg and found equivocal results, with differential hemoglobin change ranging from -0.2 to 0.7 g/dl with an average improvement of 0.3 g/dl compared to controls receiving lower level supplementation.

TABLE 6A: EFFECTS OF INTERACTION BETWEEN DOSE AND DURATION OF IRON SUPPLEMENTATION

DOSE x DURATION OF THERAPY	UNSUPPLEMENTED CONTROL GROUP		SUPPLEMENTED CONTROL GROUP	
	Range of Effect g/dl	Average Effect g/dl	Range of Effect g/dl	Average Effect g/dl
≤7,000 mg	1.7, 1.1	0.2	NA	NA
7,001 - ≤10,500 mg	0.6, 1.5	1.2	0, 0.2	0.1
>10,500 mg	0.6, 2.2	1.4	-0.2, 0.7	0.3

Looking at the results of all studies, those providing ≤7,000 mg iron supplementation had an average dose equivalent to 650 mg (there was no median value, but the middle two values were 4,368 and 5,705 mg) or approximately 11 weeks of 60 mg daily iron supplementation; the average effect of this was 0.2 g/dl better hemoglobin change than controls. Studies providing between 7,001 and ≤10,500 mg had an average dose of 8,225 mg (median 8,820 mg) over pregnancy, equivalent to about 20 weeks at 60 mg daily supplementation; these studies showed an average improvement of about 0.8 g/dl in treatment compared to control hematologic change. Studies providing >10,500 mg had an average dose of 18,900 (median 17,745 mg) over pregnancy which is the equivalent of about 45 weeks of supplementation at 60 mg per day; these studies had an average of about 1.0 g/dl better hemoglobin change than supplemented and unsupplemented controls.

TABLE 6B: EFFECTS OF INTERACTION BETWEEN DOSE AND DURATION OF IRON SUPPLEMENTATION

DOSE x DURATION OF THERAPY	Range of Effect g/dl	Average Effect g/dl
≤7,000 mg	-1.7, 1.1	0.2
7,001 - ≤10,500 mg	0, 1.5	0.8
>10,500 mg	-0.2, 2.6	1.0

Effects of Iron and folate vs. unsupplemented controls: Six studies (11,30,40,42,46) examined the effects of combined iron and folate supplementation on maternal hemoglobin levels compared to women receiving neither iron, folate (or any other supplement). Those receiving combined supplementation had consistently better hemoglobin change than did controls. Changes in hemoglobin levels ranged between 0.2 g/dl and 1.6 g/dl, with an average improvement of 1.1 g/dl (the mean and mode = 1.3 g/dl). The lowest effect was observed in a low (60 mg) dose group receiving iron supplementation, the largest effect was observed in the same study associated with a very high dose (240 mg) of iron supplementation.[8] An additional study (6) compared the effects of iron and folate supplementation above and beyond antimalarial prophylaxis. This was the sole study in this category to observe negative effects of complementary folate supplementation.

Effects of Iron and folate vs. folate supplemented controls: Similarly, two studies (40,46) comparing the combined effects of iron and folate supplementation on maternal hematologic change with the effects of folate supplementation alone found that iron supplementation improved hematologic change 1.4 g/dl and 0.5 g/dl respectively; the difference in the magnitude of these improvements is probably due to differences in dose of supplemental iron (120 vs 60 mg, respectively). Another study examined the combined effects of iron and folate, complemented by supplemental vitamin B12 in the experimental groups only, and found this triple supplementation improved hemoglobin changes by 1.1, 1.5 and 1.7 g/dl (depending on iron dose) above controls receiving folate supplementation alone. It is not possible to separate out the additional effects of vitamin B12 supplementation from those of iron supplementation in this study. A fourth study (6) compared the effects of combined iron and folate supplementation with folate supplementation above and beyond malaria prophylaxis. This was the sole study to find a decrement in hemoglobin change (0.5 g/dl) with iron and folate supplementation and antimalarial prophylaxis compared to those receiving folate supplementation and antimalarial prophylaxis only. As noted in the following section, inconsistent results were observed in studies including antimalarial prophylaxis.

Effects of Iron and Antimalarials: All studies examining the effects of iron supplementation in combination with antimalarial prophylaxis were conducted in Africa. Wide ranges of effect were observed in the few studies in this category. Two studies (43,6) examined the effects of combined iron and folate and antimalarial prophylaxis compared to antimalarial prophylaxis

[8] Both experimental and comparison control groups in this study were given additional vitamin B12 supplementation.

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alone. The Liberian study (43) found a 1.0 g/dl differential in Hb change; the same study observed an effect of 0.7 g/dl in the group receiving iron and folate supplementation without antimalarial prophylaxis to unsupplemented, untreated controls. This implies a 0.3 g/dl improvement in hematologic change associated with combined iron supplementation and antimalarial prophylaxis. The Nigerian study (6) found consistent decrements in differential hemoglobin change with antimalarials, which was reduced 0.2 g/dl with folate in the absence of iron supplementation but was reduced an additional 1.0 g/dl in the presence of iron supplementation. Iron supplementation resulted in better hemoglobin change compared to controls receiving folate and antimalarials alone. Another study (44) looked at the effects of 30 mg iron supplementation with and without thiamin supplementation in very small groups of women (group n ≤6) and very short duration (6 weeks) of supplementation. Iron supplementation showed no improvement or reduction in hemoglobin change compared to controls, probably due to the very low dose of supplementation. There was no consistent direction of effect with antimalarials regardless of other supplementation, however there were few studies in this category and all had group sample sizes of ≤40.

Effects of Iron and Vitamin C: Three studies (41,50) examined the effects of combining iron and vitamin C supplementation to see if larger effects of iron supplementation could be observed if absorption of iron were increased by the intake of vitamin C. Indeed, larger benefits were observed, with better hematologic change ranging from 0.9 to 2.6 g/dl for an average improvement of about 1.5 g/dl, about twice the effect of iron supplementation alone. Unfortunately, the validity of this effect size is questionable. Two of the studies had small sample sizes (41) and all had poor follow-up.

Effects of Iron and Vitamin B12: One study (42) looked at the incremental effects of vitamin B12 supplementation on hematologic change in pregnancy in India, a population theorctically deficient in both iron and vitamin B12. In combination with iron and folate supplementation, vitamin B12 improved hematologic change 1.1, 0.3, 1.5 and 1.7 g/dl in groups receiving 30, 60, 120 and 240 mg iron supplementation and folate compared to controls receiving neither iron or folate. To separate out the effects of iron from those of folate and B12 supplementation, the study compared women provided 120 mg daily iron, and no folate or B12, with those provided all three supplements; the additional effect of combined folate and B12 was 0.5 g/dl. Vitamin B12 and folate supplementation without iron supplementation had a much smaller effect in this sample. Comparing two control groups, one provided folate and B12 supplementation and the other no supplementation, a 0.1 g/dl greater increase in Hb change was observed.

Effects of Iron and Thiamin: One study (44) looked at the incremental effects of thiamin in a sample of women receiving antimalarial prophylaxis, some of whom received 30 mg iron supplementation. No improvement in Hb change was observed in the groups receiving 30 mg iron supplementation with thiamin compared to controls receiving thiamin only, and similarly in those receiving 30 mg iron supplementation without thiamin compared to controls without thiamin. Both experimental and control groups receiving thiamin evinced a 1.7 g/dl decrement in Hb change compared to experimental and control groups without thiamin supplementation, respectively.

Effects of Iron and Multi-Vitamins[9]: Three studies (45,48,49) provided both experimental and control groups with daily multivitamin supplements. Therefore these studies estimated

[9] It is assumed that some multivitamins contained vitamin B12, folate and/or vitamin C.

the effects of iron supplementation above and beyond that of multivitamin supplementation and found increases of Hb change of 0.9, 0.6, and 1.5 g/dl, respectively. These increases are somewhat better than those observed with iron alone, and are consistent with the observations regarding the effects of complementary vitamin C supplementation. Similarly, the validity of these studies is also debatable. Two of the studies (48,49) had very small sample sizes (<20 per group) and the remaining study (45) did not report its baseline sample, although it could be inferred to be the same at baseline and follow-up.

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IV. DISCUSSION

There are many issues to consider with the effects of oral iron supplementation in tablets on pregnancy outcome:

- dose of iron,
- duration of therapy,
- initial iron status,
- adherence to regimen, and
- the effects of iron combined with other supplements or with co-existing infection.

In the absence of iron supplementation during pregnancy, the Hb level decreases between study enrollment and term. The magnitude of the decrease depends on the time during gestation when the initial Hb was measured. Measurements closer to term will reflect smaller decreases than earlier measurements. Oral iron supplementation protects against this decrement and, as was observed in the reviewed studies, typically increases hemoglobin levels over pregnancy.

There is a positive dose-response relationship between oral iron supplement dose and Hb level change. This effect is slightly more pronounced in women who are initially anemic. Several studies noted that larger Hb responses occurred in anemic women (41,42,50,53). The dose-response relationship was reflected in the duration of therapy and in the interaction between dose and duration of therapy.

Acceptability of oral supplements may be influenced by both biological and cultural factors. Higher doses of oral iron are associated with higher rates of side effects including constipation, diarrhea, vomiting or epigastric pain. The dosage schedule may pose a problem as well. In trials of slow-release iron preparations, women preferred once-a-day dosing over other dosage schedules and adherence was thought to be better (54). Cultural aversions to supplementation may be more difficult to understand and modify (6,55). Involvement of the local population and education about the purpose and benefit of the tablets should accompany any supplementation program.

The effects of other supplements or treatments given in conjunction with iron therapy varied in the reviewed studies. In some areas of the world such as India, Western Africa, and Burma, folate deficiency is common due to low dietary folate intake (40,56,57,58,59). Approximately 30% of all the iron supplementation trials in developing countries included treatment groups to compare iron given alone and iron given with folate, and the overwhelming results were that the additional of folate to iron supplements had small additional effect on Hb levels.

Combining iron with ascorbic acid had similar effects on increasing Hb levels, demonstrating an incremental effect above and beyond the effect of iron alone up to about 0.1 g/dl or 0.2 g/dl.

Vitamin B12 deficiency is rare in most countries and thus in most pregnant women. Addition of vitamin B12 to a treatment regimen had no effect on Hb levels in pregnancy (44,60,61) except in one trial where the addition of both folate and vitamin B12 to the regular iron therapy resulted in higher final Hb levels than those receiving iron alone (42).

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A few trials were conducted in areas with endemic or superendemic malaria infection (6,43,44,56,62,63,64,65). Results from these studies were equivocal, resulting in inconsistent effects (some negative, some positive, with no real pattern).

In many developing countries, hookworm is endemic. Pregnant women have rarely been found to have heavy hookworm infection (>1000 eggs/g feces). Light hookworm infection probably does not account for much of the anemia seen in developing countries (12). The effect of deworming in addition to iron supplementation has not been evaluated in pregnant women.

Supplemental iron alone had no consistent effect on infant birthweight, either in developing or developed studies. Several trials found that iron given with folate produced a statistically significant increase in birthweight (59,66,67,68), but other trials have not shown any difference (42,57,64,69,70,71). Several studies have demonstrated that folate supplementation increases gestation which may explain the association with birthweight (50,57,67). A review of controlled clinical trials in developed countries also found that iron and vitamin supplementation had no effect on birthweight, gestation length, infant morbidity and mortality, and maternal morbidity and mortality (72). Some of these inconsistencies may be a function of problems with research design and execution.

V. CONCLUSIONS/RECOMMENDATIONS

In many trials, the prevalence of anemia (Hb<11.0 g/dl) was estimated before and after the trial; in those groups receiving iron, the prevalence of anemia was generally lower after the iron intervention, but some authors expressed disappointment that the overall prevalence was still high. In particular, after a well-conducted trial by Sood et al. (1975) in India, the prevalence of anemia was decreased from 87-88% initially to 56% in the highest iron dose group (240 mg), and the authors considered this level still to be unacceptably high. It is difficult to treat a severely iron deficient woman and provide for increased fetal needs through oral iron supplementation alone during the relatively short period of pregnancy. Severely anemic women who are diagnosed late in pregnancy may require alternate therapeutic strategies such as intramuscular iron to correct anemia, but this is an not a reasonable approach for populations. **As a public health approach, prolonged supplementation beginning before the woman becomes pregnant may be a better strategy to benefit the majority of the population (although some individuals will always require more aggressive treatment).**

Combining iron supplementation and fortification could be a useful approach. Fortification programs would improve iron nutrition in all segments of the population, and eventually, should prevent the development of severe iron deficiency anemia. Then, supplementation during pregnancy would be much more effective in preventing iron deficiency or correcting a mild iron deficiency. Food fortification has been a relatively successful strategy of nutritional improvement in the United States. Still, fortification of foods requires identification of acceptable and commonly consumed foods produced at a limited number of sites, appropriate and locally available technology and equipment, long-term funding sources or affordable and acceptable mechanisms to pass the increased price to the consumer, and a long-term commitment by the government, producer, distributors, etc.

The acceptability of supplements has not been well researched, but should be taken into account in conjunction with supplementation programs. Some education and training of staff and patients, and involvement of local population may be beneficial.

Supply side problems also need to be addressed. The availability of supplementation at the national level and how to get supplements to those who need them are important concerns.

Although this review demonstrates that iron supplementation is efficacious, there is evidence that prevalence of global maternal anemia has not changed in the past thirty years, even in the presence of iron supplementation programs. The topics discussed in this section, of prolonged iron supplementation, of investment in fortification, in promotion and education of iron supplements, and in resolving logistical problems that hinder availability of iron supplements at the community level, need to be tested through both clinic- and community-based research to find effective answers to this worldwide problem.

RANDOMIZED CONTROLLED TRIALS

TABLE 2.A - REGION: **ASIA**

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE IRON (mg)	DOSE FOLATE (mg)	DOSE VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
Srisupandit (1983;38)	THAILAND	1	109	60	0					12	8	38	100%	11.0	11.3	0.3	*			
		2	117	180	0					12	8	38	100%	11.0	11.9	0.9	0.6	*		
		3	103	180	5					12	8	38	100%	11.4	11.9	0.5	0.2	-0.4		
Charoenlarp (1988;11)	THAILAND	1	39	0	0			1		15	4	37	100%	10.1	10.1	0	*			
		2	38	120	5					15	4	37	100%	10.2	11.6	1.4	1.4	*		
		4	40	240	0					15	4	37	100%	10.3	11.5	1.2	1.2	-0.2	*	
		3	41	240	5					15	4	37	100%	10.4	11.7	1.3	1.3	-0.1	0.1	
		5	42	120	5					15	4	37	100%	10.4	11.6	1.2	1.2	-0.2	*	
		6	53	240	5					15	4	37	100%	10.5	11.8	1.3	1.3	-0.1	0.1	
Charoenlarp (1988;11)	THAILAND	7	38	0	0			1		15	4	37	100%	9.9	9.8	-0.1	*			
		10	39	120	5					15	4	37	100%	10.1	11.1	1.0	1.1	*		
		9	40	240	0					15	4	37	100%	10.0	11.2	1.2	1.3	0.2	*	
		8	34	240	5					15	4	37	100%	9.9	11.1	1.2	1.3	0.2	0	
		11	35	240	5					15	4	37	100%	10.3	11.4	1.1	1.2	0.1	-0.1	
Charoenlarp (1988;11)	BURMA	1	40	60	5					12	4	38	100%	10.6	11.1	0.5	*			
		2	32	120	5					12	4	38	100%	10.6	11.3	0.7	0.2	*		
		3	34	120	5					12	4	38	100%	10.6	11.2	0.6	0.1	-0.1	*	

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TABLE 2.A - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE IRON (mg)	DOSE FOLATE (mg)	DOSE VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
		9	46	120	5					12	4	38		100%	10.2	10.9	0.5	0	-0.2	-0.1
		6	42	240	0					12	4	38		100%	10.6	11.2	0.6	0.1	-0.1	0
		4	36	240	5					12	4	38		100%	10.5	11.2	0.7	0.2	0	0.1
		5	35	240	5					12	4	38		100%	10.6	11.1	0.5	*	-0.2	-0.1
		10	41	240	5					12	4	38		100%	10.3	10.5	0.5	0	-0.2	-0.1
Charoenlarp (1988;11)	BURMA	7	29	120	5					12	4	38		100%	10.4	11.0	0.6	*		
		8	20	240	5					12	4	38		100%	10.3	10.8	0.5	-0.1		
		11	13	120	5					12	4	38		100%	10.0	10.5	0.5	-0.1	*	
		12	11	240	5					12	4	38		100%	10.6	10.9	0.3	-0.3	-0.2	

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TABLE 2.A - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE IRON (mg)	DOSE FOLATE (mg)	DOSE VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
Thane-Toe (1982;39)	BURMA	A	16	60	5					12	6	40	100%	10.9	11.2	0.3	*			
		B	32	120	5					12	6	40	100%	10.9	11.3	0.4	0.1	*		
		D	18	240	0					12	6	40	100%	10.7	11.3	0.6	0.3	0.2	*	
		C	33	240	5					12	6	40	100%	10.5	11.1	0.6	0.3	0.2	0	
Batu (1976;40)	BURMA	C	22	0	0			1		16	3	39	100%	10.4	9.7	-0.7	*			
		D	19	0	5					16	3	39	100%	10.3	9.6	-0.7	0	*		
		A	30	120	0			1		16	3	39	100%	10.9	11.3	0.4	1.1	1.1	*	
		B	25	120	5					16	3	39	100%	10.8	11.5	0.7	1.4	1.4	0.3	
Kuizon (1979;41)	PHILIPPINES	1	55	0	0			1		13	26	39	49%	12.0	11.3	-0.7	*			
		3	43	0	0	100				13	26	39	100%	11.8	11.5	-0.3	0.4	*		
		2	49	65	0					13	26	39	53%	12.0	12.3	0.3	1.0	0.6	*	
		4	32	65	0	100				13	26	39	53%	11.7	12.1	0.4	1.1	0.7	0.1	

TABLE 2.A - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE IRON (mg)	DOSE FOLATE (mg)	DOSE VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION BASELINE	GESTATION FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
Kuizon (1979;41)	PHILIPPINES	1	28	0	0			1		13	26	39	29%	10.4	10.0	-0.4	*		
		3	34	0	0	100				13	26	39	50%	10.5	11.5	1.0	1.4	*	
		2	45	195	0					13	26	39	51%	10.2	12.3	2.1	2.5	1.1	*
		4	36	195	0	100				13	26	39	31%	9.9	12.1	2.2	2.6	1.2	0.1

RANDOMIZED CONTROLLED TRIALS

TABLE 2.B - REGION: **ASIA**

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE IRON (mg)	DOSE FOLATE (mg)	DOSE VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
Sood (1979;42)	INDIA	0	70	0	0			1		10	4	37		100%	9.6	9.3	-0.3	*		
		1	91	0	5		B12			10	4	37		100%	9.6	9.4	-0.2	0.1	*	
		2	89	30	5		B12			10	4	37		100%	9.4	10.2	0.8	1.1	1.0	
		3	91	60	5		B12			10	4	37		100%	9.4	9.4	0	0.3	0.2	
		6	107	120	0			1		10	4	37		100%	9.7	10.4	0.7	1.0	0.9	
		4	115	120	5		B12			10	4	37		100%	9.6	10.8	1.2	1.5	1.4	*
		5	84	240	5		B12			10	4	37		100%	9.4	10.8	1.4	1.7	1.6	0.2

RANDOMIZED CONTROLLED TRIALS

TABLE 2.C - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE: IRON (mg)	DOSE: FOLATE (mg)	DOSE: VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION BASELINE	GESTATION FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
Jackson (1982;43)	LIBERIA	1	30	60	0					12	4	38	100%	10.5	11.1	0.6	*		
		2	30	180	0					12	4	38	100%	10.1	11.4	1.3	0.7	*	
		3	37	180	5					12	4	38	100%	9.7	11.0	1.3	0.7	0	*
		4	35	180	5				1	12	4	38	100%	9.6	11.2	1.6	1.0	0.3	0.3
Fleming (1986;6)	NIGERIA	1	40	0	0			1		16	24	40	28%	11.2	12.6	1.4	*		
		2	40	0	0				1	16	24	40	48%	11.2	11.7	0.5	-0.9	*	
		4	40	0	1				1	16	24	40	53%	11.4	12.1	0.7	-0.7	0.2	*
		3	40	60	0				1	16	24	40	33%	11.0	12.2	1.2	-0.2	0.7	0.5
		5	40	60	1				1	16	24	40	40%	11.5	11.7	0.2	-1.2	-0.3	-0.5
Powers (1985;44)	GAMBIA	A	4	0	0			1	1	06	22	42	UNK	10.5	11.2	0.7	*		
		B	3	0	0		B1[6]		1	06	22	42	UNK	11.3	10.3	-1.0	-1.7	*	
		C	6	30	0				1	06	22	42	UNK	10.3	11.0	0.7	0	1.7	*
		D	5	30	0		B1[6]		1	06	22	42	100%	9.9	8.9	-1.0	-1.7	0	-1.7
Dommisse (1983;45)	SAFRICA	2	UNK	0	0		MV[7]			16	20	36	n=48	12.1	11.6	-0.5	*		
		1	UNK	120	0		MV[7]			16	20	36	n=57	11.9	12.3	0.4	0.9		

RANDOMIZED CONTROLLED TRIALS

TABLE 2.D - REGION: ASIA

REFERENCE	COUNTRY			DOSE												

		GROUP[1]	N[2]	IRON (mg)	FOLATE (mg)	VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE	GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]		
Fleming (1974;46)	AUSTRALIA	G1	17	0	0			1		20	16		36		100%	12.0	11.6	-0.4	*		
		G3	15	0	5					20	16		36		100%	12.0	11.8	-0.2	0.2	*	
		G2	21	60	0					20	16		36		100%	12.0	12.2	0.2	0.6	0.4	*
		G4	20	60	5					20	16		36		100%	12.0	12.3	0.3	0.7	0.5	0.1

RANDOMIZED CONTROLLED TRIALS

TABLE 2.E - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE: IRON (mg)	DOSE: FOLATE (mg)	DOSE: VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]
Freire (1989;47)	ECUADOR	2	117	0	0			1		8	4	36		100%	13.3	13.0	-0.3	*
		1	122	78	0					8	4	36		100%	13.2	13.8	0.6	0.9
Dawson (1987;48)	USA	C	13	0	0		MV[7]			22	16	38		100%	12.4	11.5	-0.9	*
		T	16	65	0		MV[7]			22	16	38		100%	12.7	12.4	-0.3	0.6
Cantlie (1971;49)	CANADA	C	12	0	0		MV[7]			16	20	36		UNK	12.4	10.5	-1.9	*
		T	15	78	0		MV[7]			16	20	36		UNK	12.2	11.8	-0.4	1.5

RANDOMIZED CONTROLLED TRIALS

TABLE 2.F - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE: IRON (mg)	DOSE: FOLATE (mg)	DOSE: VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION	BASELINE GESTATION	FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]	
Zittoun (1983;50)	FRANCE	C	82	0	0			1		12	4	40		59%	11.9	12.8	0.9	*	
		T1	48	105	0	500				12	4	40		65%	10.4	12.8	2.4	1.5	
		T2	72	105	0	500				12	4	40		58%	11.7	13.5	1.8	0.9	
Puolakka (1980;33)	FINLAND	C	16	0	0					20	16	36		94%	12.1	11.0	-1.1	*	
		T	16	200	0					20	16	36		100%	11.9	12.7	0.8	1.9	
Romslo (1983;51)	NORWAY	C	23	0	0			1		27	2	39		100%	12.4	11.3	-1.1	*	
		T	22	200	0					27	2	39		100%	12.8	12.6	-0.2	0.9	
Svanberg (1975;29)	SWEDEN	C	30	0	0			1		21	3	35		80%	12.5	11.4	-1.1	*	
		T	30	100	0					21	3	35		87%	12.5	12.4	-0.1	1.0	

TABLE 2.F - REGION: ASIA

REFERENCE	COUNTRY	GROUP[1]	N[2]	DOSE: IRON (mg)	DOSE: FOLATE (mg)	DOSE: VITAMIN C (IU)	OTHER TREATMENT	PLACEBO	MALARIA	DURATION	GESTATION BASELINE	GESTATION FOLLOW UP	% FOLLOW UP	INITIAL Hb[3] (g/dl)	FOLLOW UP Hb[3] (g/dl)	ABSOLUTE CHANGE	(ABSOLUTE Δ TREATMENT)[4] - (ABSOLUTE Δ CONTROL)[5]	
Chanarin (1977;30)	UK	C	13	0	0			1		24	4	36	100%	12.4	11.8	-0.6	*	
		T1	35	100	0					24	4	36	100%	12.6	12.8	0.2	0.8	*
		T2	16	100	3.5					24	4	36	100%	12.4	12.4	0.0	0.6	-0.2
Paintin (1966;27)	UK	C	60	0	0			1		16	20	36	90%	11.7	10.7	-1.0	*	
		T2	60	12	0					16	20	36	92%	11.5	10.8	-0.7	0.3	*
		T1	60	115	0					16	20	36	92%	10.8	12.0	1.2	2.2	1.9

* denotes Control Group

1. Group numbers assigned by the study principal investigator.
2. N = Study group sample size.
3. Hb = Hemoglobin
4. Absolute Δ Treatment = (Follow-up Hemoglobin - Initial Hemoglobin)
5. Absolute Δ Control = (Follow-up Hemoglobin Control - Initial Hemoglobin Control)
6. B1 = Thiamin
7. MV = Multivitamin

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APPENDIX 1

DISCUSSION OF META ANALYSIS AND STANDARD EPIDEMIOLOGIC LITERATURE REVIEW

APPENDIX 1: DISCUSSION OF META ANALYSIS AND STANDARD EPIDEMIOLOGIC LITERATURE REVIEW

Although meta analysis can be a powerful technique, it is frequently utilized inappropriately, relying on statistical adjustment to compensate for often unreported or unquantifiable methodologic and biologic differences. For example, Mahomed and Hytten (24) found women receiving iron supplementation were, on average, 8 times less likely to be anemic at 36-40 weeks gestation than those not receiving supplementation based on results from their meta analysis of seven studies. Only two of the seven studies, however, had results of similar magnitude (odds ratios of 7.7 and 9.1), three had much greater effects (odds ratios of 12.5, 14.3 and 16.7) and two much lower effects (odds ratios of 1.0 and 1.9). The validity of the reported "typical" effect is questionable due to the variability of the studies and therefore, of the effects observed in these studies.

Others have conducted meta analyses using all data available data, ignoring that unavailable and/or unreported data is not equivalent to absence of a condition or therapy. The effects of this are serious. For example, the authors conducted a meta analysis on the data presented in this report and found contradictory conclusions regarding the effects of malarial prophylaxis because populations not living in malaria endemic areas were inappropriately included in the comparison group information, when indeed populations living in malaria endemic areas are <u>not</u> comparable to those living in non-endemic areas.

While the concept of obtaining one number to represent a "typical" effect is attractive, these "weighted averages" are in fact not representative of typical response, partially because a typical response across population groups living under dissimilar sociologic, economic and environmental conditions may not exist. Cautionary statements are inadequate to justify using summary regression coefficients or odds ratios from meta analyses given the lack of comparability of the available data. Statistical techniques cannot make truly different populations similar, regardless of the adjustment procedure. Although a multitude of studies were reviewed for this article, few of them represent population groups or therapeutic regimens that are fairly comparable, and thus amenable to statistical analysis. If the reviewed studies were stratified into comparable groups, most of the summary statistics that could be presented would be drawn upon the results of 1 to 4 studies, and therefore not be generalizable. Taking these concerns into account, epidemiology and other sciences of research methodology have developed criteria by which to assess whether causal associations between interventions and outcome exist, including reviewing the consistency of results (direction and magnitude), whether a dose-response is observed and the patterns that emerge under different conditions (socio-environmental or therapeutic), the biologic plausibility or rationale for observed results, the temporality of cause and effect. These criteria form the basis of this report's presentation.

APPENDIX 2

ABSTRACTS OF SUPPLEMENTATION STUDIES

APPENDIX 2: ABSTRACTS OF SUPPLEMENTATION STUDIES

The following paragraphs summarize by geographic region the studies included in this report's main analysis of the effects of iron supplementation on maternal hematologic status in pregnancy. All studies described in this section are randomized or stratified controlled trials of iron supplementation. Some studies have more than one experimental group with identical treatments[10]; results for these studies are reported in the manner they are presented in the original articles. Thus, if effects for groups receiving identical treatments were reported separately they continue to be reported separately here. Similarly, the prevalence of anemia is not reported for articles that did not present this information. All doses of iron supplementation are reported as their equivalent daily doses of elemental iron.

Asia

Srisupandit et al. (38) compared 12 weeks of 180 mg iron supplementation with and without folate to 60 mg iron supplementation in Thai women attending the antenatal clinic at Siriraj Hospital, Bangkok, Thailand. The 180 mg dose plus folate group (group 3) had an initial mean hemoglobin level of 11.4 g/dl; both other groups (group 1 provided 60 mg iron and group 2 provided 180 mg iron, neither receiving folate) had initial hemoglobin levels of 11.0 g/dl. Women receiving the 180 mg iron without folate had a 0.6 g/dl greater increase in hemoglobin levels than did those receiving the 60 mg dose. Contrary to expectation, however, women receiving the 180 dose of iron with folate had only a 0.2 g/dl greater increase in hemoglobin than those receiving the 60 mg dose, or a 0.4 g/dl smaller increase with than without folate supplementation. This may, however, be partially attributable to the 0.4 g/dl higher initial mean hemoglobin level in the high dose folate supplemented group.

Charoenlarp et al. (11) conducted two studies in northeast Thailand to assess the effects of iron with and without folate supplementation in women with Hb AA (study 1) and AE (study 2), respectively. The prevalence of maternal anemia was estimated at 68% and 34% of women tested had hookworm infestations.

In the first study (11), women with Hb AA were randomly assigned by village to one of six study groups, placebo (P1), 120 mg iron and folic acid (P2), 240 mg iron and folic acid (P3), 240 mg iron without folic acid (P4), 120 mg iron and folic acid (P5), and 240 mg iron and folic acid (P6; see Table 2.a). Baseline mean hemoglobin levels, measured at 4 weeks gestation, ranged between 10.2 g/dl and 10.4 g/dl in the low dose group, and between 10.3 and 10.5 in the high dose group; mean hemoglobin in the control group was 10.1 g/dl. At baseline, the prevalence of anemia (Hb <11 g/dl) was 68% in the placebo group (P1), 65% in those receiving 120 mg iron and folic acid (P2) and in those receiving 240 mg iron without folic acid (P4), 73% in those receiving 240 mg iron and folic acid (P3), 70% in those receiving 120 mg iron and folic acid (P5), and 63% in those receiving 240 mg iron and folic acid (P6). The duration of supplementation averaged 15 weeks. The effect of iron supplementation ranged between 1.2-1.4 g/dl at 37 weeks gestation; this may slightly underestimate the effects of iron supplementation, as absorption in the control group would be expected to be greater than that of the experimental groups due to baseline differences. There was little difference in effect associated with dose (120 vs. 240 mg elemental iron daily), and folate had a consistent

[10] There was little or no explanation for the separation of study groups receiving identical treatments, or conversely for the provision of identical treatments to separate study groups.

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although minimal effect (0.1-0.2 g/dl) on increasing hemoglobin concentrations above and beyond the effects of iron supplementation alone. The prevalence of anemia declined in all groups receiving iron to between 20% and 28%, in contrast to the control group where the prevalence of anemia increased to 74%.

In the second study (11) Thai women with Hb AA were randomly assigned by village to one of five study groups, placebo (P7), 240 mg iron and folic acid (P8), 240 mg iron without folic acid (P9), 120 mg iron and folic acid (P10), 240 mg iron and folic acid (P11; see Table 2.a). Average baseline hemoglobin levels ranged between 9.9-10.1 g/dl at 4 weeks gestation. The prevalence of anemia (Hb <11 g/dl) was 86% in the placebo group (P7), 82% in those receiving 240 mg iron and folic acid (P8) 78% in those receiving 240 mg iron without folic acid (P9), 69% in those receiving 120 mg iron and folic acid (P10) and in those receiving 240 mg iron and folic acid (P11). Iron supplementation with and without folate was provided to the experimental study groups for a period of about 15 weeks. Iron supplementation increased hemoglobin levels 1.1-1.3 g/dl compared to controls at 37 weeks gestation. An increase of 0.2 g/dl was observed in 240 mg compared to 120 mg doses. No differential effect was observed with folate supplementation. The prevalence of anemia declined in all experimental groups to between 26% and 38%, in contrast to the control group where the prevalence of anemia increased to 87%.

Charoenlarp et al. (11) also conducted two studies in urban communities of Rangoon, Burma comparing varying doses of iron with folate in supervised and unsupervised groups. Results for women with Hb (AA) and Hb (AE) are presented separately here, as study 1 and study 2, respectively.

The comparison group (P1) in the first study (11) was provided with 60 mg iron and folic acid, with 120 mg iron and folic acid provided in a single dose to groups 3 and 9, 120 mg iron and folate divided and provided in two doses to group 2, 240 mg iron divided into two doses without folate to group 6, 240 mg iron and folate in a single dose to group 5, and 240 mg iron and folate divided into two doses to groups 4 and 10. The pre-intervention hemoglobin level was 10.6 g/dl for the 60 mg dose comparison group, ranged between 10.2 g/dl and 10.6 g/dl for the 120 mg dose groups and between 10.3 g/dl and 10.6 g/dl for the 240 mg dose groups at 4 weeks gestation. After 12 weeks of supplementation initiated at 26 weeks gestation, little difference (ranging from 0-0.2 g/dl) was found between the comparison, 120 mg, and 240 mg groups. (One of the study groups was not given folate supplementation, but no difference was seen regardless.)

In the second study (11) the comparison groups (P7 and P11) were provided with 120 mg iron (as single doses), with 240 mg iron divided in two doses given to groups 8 and 12. All groups were provided daily folate supplementation. Pre-intervention hemoglobin levels were 10.0 g/dl and 10.4 g/dl for the 120 mg groups and 10.3 g/dl and 10.6 g/dl for the 240 mg dose study groups at 4 weeks gestation. Contrary to expectation, slight reductions (0.1-0.2 g/dl) in hemoglobin at 38 weeks gestation were seen with 12 weeks of higher iron supplementation. It is possible that the unexpected observed results are a function of differences in initial hematologic status for which larger benefits of iron supplementation would be expected for the low dose groups. Taking initial status into account would possibly result in observing no dose effect.

Thane-Toe (the principal investigator of the Charoenlarp studies conducted in Burma) et al. (39) studied the effects of 12 weeks of 120 mg and 240 mg doses of iron supplementation, mostly accompanied by folate, compared to 60 mg doses of daily iron in Burmese women. Approximately 55% of the pregnant women participating in the study were identified as anemic

by low serum ferritin levels (<10 μg/L). Mean baseline hemoglobin levels ranged from 10.5-10.7 g/dl in the 240 mg groups (group C with folate and group D without folate, respectively), and were 10.9 g/dl in both the 120 mg and 60 mg groups (groups B and A, respectively, both receiving folate). Treatment effect was dose related, with 0.1 g/dl greater increase in the 120 mg group and 0.3 g/dl greater increase in the 240 mg group dose groups compared to the comparison 60 mg dose group. Folate had no added effect.

Aung-than-Batu et al. (40) studied the effects of 16 weeks of 120 mg iron supplementation with and without folate in Burmese women. The prevalence of anemia (Hb <11 g/dl) in the entire sample was 72% at baseline. Initial hemoglobin levels were 10.4 g/dl in the untreated control group (group C), 10.3 g/dl in the folate treated control group (group D), 10.9 g/dl in the experimental group not receiving folate (group A), and 10.8 g/dl in the experimental group receiving both iron and folate (group B). The groups receiving iron supplementation had greater increases in hemoglobin levels of 1.0 g/dl (without folate) and 1.1 g/dl (with folate) compared to the control groups. Folate had no effect in the non-iron supplemented group compared to the untreated control, but accounted for a 0.3 g/dl increase in hemoglobin above that observed in the non-folate iron supplemented group.

Kuizon et al. (41) examined the effects of 13 weeks of 65 mg dose iron supplementation with and without vitamin C supplementation in non-anemic Filipino women. Baseline hemoglobin levels were 11.3 g/dl in the untreated group (group 1), 11.5 g/dl in the vitamin C supplemented comparison group (group 3), 12.3 g/dl in the iron supplemented group (group 2) and 12.1 g/dl in the group receiving iron and vitamin C supplements (group 4). The iron supplemented groups had increased hemoglobin levels of 1.0 g/dl (no vitamin C) and 1.1 g/dl (with vitamin C) greater than the untreated control group and 0.6-0.7 g/dl greater increases than the control group supplemented with vitamin C alone. The relative increases may be slightly underestimated as the control groups had lower initial hemoglobin levels. Vitamin C alone improved maternal hematologic status 0.4 g/dl above that of the control group, but had little additional effect (0.1 g/dl) on increasing hemoglobin levels in iron supplemented women. All groups experienced an increased prevalence of anemia, with 21% of women in the control group, 35% of women in the vitamin C only group (group 3), 23% of women in the iron without vitamin C group (group 2) and 12% of the women in the iron with vitamin C group (group 4) having Hb values decline below 11 g/dl at 39 weeks gestation, respectively. Both groups receiving vitamin C had slightly lower initial hemoglobin levels and may explain why the prevalence of anemia was ultimately greater in these groups than those not receiving vitamin C.

Kuizon et al. (41) also studied the effects of 13 weeks of 195 mg compared to no supplemental iron with and without supplemental vitamin C in anemic Filipino women. Women were randomly assigned to four groups, placebo (group 1), vitamin C only (group 3), 195 mg iron (group 2) and 195 mg iron plus vitamin C (group 4). Baseline hemoglobin levels were low (because the study consisted of anemic women only and because Hb was first measured at 26 weeks gestation), 9.9 g/dl in the 195 mg iron plus vitamin C group, 10.2 g/dl in the 195 mg iron without vitamin C group, 10.5 g/dl in the vitamin C supplemented control group, and 10.4 g/dl in the untreated control group. The iron supplemented group had increased hemoglobin levels 2.5 g/dl (no vitamin C) and 2.6 g/dl greater than the untreated control group and 1.1-1.2 g/dl greater increases than the control group supplemented with vitamin C. The relative increases may be slightly overestimated as the control groups had higher initial hemoglobin levels. Vitamin C alone improved maternal hematologic status 1.4 g/dl above that of the control group, but had little additional effect (0.1 g/dl) on increasing hemoglobin levels in iron supplemented women (and perhaps no effect given the higher initial Hb levels of those receiving iron without vitamin C (group 2) than those receiving iron and vitamin C (group 4).

All women in the control group remained anemic at final Hb measurement (39 weeks gestation), while the prevalence of anemia in groups receiving vitamin C (group 3), iron without vitamin C (group 2) and iron with vitamin C (group 4) was reduced to 71%, 13%, and 36%, respectively.

Middle South Asia

Sood et al. (42) studied the effects of a variety of doses of iron supplementation with and without supplemental folate and vitamin B12 in Indian women for a period of 10 weeks. The study has two control groups, a placebo group (group 0) and a group provided folate and B12 supplements (group 1). One experimental group (group 2) was provided 30 mg iron, folate and vitamin B12, another (group 3) 60 mg iron, folate and B12, two groups were provided 120 mg iron, one with a placebo (group 6) and the other with folate and B12 (group 4), and a final group received 240 mg iron, with folate and B12 supplements (group 5; see Table 2.b). Thirty percent of the sample was lost to follow-up. Women followed through 37 weeks gestation had very low mean baseline hemoglobin levels of 9.4-9.7 g/dl at 4 weeks gestation. Depending on therapeutic regimens, iron supplementation produced hemoglobin levels between 0.2 and 1.7 g/dl greater than the control groups levels at 37 weeks gestation. Larger increases were generally found with higher doses of iron; folate and vitamin B12 supplementation had no differential effect on outcome.

Africa

Jackson et al. (43) studied the effects of 180 mg compared to 60 mg doses of iron supplementation with and without supplemental folate and malaria prophylaxis in Liberian women with very low initial hemoglobin levels for a period of 12 weeks. Women were assigned to study groups in an effort to obtain similar initial hematologic status. The comparison group (group 1) received 60 mg iron, group 2 received 180 mg iron, group 3 received 180 mg iron and folate supplementation, and group 4 received 180 mg iron, folate and antimalarial prophylaxis. Initial hemoglobin levels at 4 weeks gestation were 10.5 g/dl (group 1), 10.1 g/dl (group 2), 9.7 g/dl (group 3) and 9.6 (group 4). Iron supplementation produced hemoglobin levels between 0.7-1.0 g/dl higher than control groups at 38 weeks gestation, however this probably overestimates the true effect of higher dose therapy as the control group would have relatively lower absorption due to better initial status. No differential effects of folate were observed, however the anti-malarial regimen produced hemoglobin levels 0.3 g/dl higher than those produced by iron supplementation alone. Seventy-eight percent of women were anemic (Hb <11 g/dl) at the beginning of the study; this remained unchanged at 38 weeks gestation although the prevalence of anemia declined in those initially identified as anemic (and conversely increased in those not initially anemic). Inference from this study is limited due to its small sample size.

Fleming et al. (6) studied the effects of 60 mg iron supplementation with (group 5) and without folate (group 3) and malaria prophylaxis in Nigerian women. The study has three comparison groups, a placebo group (group 1), a group receiving antimalarials only (group 2) and a group receiving folate and antimalarials (group 4). Initial hemoglobin levels varied between 11.2 g/dl in the control groups (untreated and given malaria prophylaxis, groups 1 and 2) and 11.4 in those given malaria prophylaxis and folate (group 4), and 11.0 g/dl and 11.5 g/dl in the iron supplemented groups (supplemented with and without folate, groups 5 and 3, respectively). The sample is representative of women with reasonable mean hemoglobin levels obtained around 24 weeks gestation, when hemoglobin levels have already declined in pregnancy. Still, 46% of women were identified as anemic, 26% had sickle cell trait, and 27% were positive for

malaria (predominantly P. falciparum). Results from this study are contrary to expectation, indicating inverse associations between iron supplementation and third trimester change in hemoglobin status and malaria prophylaxis and change in hematologic status. All treatment groups did less well than the untreated control group, with 0.2 g/dl to 1.2 g/dl lower changes in hemoglobin levels. Effects of folate supplementation are contradictory; those receiving folate and iron did less well than those not receiving folate or iron but those receiving folate and antimalarials did slightly better than those receiving antimalarials alone. The results of this study are particularly difficult to interpret as loss to follow-up was large (much due to requisite iron and or malaria therapy), therefore the initial hematologic status and thus change in hematologic status of the groups actually followed is unknown. For example, the apparent large improvement in hematologic status of the control group may be an artifact due to the exclusion of more women with poorer hematologic status. Although loss to follow-up was substantial in all groups, the groups with over 40% follow-up had substantially smaller hematologic differences between initial and final hemoglobin measurement than those with lower follow-up.

Powers et al. (44) studied the effects of 6 weeks of 30 mg dose iron supplementation with (group D) and without (group C) supplemental thiamin compared to women receiving a placebo (group A) or thiamin supplementation (group B) on a very small sample (group size ranged between 3 and 6 women) of Gambian women. All women received anti-malarial prophylaxis. All women with Hb <9 g/dl were assigned to group C or D. Nine subjects had sickle cell trait. Hookworm is endemic in the area. Regardless of iron supplementation, women receiving thiamin supplementation had a decrease in hemoglobin levels of 1.7 g/dl compared to those not receiving thiamin. This observation is not associated with initial hemoglobin status (measured at 22 weeks gestation); groups receiving thiamin had both the highest (group B 11.3 g/dl) and lowest (group D 9.9 g/dl) initial Hb values. Unsupplemented controls (group A) had an initial value of 10.5 g/dl, slightly higher than women receiving iron but no thiamin (group C 10.3 g/dl). Women receiving iron supplements without thiamin had a 1.7 g/dl greater increase in hemoglobin levels compared to non-supplemented controls.

Dommisse et al. (45) examined the effects of 16 weeks of 120 mg iron supplementation on South African women. Both groups were provided daily multivitamins and had reasonable initial hemoglobin levels (12.1 g/dl control group, group 2, and 11.9 g/dl treatment group, group 1) at 20 weeks gestation. As expected, the control group experienced a decline in hemoglobin levels (0.5 g/dl), however hemoglobin levels increased (0.4 g/dl) in the supplemented group, an equivalent of 0.9 g/dl greater change in hemoglobin levels compared to the control group. This may slightly overestimate the effects of iron supplementation as the treatment group had lower initial hemoglobin levels than the control group.

Oceania

Fleming et al. (46) conducted a double blind study of the effects of 20 weeks supplementation of 60 mg iron with (G4) and without (G2) folate supplementation in well nourished Australian women compared to placebo (G1) and folate only (G3) comparison groups. Group sample size ranged between 15 and 21. Women with baseline Hb <10 g/dl were excluded from study. All groups had initial hemoglobin levels of 12.0 g/dl at 16 weeks gestation. Both comparison groups (with and without folate supplementation) demonstrated reductions in hemoglobin levels over gestation, however the folate supplemented group had half the reduction of the unsupplemented control group (0.2 g/dl vs. 0.4 g/dl decrement, respectively). Those receiving iron supplementation with and without folate (G4 and G2) showed some improvement in hemoglobin levels over pregnancy (0.3 g/dl and 0.2 g/dl, respectively) demonstrating 0.7 g/dl

and 0.6 g/dl greater differences in hematologic change compared to the unsupplemented control group. The iron and folate supplemented group had a 0.1 g/dl greater difference in hemoglobin change compared to the iron only supplemented group.

Americas

Freire et al. (47) examined 8 weeks of 78 mg iron supplementation on reasonable large groups (n=117 control, group 2, n=122 experimental, group 1) of hispanic (non-black) Ecuadorian women. Initial hemoglobin levels were relatively high, 13.3 g/dl in controls and 13.2 g/dl in supplemented women at 4 weeks gestation, however this represents an estimated 1.6 g/dl higher level due to the effects of altitude (2,800 m above sea level) on hemoglobin levels. Loss to follow-up was 30%-35%, but baseline hemoglobin levels were reported only for those followed through pregnancy. While the control group showed some (0.3 g/dl) reduction in hemoglobin levels over gestation, the experimental group had a 0.6 g/dl increase in Hb levels. Although the study sample was relatively well nourished and duration of supplementation was relatively short and limited to the third trimester, a 0.9 g/dl better change was observed in the iron supplemented compared to
the control group.

Dawson et al. (48) observed the effects of 22 weeks of 65 mg iron supplementation in two small (control n=13, group C, and experimental n=16, group T) groups of non-anemic Texan women in the United States. The small sample size limits the generalizability of the study. Multivitamins were provided to both groups. Initial hemoglobin levels were 12.4 g/dl in the control and 12.7 g/dl in the experimental groups at 16 weeks gestation. Both groups experienced reductions in hemoglobin levels over gestation (0.9 g/dl reduction in controls and 0.3 g/dl reduction in supplemented women), representing a 0.6 g/dl better change in hemoglobin levels among women receiving iron supplementation. This may underestimate the effects of iron supplementation given the higher initial hemoglobin levels of the experimental group.

Cantlie et al. (49) examined the effects of 16 weeks of 78 mg dose iron supplementation on small numbers of non-anemic Canadian women. Hemoglobin values were 12.4 g/dl in the control (group C, n=12) and 12.2 g/dl in supplemented women (group T, n=15) at 20 weeks gestation. Both groups received daily multivitamin supplementation. The control group experienced a decline of 1.9 g/dl and the supplemented group experienced a decline of 0.4 g/dl in hemoglobin levels over gestation. The supplemented group had a 1.5 g/dl smaller decline in hemoglobin levels than did the control group. This cannot be explained by differences in initial hematologic status, which could account for only a minimal reduction in the observed effect. Due to the small sample size, however, the study results are not generalizable.

Europe

Zittoun et al. (50) compared the effects of 12 weeks of 105 mg supplemental iron and vitamin C on anemic (group T1) and non-anemic (group T2) French women compared to non-anemic women receiving a placebo (group C). Non-anemic women were randomly assigned to group T2 or group C; all women with Hb <11 g/dl were assigned to group T1. Anemic women had a 1.5 g/dl greater increase in hemoglobin levels associated with the combined iron/vitamin C supplementation than did controls receiving placebos. The observed effect is inflated due to the disparity in initial hemoglobin levels (11.9 g/dl control group, 10.4 g/dl anemic

supplemented group) and thus potential to response to therapy. Given ethical concerns, however, there was no unsupplemented anemic control group. The non-anemic group had a 0.9 g/dl greater increase in hemoglobin levels than the control group, which may be slightly overestimated given the lower initial hemoglobin levels (11.7 g/dl) of the non-anemic treatment group. Loss to follow-up was substantial, 41% in the control group, 42% in the non-anemic treatment group, and 35% in the anemic treatment group. This may indicate that the estimates of hematologic change are not valid. Interestingly, loss to follow-up was lowest in the anemic group, probably reflecting good response to therapy. Follow-up was lower in the non-anemic groups, possibly due to declining hematologic status and the need for (additional) therapy and consequent exclusion from the study groups[11].

Puolakka et al. (33) studied the effects of 20 weeks of 200 mg supplemental iron in a small group (n=16 in each group) of women in Finland. Supplemented (group T) and unsupplemented (group C) women had similar baseline hemoglobin levels (11.9 g/dl and 12.1 g/dl at 16 weeks gestation, respectively). Follow-up of both groups was high, 94% in controls and 100% in supplemented women. Regardless of any slight overestimation of effects due to the relatively small differences in initial hemoglobin status, iron supplementation in the second and third trimesters produced a very large increase, 1.9 g/dl, in hemoglobin levels compared to controls.

Romslo et al. (51) examined the effects of second and third (27 weeks) trimester iron supplementation (200 mg) in a small group (control group C, n=22, treatment group T, n=23) Norwegian women. Hemoglobin levels in the first month of pregnancy were 12.4 g/dl in the control and 12.8 g/dl in the treatment group. Both groups experienced declines in hemoglobin levels over pregnancy, but declines in the control group were substantial, 1.1 g/dl, compared to the treatment group with a 0.2 g/dl decline. This represents 0.9 g/dl less decline in the treatment group.

Svanberg et al. (29) compared 21 weeks of 100 mg iron supplementation (group T) with unsupplemented (group C) Swedish women. Initial hemoglobin levels were 12.5 g/dl in both groups in the first month of gestation. Sample size was small (30 in each group). Rates of follow-up were good, 80% in controls and 87% in the experimental group. Both groups experienced reductions in hemoglobin levels over gestation, with controls showing a 1.1 g/dl decrement and supplemented women a 0.1 g/dl decrement at follow-up (35 weeks gestation). A differential of 1.0 g/dl was associated with iron supplementation. The magnitude of this difference can not be attributed to differential follow-up. The control group had a larger loss to follow-up rate and thus might have been more likely to have exclusions of hematologic problems encountered in pregnancy; had such women been retained in the study the decline in hemoglobin levels in the control group would be expected to be larger than that observed.

Chanarin et al. (30) studied the effects of 24 weeks of 100 mg iron supplementation with (group T2) and without (group T1) folate supplementation on small groups of non-anemic British women. The control group (group C) contained 13 women, the iron only group had 35 women, and the iron and folate supplement group contained 16 women. All were well nourished; the control and the group receiving both iron and folate supplementation groups had initial hemoglobin levels of 12.4 g/dl; the group provided iron only had baseline hemoglobin levels of 12.6 g/dl. The experimental group provided iron only showed a 0.8 g/dl better change in Hb than the control group, however the iron and folate supplemented group had only a 0.6 g/dl better change in Hb compared to the control group.

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[11] This type of exclusion is common, although epidemiologically erroneous.

Paintin et al. (27) examined the effects of 16 weeks of 12 mg (group T2) and 115 mg iron supplementation (group T1) compared to controls (group C) in British women. Women with baseline Hb below 10 g/dl were excluded from study. Baseline hemoglobin levels, measured at 20 weeks gestation, were highest in the control group (11.7 g/dl), slightly lower in the low dose group (11.5 g/dl) and considerably lower in the supplemented group (10.8 g/dl). Both the control and low dose group experienced reductions in hemoglobin levels over gestation, although the low dose group showed a 0.3 g/dl smaller decrease in Hb. The group receiving intermediate level supplementation demonstrated substantial improvement in hemoglobin levels (1.2 g/dl) over gestation, for a 2.2 g/dl difference in hematologic change compared to controls. Follow-up was excellent, but due to the discrepancy in initial hematologic values, the effect of supplementation is overestimated.