

Iron supplementation

# Absorption of iron supplements administered daily or weekly: a collaborative study

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## 1. Background and theoretical basis

Nutritional anemias, the great majority of which are due to iron deficiency, are highly prevalent throughout the world but particularly in developing countries (DEMAEYER and ADIELS-TEGMAN, 1985; VITERI, 1993) (Table 1).

In both the developing and the industrial world, but significantly more in the former, women of reproductive age and children have a high

Table 1. Prevalence of iron deficiency or anemia

WHO Health Regions	Iron-deficient or anemic (millions)
Africa	206
America	94
South-East Asia	616
Europe	27
Eastern Mediterranean	149
Western Pacific*	1058
<b>TOTAL</b>	<b>2150</b>

\* Includes the People's Republic of China.

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prevalence of iron-deficiency anemia, pregnant women and younger children being at an even greater risk. In many tropical areas, even the adult male population is affected (VITERI, 1993; WHO, 1992).

The causes of iron-deficiency anemia are well known and explain the figures in Table 1 and relative proportions among age and sex groups (HERCBERG, GALAN and DUPIN, 1987). These include inadequate quantity and bioavailability of iron in the diet, increased iron needs during rapid growth and pregnancy, elevated iron losses, particularly among 15-20% of menstruating women, and impaired iron utilization because of infection and other nutrient deficiencies, especially those of vitamins A and B<sub>2</sub>.

It is also recognized that iron-deficiency anemia has severe functional, developmental and health consequences (SCRAMSHAW, 1989; VITERI, 1992), several of which appear to be long-lasting and, if they occur early in life, may persist through childhood and even become permanent (LOZOFF, JIMENEZ and WOLF, 1991; WALTER *et al.*, 1989). Thus, iron-deficiency anemia significantly hinders individual and societal development.

Because of all these very disturbing facts, health and political leaders all over the world have agreed that the control of iron-deficiency anemia is urgent. Different goals have been set, the least demanding being "to reduce the present prevalence of iron-deficiency anemia among pregnant women by 1/3 before the end of this century" (World Declaration, 1990; ICN, 1992). More demanding goals are to reduce the prevalence of iron-deficiency anemia in pregnant women and small children by 85-90% of present levels, or at least to less than 10% throughout all nations (VITERI, 1992; 1994).

Efforts to control - prevent and correct - iron-deficiency anemia should be based on a set of complementary strategies aimed at reducing its causes. However, most food-based and environmental health measures depend directly or indirectly on general socioeconomic development, and unfortunately, even where high-quality diet and iron fortification exist, a significant proportion of women of fertile age and most pregnant women fail to attain a desirable iron nutritional status (HALLBERG and ROSSANDER-HULTÉN, 1991; HALLBERG, 1992). They must therefore receive iron supplements. Iron supplementation and health programs are less dependent on socioeconomic development but, as presently conceived, rely heavily on health service availability and efficiency. These health-service-based programs demand community conscientization, availability of health care facilities, good logistic support, and trained personnel. Table 2 shows that health services are not readily available to a large proportion of the developing world.

These figures do not take into account actual service use or compliance with established programs. In Latin America, for example, the average compliance with established supplementation programs for pregnant women is estimated to be 40%. Taking average

1990  
1992  
2000

Table 2. Populations lacking health care

Continent	(millions)		(percent)	
	Total	Rural	Urban	Total
Africa	278	238	40	43
America	116	67	49	26
Asia	1040	864	176	35
TOTAL	1434	1169	265	35
				47
				18

From: WHO, in UNDP Human Development Report, 1991.

coverage/use of programs, and compliance figures in this region into account, efficiency is estimated at 19% at the most (VITERI, GALAN and HERCBERG, 1994).

In spite of this precarious situation, most developing countries have, for many years, based their iron-deficiency anemia control efforts on iron supplementation programs directed to the most affected group, i.e. pregnant women. Pilot studies have repeatedly demonstrated their effectiveness when large investments in supplies, personnel, supervision, and motivation were made (i.e. CHAROENLARP *et al.*, 1988; SOOB *et al.*, 1975). However, 'normally operating programs' are generally ineffective (WHO, 1990; ICMR, 1989), their impact being hampered by their small size, limited coverage in rural areas, and generally poor efficiency, even in urban centers (GILLESPIE, KEVANY and MASON, 1991). The inefficiency stems directly from both the supply side, with costs, poorly trained and little-motivated personnel, defective iron preparations, and irregular and inefficient delivery systems of supplements to the health outposts and from these to the public, as well as from the recipient side, with poor compliance due to little understanding of the programs, cultural factors, years of frustration, and frequent undesirable side-effects when iron tablets are taken at the frequency and for the duration recommended at the clinics (CHAROENLARP *et al.*, 1988).

Given the large proportion of populations with poor health-care coverage or none at all, community-based programs for the control of iron-deficiency anemia must be sought. Among them, for the reasons explained above, supplementation programs must be included. These should be: (1) effective and efficient, (2) safe, and (3) inexpensive and simple. We believe this is feasible both in the developing and the industrialized world, if the following concepts and experimental findings are taken into account:

1. Iron absorption is partially blocked by the previous intake of a large dose (HAHN *et al.*, 1943; BROWN, DUBACH and MOORE, 1958). This blockage lasts from several hours to over a day, depending on the species, and involves iron from food and supplements; however, the extent and duration of the blockage are not yet well characterized in humans. What is known is that blockage exists (HÖGLUND, 1969). For example, after oral administration of FeSO<sub>4</sub>·7H<sub>2</sub>O, to provide 100 mg of elemental iron twice daily to pregnant women, an average of 14% was absorbed in the first seven days, followed by absorptions of 7% and 2% in the two subsequent 14-day periods (HALLBERG *et al.*, 1966). A similar decline was observed in another study where 300 mg of iron were administered daily, except that absorption stabilized at 8% (NORRBY and SOLVELL, 1974). These declines in the proportion of iron being absorbed have been interpreted as indicating progressive iron depletion, but some degree of iron blockage may very well exist too. Iron absorption in the first few days may have fallen precipitously, from about 30% for the first dose, to about 15% for the third dose, and down to 8% for the 10th dose, as has been demonstrated in animal studies (VITERI, LIU and MORRIS, 1993). This absorption pattern would still result in an average absorption of 14% for the first 10 days. Even if this regimen of iron administration is effective, it is clearly inefficient, because more than 90% of the iron remains in the gut (lumen and wall) by the 10th day (MARTIN, TOLOMEI and VITERI, 1994).

Theoretically, if, by spacing, iron dosage blockage is avoided and the absorbed proportion is maintained at higher levels, smaller total iron intakes should be effective, and efficiency would increase. Experimental studies of supplemented iron-deficient rats in Berkeley, California, USA (VITERI, LIU and MORRIS, 1993) and in Norwich, UK (WRIGHT and SOUTHON, 1990) have shown that iron supplementation on an intermittent schedule (every three days, rather than daily) is almost as effective in replenishing deficient iron stores as is chosen at Berkeley because intestinal cells turn over about every three days in the rat. As predicted, the proportion of absorbed iron remained high on the intermittent schedule, so that by the 15th day of supplementation the total iron retained was 85% of that retained on a daily schedule. Thus, efficiency was 2.6 times greater on the intermittent schedule.

2. During supplementation on a daily schedule, iron concentrations become very elevated in the liver and particularly in the lumen and mucosa of the gut of experimental animals. This 'temporal but continuous overload' was avoided by intermittent dosage (MARTIN, TOLOMEI and VITERI, 1990), making supplementation safer because iron excess and overload have been recognized as undesirable

(GUTTERIDGE, 1990). There is also a high probability that gastrointestinal symptoms associated with current iron supplementation practices are a manifestation of temporary iron overload, particularly since they are dose-related (SOLVELL, 1970). These manifestations of 'intolerance to iron' contribute to the recognized rejection of, or poor compliance with, current supplementation programs (WHO, 1990).

It is possible that this temporary iron overload is not harmless. Clinically, when the natural immune systems are defective and iron-transporting capacity is reduced, as is the case in severely undernourished children, increased infection rates among those receiving 'therapeutic doses' of iron have been noted (OPPENHEIMER *et al.*, 1986a); similarly, a higher incidence of clinical malaria has been documented in small children living in hyperendemic regions and receiving parenteral iron (OPPENHEIMER *et al.*, 1986b). However, this higher incidence of clinical malaria has not occurred in older children or in populations receiving oral iron (HARVEY *et al.*, 1989). It thus seems that the malaria-infected infant receiving parenteral iron is at greater risk of getting clinical malaria.

In the industrial world, some epidemiological evidence suggests that the 'hemochromatotic gene' is more common than previously suspected (EDWARDS, GRIFFEN and KUSHNER, 1991) and that in populations with already high risk of chronic diseases, 'excess iron' can probably increase this risk further. This appears to be the case in heart disease, at least when high low-density lipoprotein cholesterol and high overall risk of atherosclerosis exist, and possibly cancer (SALONEN *et al.*, 1992; STEVENS *et al.*, 1988).

It must be emphasized, however, that in developing countries and among women of reproductive age and children throughout the world, the negative consequences of iron-deficiency anemia are much greater than the possible negative effects of iron excess, and that there is a broad range of iron nutrition normality within which function is optimal. A system for monitoring iron nutrition among women receiving iron supplements (as well as among men) should be considered in the industrial world (HERBERT, 1992).

3. Supplementation programs, as conceived now, are expensive to run. A new operational concept applicable to these programs and influencing their cost/efficiency ratio is explained below.

Iron supplementation programs can be classified into Therapeutically Oriented Supplementation (TOS) and Preventive Supplementation (PS). These should be considered on their own, and are complementary. Even though the line of demarcation between TOS and PS is not absolute, the conceptual difference is clear (MIRI, 1993).

## I. Therapeutically Oriented Supplementation (TOS)

(i) TOS is what most current supplementation programs for the control of iron deficiency provide, and is based on short-term, slightly modified therapeutic regimens. In fact, much of the motivation for TOS is therapeutic, in that it is either based on the high prevalence of anemia of specific risk groups (i.e. pregnancy) or is implemented after screening for anemia on an individual basis. It is an important tool within the primary prevention effort in that its basic aim is to prevent damage from iron-deficiency anemia.

(ii) It is greatly dependent on health personnel and therefore relatively expensive to implement.

(iii) Present TOS schedules are rigid; one or more daily iron doses must be ingested. They could probably be modified to make them more tolerable and less rigid, approaching PS.

(iv) Daily administration of high iron doses is biologically inefficient, particularly in individuals who are not severely iron-deficient.

(v) With present schemes, the rates of undesirable side-effects are dose-dependent and not negligible, contributing to the rejection of iron supplements.

(vi) TOS requires sustained motivation of suppliers and recipients in the face of significant logistical demands and often prejudices against iron supplementation further enhanced by a high rate of side-effects.

## II. Preventive Supplementation (PS)

(i) PS delegates most of the preventive micronutrient supplementation efforts to community organizations (no need to depend on overburdened or non-existent health personnel), and aims at improving iron status (including correcting moderate iron-deficiency anemia and increasing iron reserves) of vulnerable groups, thus reducing the risk of iron-deficiency anemia. PS should be used for multiple micronutrient interventions (i.e. iron, vitamin A and iodine).

(ii) The basic concept is that a longer-term periodic dose of iron can achieve this objective. For example, 8-10% absorption of a 60 mg weekly dose of iron is able to replace menstrual iron losses of the great majority of women. This level of absorption of such a dose has been achieved in non-anemic humans; it can be expected to be higher (up to 25% or more) in iron-deficient individuals. If such an iron supplementation scheme were established among women of childbearing age, anemia during pregnancy could be drastically

reduced, particularly if women, when realizing they are pregnant, would double the weekly dose they had been taking before pregnancy.

(iii) The risks of temporary iron overload are almost nil in comparison to daily iron administration.

(iv) Because of its simplicity, PS can be placed directly in the hands of minimally trained community groups (teachers, market directors, civil authorities, clergy, mothers' clubs, agricultural cooperatives, etc.)

(v) Because it does not depend on health personnel, costs are much lower and coverage can be significantly expanded.

(vi) A weekly dose is essentially free of undesirable side-effects, as has recently been shown in children (LUU, ZHAO and VITERI, 1994).

(vii) PS is markedly less expensive and clearly biologically more efficient than the present practice of daily iron administration.

(viii) By being less stringent (more flexible in terms of compliance), PS is more manageable.

(ix) The previous points suggest that PS should be of longer duration than TOS and amenable to modifications according to needs and objectives. Sustained motivation of suppliers and recipients would also be needed, but it would be less demanding.

PS should be part of primary prevention, together with food-based and overall health strategies, in that it should decrease the risk and prevent the development of deficiencies. The more effective PS is, the lower the need for TOS. As with all effective and sustainable programs, community information and participation in all phases of PS are essential. Surveillance should be part of any supplementation program.

## 2. Hypotheses

1. Absorption of supplemental iron administered on a daily schedule decreases rapidly, becoming inefficient in a few days. This is partly because of the effect of the partial blockage of absorption resulting from repeated doses.

2. Absorption of supplemental iron administered every seven days does not have the blockage effect of daily doses in the human mucosal renewal in humans is about six days (TRIER, 1968)) and remains high enough to meet needs, thus being more efficient.

3. The intermittent regimen, administered for a slightly longer term than the daily regimen, is almost as effective in correcting iron deficits as the daily regimen, and can increase iron reserves.

4. Undesirable secondary effects are significantly less frequent with the intermittent regimen than with the daily regimen.

## 3. Objectives

1. Compare longitudinally the absorption of supplemental iron (60 mg per dose) provided daily or weekly.

2. Measure the absorption of supplemental iron (120 mg per dose) provided weekly.

3. Measure the total amount of absorbed supplemental iron (60 mg per dose) in 36 days with the daily 60 mg dose and weekly 60 and 120 mg doses.

4. Measure iron reserves at different durations of supplementation.

5. Measure the incidence of undesirable effects of the different iron supplementation regimens.

## 4. Justification of the research

Before any changes in iron supplementation programs are accepted, proof must be provided that in humans iron absorption is significantly more efficient when iron supplements are administered intermittently than when they are administered daily.

## 5. Subjects and methods

### 5.1. Subjects

Adult volunteers, healthy except for possibly having iron deficiency and/or hookworm infection, are being recruited in Senegal. Their characteristics will be the following:

(a) Males 18 to 55 years of age, preferably at risk of being iron-deficient because of a history of iron-deficiency anemia, poor diets and/or chronic blood loss.

(b) Post-menopausal women, between the ages of 45 and 55 years, preferably at risk of being iron-deficient because of a history of iron-deficiency anemia, poor diet, chronic blood loss and multiparity.

(c) Women of reproductive age, between the ages of 18 and 45 years, preferably at risk of being iron-deficient because of a history of iron-deficiency anemia, poor diet, chronic blood loss or multiparity, and who are permanently infertile (tube ligation) or temporarily infertile but for an extended period (having an IUD implanted, having proof of continuous and reliable intake of anovulatory pills and



Table 4. Occasions when iron absorption is being measured in all groups

Days	Supplementation																			
	0	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37
	r	w	r	w	r	w	r	w	r	w	r	w	r	w	r	w	r	w	r	w
	r	d	d	d	r	d	r	d	r	d	r	d	r	d	r	d	r	d	r	d

r = <sup>59</sup>Fe reference dose; w = <sup>55</sup>Fe labelled weekly supplemental doses (60 and 120 mg Fe); d = <sup>55</sup>Fe labelled daily supplemental doses (60 mg Fe)

casation when blood is drawn for measuring the incorporation of radioactive iron into hemoglobin.

Reference dose (Fe-ascorbate) absorption is measured twice in each subject, by lagging the 15 mg FeSO<sub>4</sub>·7H<sub>2</sub>O (3 mg Fe) with 37.8 kBq (1.5μCi)<sup>59</sup>FeCl<sub>3</sub> at the following times: one day prior to the beginning of supplementation (day 0), and again two days before the last time supplemental iron absorption is measured in each group. The measurement of Fe-ascorbate on day 0 allows us to express iron absorption measurements in groups D1 and T1 as if initial iron absorptive capacity were constant at 40% absorption of reference dose, thereby eliminating initial differences in iron absorptive capacity among these groups. This level of reference dose absorption is observed among populations that are marginally iron-deficient (MAGNUSSON *et al.*, 1981).

Table 4 presents a scheme of the occasions when Fe absorption is measured in all groups.

## 6. Data analysis

(a) Descriptive statistics of the subjects and of their hematological, infection and iron nutritional status at the beginning of the absorption studies will be obtained.

(b) The subgroups will be compared by analysis of variance. The variables will be: personal characteristics (age, sex), infection status (recent history of acute infection), hematological characteristics (hemoglobin, hematocrit), initial Fe-ascorbate absorption level, and iron stores, estimated on the basis of Cook *et al.*'s algorithms (1986) and using ferritin and serum transferrin receptors (SKIKNE, FLOWERS and Cook, 1990). This will determine the homogeneity of the subgroups.

(c) Descriptive statistics of hematological, acute infection and iron nutritional status (iron stores), and Fe-absorption at the end of the supplementation periods will be provided. These same statistics (except for Fe-ascorbate absorption) will be calculated from the

data obtained two weeks after the end of supplemental intakes (post-supplementation).

(d) Changes in hematological and iron nutritional status between the beginning, the end of supplementation and post-supplementation samples, and differences between subgroups will be estimated. The technique to be used will be analysis of covariance with the following variables: hemoglobin concentration, iron stores, supplementation schedule, dose in supplement, and time of supplementation. This analysis will determine the impact on hematological status and iron stores of the three supplementation schedules by the end of supplementation period and their persistence, two weeks later without supplementation, corrected for initial differences in hematological status and iron stores.

(e) Descriptive statistics and comparisons among subgroups will be provided with regard to first and second reference dose absorption and their change.

(f) The effect of supplementation schedules and dose on total supplemental iron absorption in 36 days will be estimated. The last of these variables will be estimated as the area under the curve calculated by means of the sequential Fe absorption data will be available for doses 1, 3, 5, 8, 15, 22 and 29, for group D, and for doses 2, 3, 4, 5 and 6 (on days 8, 15, 22, 29 and 36), for groups W and T. Group T will also provide information on the absorption of 120 mg of iron in dose 1. Iron absorption of dose 1 (groups D1 and T1) will be adjusted for a 40% absorption of initial Fe-ascorbate. This adjusted value will anchor the curve for estimations of the area under the curve. All the other points for drawing the curve will be estimated in two ways: either without adjustment, or adjusted by the ratio of 40% initial Fe-ascorbate absorption by the subgroup contributing to the specific point in the curve (D1 for the point corresponding to dose 15; D2 for points of doses 3 and 22; D3 for points of doses 5 and 29; and D4 for point of dose 8). The same procedure will be followed for estimating the areas under the curve for groups W and T. T statistics will be used for this comparison.

(g) Rates of undesirable side-effects in 36 days will be compared between groups. The analysis of this information will be as follows. Firstly, the frequency of each individual symptom by all members of groups D, W and T will be estimated. Secondly, the frequency of all the symptoms will be added for each group. Thirdly, both frequencies will be expressed as a proportion of a maximal symptom score possible, considering a maximum of 36 days x 10 subjects for each symptom. Fourthly, the number of symptoms per subject per week will be calculated, and descriptive statistics will be generated. The differences between groups in the first three frequencies will be an-

alyzed by  $\chi^2$  or other non-parametric techniques. Analysis of variance will be used for the last set of data, considering total number of symptoms, supplementation schedule, dose per supplement, week number, and iron stores. We realize that the experimental protocol is not specifically designed for determining the incidence of side-effects (not double blind, with placebo controls, etc.), but nonetheless, we expect some valuable information on them.

## 7. Importance of the study

The capacity to maintain and improve iron nutrition of populations can be rapidly and efficiently expanded if intermittent iron supplementation proves effective. The first step in the process of acceptance of this new concept is to prove that iron absorption is significantly more efficient with intermittent dosage by avoiding the blockade effect. Theoretically – and to some degree – this is almost certain in humans.

The collaborative study involving populations in an industrialized country (France) and in a developing country (Senegal) will enhance the external validity of the investigation.

The greatest value of intermittent iron supplementation is in preventive supplementation. However, it may also prove very useful in therapeutically oriented supplementation.

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## References

- BROWN E.B. Jr., DUBACH R., MOORE C.V.: Studies in iron transportation and metabolism. XI. Critical analysis of mucosal block by large doses of iron in human subjects. *J. Lab. Clin. Med.*, 52, 335 (1958).
- CHAROENLAPP P. *et al.*: A WHO collaborative study on iron supplementation in Burma and in Thailand. *Am. J. Clin. Nutr.*, 47, 280 (1980).
- COOK J.D., SKIKNE B.S., LYNCH S.R., REUSSER M.E.: Estimates of iron sufficiency in the US population. *Blood*, 68, 726 (1986).
- DEMAEYER E., ADIELS-TEGMAN M.: The prevalence of anaemia in the world. *World Health Stat. Quart.*, 38, 302-316 (1985).
- EDWARDS C.G., GRIFFEN L.M., KUSHNER J.P.: Disorders of excess iron. In: *Diagnosis and Treatment of Iron Disorders*, V. HERBERT (Ed.), Hosp. Pract. (Off), 26 (Suppl. 3), 30, 1991.
- GALAN P., CHEROUVRIER F., MASHAKO L., NISBU C., KAPONGO C., PREZIOSI P.: Iron bioavailability from African meals with rice, cassava or plantain forming the staple food. *J. Clin. Biochem. Nutr.*, 38, 231, 1988.
- GALAN P. *et al.*: Iron absorption from typical West African meals containing contaminating iron. *Br. J. Nutr.*, 64, 541 (1990).

- GILLESPIE S., KEVANY J., MASON J. (Eds.): *Controlling Iron Deficiency. A report based on an ACC/SCN Workshop. ACC/SCN State-of-the-Art Series. Nutrition Policy Discussion Paper No. 9. ACC/SCN, Geneva, 1991.*
- GUIRO A.T., HERBERG S.: Iron exchangeability from pearl millet and Senegalese pearl millet meals. *Nutr. Rep. Int.*, 38, 231 (1988).
- GUTTERIDGE J.M.C.: Iron and oxygen: a biologically damaging mixture. *Acta Paediatr. Scand. (Suppl.)*, 365, 78 (1990).
- HAHN P.F., BALE W.F., ROSS J.J., BALFOUR W.M., WHIPPLE G.H.: Radioactive iron absorption by the gastrointestinal tract: influence of anemia, anoxia and antecedent feeding: distribution in growing dogs. *J. Exp. Med.*, 78, 169 (1943).
- HALLBERG L.: Iron balance in pregnancy and lactation. In: *Nutritional Anemias*, pp. 13-28, S.J. FOMON, S. ZLOTKIN (Eds.), Nestlé Nutrition Workshop Series, Vol. 30. Nestec Ltd., Vevey/Raven Press Ltd., New York, 1992.
- HALLBERG L., ROSSANDER-HULTÉN L.: Iron requirements in menstruating women. *Am. J. Clin. Nutr.*, 54, 1047 (1991).
- HALLBERG L. *et al.*: Search for substances promoting the absorption of iron. Studies on absorption and side effects. *Acta Med. Scand. (Suppl.)*, 459, 11 (1966).
- HARVEY P.W.J. *et al.*: The effect of iron therapy on malarial infection in Papua New Guinean school children. *Am. J. Trop. Med. Hyg.*, 40, 12 (1989).
- HERBERT V.: Everyone should be tested for iron disorders. *J. Am. Diet. Assoc.*, 92, 1502 (1992).
- HERBERG S., GALAN P., DUPIN H.: Iron deficiency in Africa. *World Rev. Diet.*, 54, 201 (1987).
- HÖGLUND S.: Studies in iron absorption VI. Transitory effect of oral administration of iron on iron absorption. *Blood*, 34, 505 (1969).
- Indian Council of Medical Research (ICMR): *Evaluation of the National Nutritional Anemia Prophylaxis Programme*. ICMR, New Delhi, India, 1989.
- International Conference on Nutrition: *World Declaration and Plan of Action for Nutrition*. FAO/WHO, Rome, 1992.
- LIU X., KANG J., ZHAO L., VITERI F.E.: Weekly iron supplementation in Chinese preschool children is efficient and safe. *FASEB J. (Abstract)*, 1994 (in press).
- LOZOFF B., JIMENEZ E., WOLF A.W.: Long-term developmental outcome of infants with iron deficiency. *N. Engl. J. Med.*, 325, 687 (1991).
- MAGNUSON B., BJÖRN-RASMUSSEN E., HALLBERG L., ROSSANDER L.: Iron absorption in relation to iron status. Model proposed to express results of food iron absorption measurements. *Scand. J. Haematol.*, 27, 201 (1981).
- MARTIN A., TOLOMEI K., VITERI F.E.: Iron metabolism in Fe supplemented rats. *FASEB J.*, 4, A1076 (1990). Submitted for publication, 1994.
- NORRBY A., SOLVELL L.: Iron absorption and hemoglobin regeneration in post-hemorrhagic anemia. Studies on the absorption pattern during oral iron therapy. *Scand. J. Haematol. (Suppl.)*, 20, 75 (1974).
- OPPENHEIMER S.J. *et al.*: Effect of iron prophylaxis on morbidity due to infectious disease. Report on clinical studies in Papua New Guinea. *Trans. R. Soc. Trop. Med. Hyg.*, 80, 596 (1986a).
- OPPENHEIMER S.J. *et al.*: Iron supplementation increases prevalence and effects of malaria: report of clinical studies. *Trans. R. Soc. Trop. Med. Hyg.*, 80, 603 (1986b).
- SALONEN J.T. *et al.*: High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. *Circulation*, 86, 803 (1992).
- SCRIMSHAW N.S.: Functional significance of iron deficiency. In: *Functional Significance of Iron Deficiency*, pp. 1-13, C.O. ENWONWU (Ed.), Center for Nutrition, Meharry Medical College, Nashville, TE, 1989.

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- SKIRNE B.S., FLOWERS C.H., COOK J.D.: Serum transferrin receptor: a quantitative measure of tissue iron deficiency. *Blood*, 75, 1870 (1990).
- SOLVELL L.: Oral iron therapy. Side effects. In: Iron Deficiency. Pathogenesis, Clinical Aspects, Therapy, pp. 573-583, L. HALLBERG, H.G. HARWERTH, A. VANNOTTI (Eds.), Academic Press, New York, NY, 1970.
- SOOD S.K. et al.: WHO-sponsored collaborative studies on nutritional anaemia in India. I. The effect of supplemental oral iron administration to pregnant women. *G. J. Med.* 44, 241 (1975).
- STEVENS R.G., JONES Y., MICOZZI M.S., TAYLOR P.: Body iron stores and the risk of cancer. *N. Engl. J. Med.*, 319, 1047 (1988).
- FRIER J.S.: Morphology of the epithelium of the small intestine. In: *Handbook of Physiology*, Section 6. Vol. III: Alimentary canal. Chapter 63. *Am. Physiol. Soc.*, pp. 1125-1175. Washington, DC, 1988.
- VITERI F.E.: Iron. Global perspective. In: *Ending Hidden Hunger. A Policy Conference on Micronutrient Malnutrition*, pp. 139-144. The Task for Child Survival and Development. Atlanta, GA, 1992.
- VITERI F.E.: Report to WHO on global strategy for the control of iron deficiency. WHO Nutrition Unit, 1993.
- VITERI F.E., LIU X.N., MORRIS M.: Iron retention and utilization in daily vs. every-3-days iron supplemented rats. *FASEB J.*, 6, A1091 (1992). Submitted for publication, 1993.
- VITERI F.E., GALAN P., HERBERG S.: Perceptions of the Problems of Nutritional Anemia and Iron Deficiency in the World as Reported by Informed Professionals. I. Latin America and the Caribbean, 1994 (in preparation).
- VITERI F.E., GUERI M., CALVO E. (Eds.): Final Report of the South American Workshop on the Control of Iron Deficiency, UNI, PAHO/WHO and CESNI. PAHO/WHO and Food, Nutrition and Development Programme, UNU, Boston, MA, 1994 (in press).
- WALTER T., DE ANDRAGA I., CHADUD P., PERALES C.G.: Adverse effect of iron deficiency on infant psychomotor development. *Pediatrics*, 84, 7 (1989).
- World Declaration on the Survival, Protection and Development of Children and a Plan for the 1990s. World Summit for Children. United Nations, New York, NY, 1990.
- World Health Organization. Maternal Health and Safe Motherhood Programme. Division of Family Health: Iron Supplementation During Pregnancy: Why Aren't Women Complaining? A review of available information. WHO Division of Family Health, 1990.
- World Health Organization. Maternal Health and Safe Motherhood Programme. Division of Family Health: The Prevalence of Anaemia in Women: A Tabulation of Available Information. Second Edition. WHO Division of Family Health, 1992.
- WRIGHT A.J.A., SOUTHON S.: The effectiveness of various iron-supplementation regimens in improving the Fe status of anaemic rats. *Br. J. Nutr.*, 63, 579 (1990).