

## Iron supplementation as a strategy for the control of iron deficiency and ferropenic anemia

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**SUMMARY.** Iron supplementation is a public health strategy designed for the prevention of iron deficiency and its consecutive anemia. It should be targeted, safe, flexible, long term and ideally, community based under the supervision of the health sector. It must be differentiated from iron therapy, even though, in the intermediate and long term it corrects mild-moderate deficiency of iron and ferropenic anemia. It should complement other measures for the control of iron deficiency.

A summary of results comparing daily and intermittent iron supplementation (every 3-days in rats, and weekly in humans) is presented, including studies in an animal model, human supplementary-iron absorption studies, clinical research and field studies. It is concluded that intermittent iron supplementation is efficacious and, that in the long term it achieves an increase in iron reserves while avoiding sustained oxidative stress caused by current practices of excess daily iron supplementation, particularly in the developing world. The stage is set for long-term weekly iron supplementation programs in large population groups to determine its sustainability and effectiveness.

**Keywords:** Iron, supplementation, daily supplementation, weekly supplementation, efficacy, safety, oxidative stress.

**RESUMEN.** La suplementación con hierro como estrategia para el control de la deficiencia de hierro y la anemia ferropénica. La suplementación con hierro es una estrategia de salud pública diseñada para la prevención de la deficiencia de hierro y la anemia consecuente. Esta estrategia debe ser dirigida, segura, flexible, a largo plazo e idealmente realizada en la comunidad con supervisión del sector salud. Debe estar diferenciada de la terapia con hierro, aunque a mediano y largo plazo, esta estrategia corrige la deficiencia leve-moderada de hierro y la anemia ferropénica. Debe complementarse con otras medidas de control de la deficiencia de hierro. Se hace una revisión de los resultados de estudios que comparan la suplementación diaria e intermitente (cada 3 días en ratas, y semanal en humanos), incluyendo estudios en modelos animales, estudios de absorción de hierro suplementado en humanos, estudios clínicos y estudios de campo. Se concluye que la suplementación intermitente es eficaz y que a largo plazo logra el aumento de las reservas de hierro evitando el estrés oxidativo sostenido causado por las prácticas actuales de suplementación diaria, particularmente en países en desarrollo. La plataforma está lista para determinar la sostenibilidad y efectividad de programas a largo plazo de suplementación con hierro semanalmente en grupos poblacionales grandes.

**Palabras clave:** Hierro, suplementación, suplementación diaria, suplementación semanal, eficacia, seguridad, estrés oxidativo.

### The concept of iron supplementation

According to Webster's dictionary, a "supplement is something added especially to make up for a lack or deficiency". Applied to public health nutrition and to iron in particular, the concept of supplementation consists in providing a defined amount of the mineral in a pharmaceutical preparation that can be consumed with or apart from meals, with the purpose of safely bringing the total utilizable iron to a level considered optimal for the health of individuals and populations.

The following is implied in that definition:

- 1- That an iron supplement should be given when the total dietary iron intake from native and/or fortified foods fails to reach that desired level in individuals or populations.
- 2- That its primary purpose is preventive rather than therapeutic of an established iron deficiency. In the long term it should correct mild-moderate deficiencies.
- 3- From the above considerations, it is obvious that

supplementation should be targeted to vulnerable populations or groups at risk of developing iron deficiency.

- 4- That it should be integrated with other measures aimed at controlling iron deficiency (and ideally at controlling other nutritional deficiencies). Therapeutic iron, when indicated, should be included among other control measures.
- 5- That as with any other intervention, it should be monitored and evaluated, and should be flexible to the point of discontinuing it when considered no longer necessary.

Just as I have stated what iron supplementation should be or include, I would like to present what it is not or should not be:

- 1- It should not be considered a therapeutic intervention aimed at correcting ferropenic anemia in particular, and much less anemia in general, in a short period of time.

- 2- It should not be seen as an intervention that excludes all others aimed at controlling iron deficiency: food-based strategies, infection control measures, iron therapy, etc., but rather as a complement to these other measures.

### Brief historical background

Iron supplementation is an off-shoot of iron therapy and has been applied almost exclusively to the correction and prophylaxis of ferropenic anemia in pregnancy. After many publications and several conferences on the clinical management of iron deficiency (e.i.1). The World Health Organization (WHO) started a series of studies of gestational anemia in India (2), and in 1972 it convened a group of experts (3) which concluded that vulnerable segments of the population, especially in areas with a high prevalence of iron deficiency, should be covered by iron supplementation (a preventive approach). They indicated that in pregnant women whose caloric intake is more than 25% from animal sources and who have iron stores at the beginning of pregnancy, 30 mg daily is sufficient to maintain hemoglobin concentrations. However, under other circumstances 60 mg of iron daily, and up to 120-240 mg are recommended when animal sources provide less than 10% of calories, iron deficiency is prevalent and many women are anemic at the commencement of pregnancy. Importantly, they recommended that in areas where iron deficiency anemia is prevalent among school children, 30 mg of elemental iron, in the ferrous form, should be given daily to each child throughout the school year. Therefore, the distinction between therapy for anemia and prevention of iron deficiency was blurred and has remained so till now. The American Academy of Pediatrics has, since 1976, recommended iron supplementation for infants (4), but in contrast to antenatal iron supplementation which has become law in many countries, its implementation is not mandatory and in most countries is not practiced. Also, I know of no program that has implemented the recommendation of supplementing school children following the WHO guidelines, although there are school feeding programs that include vitamin and mineral enriched foods at levels intermediate between those generally accepted in fortification and supplementation programs.

The most recent document by INACG, WHO and UNICEF (5) continues, in part, this confusion, even in its title: "Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia". In this document the highest oral iron dose to treat anemia has been reduced from 240 mg/d, or even higher doses, to 120 mg daily. Except for therapy, that includes a period of 3 months, the duration of preventive iron supplementation is not stated. Other WHO documents indicate giving several repeated courses of daily iron supplements to vulnerable populations (6). The rationale for this indication is lacking.

Although therapy and prevention are clearly different conceptually, the lack of definition in practice is understandable

because the difference in correcting iron deficiency and anemia through therapy or through prophylaxis is a matter of the speed by which correction is indicated or desired. This basically depends on dose and duration. Obviously, in severe anemia, particularly when there is danger of decompensation or when permanent damage from anemia can ensue, therapy is important.

### Present situation regarding iron deficiency and anemia and the effectiveness of current iron supplementation programs

The prevalence of iron deficiency and ferropenic anemia in the U.S. and in several industrialized countries has declined throughout the last 30 years but the contribution of iron supplementation to this decline remains unknown (7). Hallberg has suggested that self-prescribed iron supplementation, mostly through the intake of multivitamin-multimineral over the counter nutritional supplements has contributed significantly to the decline of ferropenic anemia observed in Sweden, but he has retracted earlier estimates of the relative contribution of this practice. I am sure that self-prescribed iron supplement intake does contribute, in the long term, to lowering the prevalence of iron deficiency and to increasing iron reserves.

The latest figures on prevalence of anemia in "non-industrialized countries" according to the WHO Micronutrient Deficiency Information System are presented in the following table (8):

Children		Women		Men
0-4 y.o. % (millions)	5-14 y.o. % (millions)	All % (millions)	Pregnant % (millions)	15-59 y.o. % (millions)
34 (190)	53 (526)	43 (535)	56 (54)	34 (456)

In industrialized countries the prevalence and the numbers of people with anemia are significantly lower, but there exist pockets of mostly poor populations where these prevalences are close to those in the non-industrialized world, particularly among infants and pregnant women. In California there are many counties where anemia in low income, 1 to 3 y.o. children reaches prevalences above 20% (9), and we have repeatedly found an iron deficiency prevalence of close to 20% and ferropenic anemia in 9% among childbearing age women students in Berkeley (10).

Based on these figures, the overall anemia prevalence in non-industrialized countries is estimated at 1,707 million people, of which 54 million are pregnant women (3.3% of all anemics). If 80% of anemia is due to iron deficiency or has an iron deficiency component (an accepted estimate) and for each of these ferropenic-anemic subjects there is another individual with iron deficiency without anemia, the total number of iron deficient people in this group of countries reaches 2,731 million. These numbers bring forth not only the huge problem of iron deficiency but also the fact that even if

all gestational iron deficiency were eliminated (an utopic situation) the total prevalence of iron deficiency and anemia would be reduced only by 3.3%. The International Conference on Nutrition (11) has set the goal to reduce by 1/3 the prevalence of gestational anemias by the end of this millennium. This goal is far from being reached, in spite of almost universal legislation in the developing countries establishing antenatal iron supplementation. These figures are not intended to diminish the importance of addressing the gestational anemia situation, nor its priority. They intend to show that more general approaches besides antenatal iron supplementation must be considered if the total iron deficiency problem is to be resolved.

Nutrition education, food fortification with iron, public health measures to diminish various types of infections, adequate perinatal practices, and the correction of other accompanying anemia-causing nutritional deficiencies are important steps in this regard (7), and are covered in this symposium. However, targeted, community based, preventive iron supplementation should not be discarded as another viable option. I contend that this strategy should be considered with a higher interest than that which is presently receiving. The reasons for this are the following:

- 1- Dietary improvement to a level where bioavailable iron meets the needs of vulnerable populations is far removed in time, particularly in a vast majority of the developing world population, even with important advances in biotechnological improvements of foods to increase iron bioavailability.
- 2- Food fortification can improve iron nutrition of populations (12), but its vehicles often do not reach the target populations in a significant proportion (e. g. infants of low income families, rural subsistence farmers in the developing world). Important advances are taking place in this regard, as will be addressed in this Symposium. Our findings and those of others in the industrial world indicate that iron deficiency affects a significant population even with current practices of food fortification.
- 3- New developments in this strategy are taking place which could make targeted, community based, preventive iron supplementation affordable, safe, multinutrient, and with high coverage (please see below).

An analysis of the effectiveness of antenatal iron supplementation programs in the developing world is revealing and must be considered in the promotion of efficacious preventive iron supplementation. Several studies (13-17) demonstrate that current practices of antenatal iron supplementation in most countries of the developing world have failed and explore the causes of this failure. These can be summarized in problems on the supply side as well as on the demand or recipient side.

There is consensus that the dominant causes of failure are in the supply side, including the structure of the programs: a)

poorly trained and/or motivated personnel at all decision and delivery points, these being essentially hospitals and health centers; b) inadequate coverage because a large proportion of pregnant women have little or no access to health centers (WHO estimates that 47% of the rural population in the developing world lack access to adequate health care) (18); c) insufficient and inconstant supply of the desired amounts of supplements; d) presentation and shelf life of iron supplements, and e) cost.

On the demand or recipient side, the causes of failure are mainly: a) poor knowledge of the importance of adequate iron nutrition and anemia prevention, leading to late consultation and poor adherence to the supplementation regimen; b) undesirable side effects secondary to the ingestion of iron tablets; c) lack of family and/or community support, and d) cost where free iron tablets are not supplied.

Considering coverage and adherence to antenatal supplementation programs, estimates of effectiveness of such programs in Latin America, including both urban and rural areas, do not reach 20% of intended (17). There are no figures on which to estimate the coverage and adherence of supplementation programs aimed at the infant and school children populations, but they are perceived as very low to nil.

#### **New developments in the strategy of preventive iron supplementation**

Given the synthesis of the problem of iron deficiency, the directives provided by WHO and other international agencies and specialized groups (e. g. INACG) and the poor effectiveness of currently operating iron supplementation programs in the developing world, we decided to explore new schemes of this strategy with emphasis on prevention.

Current recommended schemes are based on the daily administration of supplements either during pregnancy or in repeated cycles of 2-4 months or several weeks every year to population groups vulnerable to iron deficiency. The only widespread operating system in the developing world is almost exclusively directed to pregnant women and is fundamentally based in hospital and health center settings, with little active community participation. In many instances iron supplementation is directed towards the therapy of anemia (therapeutically-oriented supplementation) and is administered in high doses (often associated with undesirable side effects) only to those individuals already presenting anemia. An interesting development in this regard, is the pharmaceutical production of a gastric delivery system that improves iron absorption and reduces undesirable side effects (19,20). Unfortunately the commercial production of this preparation was never reached.

Based on a series of studies in animal models, and in humans (clinical studies and field trials), where efficacy, efficiency and safety of supplementation schemes have been evaluated, we are proposing the community-based, preventive, weekly iron + folate supplementation targeted to vulnerable

population groups. As indicated above, this strategy should be integrated with other measures aimed at controlling iron deficiency (and ideally at controlling other nutritional deficiencies), including the therapy of severe ferropenic anemia.

The studies we have performed are summarized as follows:

1- Efficacy and efficiency of intermittent iron supplementation:

a) *Animal model.* We developed an animal model where weanling rats were trained to meal-feed twice daily and to consume a small pre-meal containing the desired amount of iron. That way we could study iron-deficient and iron-normal rats, supplemented or not. We decided to study the effect of iron supplements administered to both iron-deficient and iron-normal at a dose comparable to that universally recommended to pregnant women where iron deficiency is prevalent and when they begin supplementation late in pregnancy. This dose is roughly 10 times the usual iron intake by unsupplemented women. Our findings (21) showed that iron absorption declined very rapidly when iron was administered daily while it declined at a slower rate when the dose was administered every 3 days (in synchrony with gut mucosal turnover). Iron deficiency, measured by blood hemoglobin and liver iron levels were restored equally fast with both regimens, suggesting that the efficacy in repleting the iron deficit was similar. Calculations of iron absorption rates, adjusted to the same level of total iron absorption prior to the dose where radioactive whole-body counting measurements were made, indicated more than a 2 fold higher efficiency in the every-3 days iron deficient supplemented animals. We recognize the limitations of this animal model and the risks incurred in extrapolating these results to the human.

b) *Human iron absorption studies.* The pioneering work of Dr. Layrisse and collaborators in this regard must be recognized and admired, and specifically pertinent to this presentation is his contribution in measuring the absorption of therapeutic doses of iron under different conditions (22). Importantly, they showed that iron deficient subjects could absorb as much as 22% of a 60 mg dose of iron as FeSO<sub>4</sub> when consumed away from meals, that when consumed with meals, or immediately before or after meals, absorption decreased to less than half, and that the addition of ascorbic acid to that "therapeutic" iron dose had a small effect but in an iron deficient-anemic case absorption reached 29.5 %.

The question of whether weekly iron supplementation in the human is more efficient than daily supplementation, has provoked several studies which can be summarized as follows:

i) In normal or mildly iron deficient populations, mean iron absorption from a dose of 50 - 60 mg of iron as FeSO<sub>4</sub> is between 8 and 10%, in the absence of meals (23) showed, in Kansas, that iron absorption was only

13% lower when measured after one week of daily supplementation with 50 mg of iron when compared with the absorption after not receiving iron supplements for one week. If an outlier is removed, absorption is 30% lower. Importantly, absorptions as high as 28% were observed in iron deficient subjects when iron was administered without a meal. They demonstrated also a dramatic reduction in percent absorption when the supplements were ingested with food. Pizarro et al. (unpublished, cited in 24) using an identical design to that of Cook and Reddy (23) apparently reached similar conclusions in Chile. In a study of longer duration, Viteri et al (25) also found in a population in California, about a 13% decline in iron absorption from a 60 mg dose after one week of daily supplementation. Maximal absorptions were also between 25 and 30%. However, after two weeks of daily iron supplementation, mean iron absorption had declined to 6% and maximal iron absorption was only 12%. In contrast, iron absorption in subjects receiving 60 mg of iron weekly remained elevated after two weeks (3 doses) and even after 4 weeks iron absorptions of 21 and 20% were still observed. When adjusted to a plasma ferritin of 20 µg/L, mean iron absorption from weekly doses was stable at 14-15% even after 4 weeks of supplement intake (5 doses), while mean absorption in daily supplemented subjects was reduced to 7%. Adjusted percent iron absorption from weekly 120 mg doses, although slightly lower than those from 60 mg doses, do not differ significantly. Therefore, the total iron absorbed from 120 mg weekly doses is close to double that absorbed from 60 mg doses.

ii) In iron deficient, anemic subjects in Dakar, Senegal, results are essentially similar but at higher percent absorptions. In the case of weekly supplementation, maximal absorptions remained above 35% for 2 weeks and from then on they declined to 24 and 20% after 5 weekly doses. By then subjects receiving daily iron were absorbing only 10% of the dose. Weekly supplemental iron absorption adjusted to a plasma ferritin of 20 µg/L again showed a greater stability than daily iron absorption and did not differ from the values obtained in the Berkeley subjects. Adjusted daily iron absorption in Senegal remained higher than in Berkeley but showed a similar 30% decline between the first and the last two week periods of study. Again, adjusted percent iron absorption from weekly 120 mg doses, although only 70% of that from 60 mg doses, does not differ significantly. Therefore, the total iron absorbed from 120 mg weekly doses is substantially higher than that absorbed from 60 mg doses.

These results reinforce the following: a) Even when daily iron absorption declines more rapidly than weekly, total mg of iron absorbed during the month of study is

higher than that absorbed from weekly supplementation, and therefore, daily iron supplementation is recommended for therapy. And b) Total iron absorbed from weekly 60 mg supplements in iron deficient subjects can reach over 20 mg of iron per week, or the equivalent of 3.2 mg of extra iron daily. With 120 mg/

week, iron absorption can reach the equivalent of 5.4 mg of extra iron/day.

c) *Field trials.* The following table, summarizes the information available to me and to the Task Force for the control of iron deficiency of the ACC/SCN actualized to early 1999.

Weekly iron supplementation efficacy trials

Country status	No OF Studies	Population	No OF Subjects	Results
Brazil	1	6 - 12 m, children	1,280 Ua	+wb Prepc.
France	1	6 - 36 m, children	204 U	+ w Sub
Indonesia	1	6 - 36 m. children	442 S	+ d and w
			390 U	+ d; w ± Draft
China	1	6 - 36 m. children	246 S	+ d and w; - p Publ.
China	3	3 - 6 yr old children	673 S	+ d and w Publ.
Indonesia	2	3 - 6 yr old children	65 S	+ d and w Publ.
			289 U	+ w Prep.
Viet Nam	1	1 - 2 year old children	300 S	+ d and w Publ..
Bolivia	1	3 - 6 yr old children	300 S	+ d and w Publ.
Indonesia	1	School-age children	545 S	+ d and w Publ.
Guatemala	1	School-age girls	350 S	+ d and w Publ.
Panama	2	School-age children	5,021 S	+ d and w Prep.
Mali	1	School-age children	545 S	+ d and w Draft.
Indonesia	1	Adolescent girls	273 S	+ d and w Publ.
Malaysia	1	Adolescent girls	590 S	+ w Publ.
Tanzania	1	Adolescent girls	237 U	+ w plus motiv. Prep.
Peru	1	Adolescent girls	296 U	+ d; ± w; - p Prep.
United States	1	Fertile-age women	116 U	+d and w In press.
Indonesia	2	Fertile-age women	380 S	+ d and w Publ
Indonesia	2	Pregnant women	139 U	+ d and w Publ.
		Pregnant women	?? S	+ d; ± wc; - p Publ.
China	1	Pregnant women	389 S	+ d and w; - p In Press
Guatemala	1	Pregnant women	218 U	+ d and ± w Draft.
Malawi	1	Pregnant women	413 S	+ d and w Prep.
Venezuela	1	Pregnant women	104 U	+ bi-w; + w Prep.
Mexico	1	Pregnant women	165 U	+ dc and ±wc Prep.

TOTAL 16 Countries 30 studies through the life cycle except the elderly, involving 13,900 + subjects. 13 published; 2 in press; 1 submitted; 3 in draft form, and 8 in preparation. Results were positive for daily and weekly supplementation in all studies where the supplement was administered under supervision. In 4 of 9 unsupervised, unmotivated studies weekly is ±.

a U = unsupervised intake; S = supervised intake. One study comparing weekly and twice weekly iron supplementation in pregnant women. Slight advantage of twice weekly dosing.

b + results are better than placebo and/or are comparable to daily supplementation, considered the «golden standard» in terms of the efficacy. ± = less efficacious than daily or of doubtful efficacy. In the case of pregnancy, however, ± means no significant improvement in Hb or ferritin between early pregnancy and term. It must be recognized that in the absence of iron both fall. Therefore, ± in pregnancy is positive in preventing the otherwise expected deterioration. - = deterioration. w = weekly; d = daily; p = placebo.

c Prep. = in preparation; Draft = in draft form; Sub. = submitted; Publ. = Published.

These results demonstrate the efficacy of weekly iron supplementation in supervised field trials, where overall results in terms of hemoglobin and ferritin levels are no different from those of daily iron supplementation, except

in pregnancy and in some unsupervised trials where daily iron supplementation is often more efficacious and effective respectively. In spite of these differences, which are small and most often neither statistically or biologically

significant, weekly iron supplementation improves iron nutrition significantly when compared to current practices. In the specific case of pregnancy, weekly iron supplementation has proven effective in preventing hemoglobin levels below 90 g/l at term. Risk of perinatal complications increase when hemoglobin concentrations fall below this level (26). An important factor in the success of antenatal iron supplementation is the level of iron stores and hematological condition with which women enter pregnancy (27). Several studies have demonstrated that the most important determinant of hemoglobin level at term is the hemoglobin level early in pregnancy, even among women receiving supplements (28). This should serve as a strong incentive to promote "pre-pregnancy iron health", including iron reserves in the order of 300 or more mg (29-32). Preventive weekly supplementation with iron and folate to women prone to become pregnant cannot only achieve the desired iron health but also a safe level of folate nutrition that will prevent neural tube defects. We have recently demonstrated in a group of non-pregnant Berkeley women that weekly folate at a dose of 3.5 mg sustains plasma and red cell folate at desirable levels. Currently we are determining if 2.5 mg a week will achieve similar levels.

## 2- Studies on the safety of different iron supplementation schemes.

Iron excess is dangerous because it promotes the development of reactive oxygen species (ROS) which in turn produce oxidative damage to proteins, nucleic acids and lipids, altering cell membrane and cell duplication and function secondary to altered enzymatic functions (33, 34). Iron excess can be chronic as in the case of genetic hemochromatosis or temporarily produced by the ingestion of iron at doses that surpass the antioxidant capacity of the body.

The results from our animal studies which demonstrated that daily iron supplementation at 10 times the normal level of iron intake (comparable to ingesting 120 mg of supplementary iron daily in the adult human) maintained a high level of intestinal mucosal and liver iron, prompted us to explore if this situation resulted in oxidative stress secondary to the production of ROS. In order to measure this condition we developed a method to measure ethane and pentane exhalation rates (35,36), and in collaboration with Drs. B. N. Ames and P. Walter, we modified a specific method to measure malondialdehyde in the presence of high levels of tissue iron (37) and have measured mitochondrial DNA damage and respiratory function in liver and kidney. Ethane and pentane are end products of lipid peroxidation and malondialdehyde (MDA) is a byproduct of lipid hydroperoxides. Of these three biomarkers of oxidative stress, ethane is the only that is not

metabolized to any significant extent in the body, making it the most sensitive indicator of what we call early iron overload conditions (EIOC). However, in the presence of excess iron, ethane can be produced by intraluminal processes in the gut, making it less specific of tissue peroxidative damage. On the other hand, elevations in tissue and plasma MDA concentrations are very specific indicators of tissue oxidative stress. At the same time, we adapted and validated the breath ethane and pentane methods to measure oxidative stress in humans. A summary of recent results follow:

- i) In daily supplemented, as well as in iron deficient rats, elevated liver and kidney MDA and ethane exhalation rates, impaired mitochondrial respiration and significant mitochondrial DNA ruptures are present and are strongly correlated with the excess liver iron observed in daily supplemented rats, suggesting a situation of EIOC (38,39).
- ii) Every 3-day iron supplementation significantly ameliorates these indicators of EIOC in rats. They are present the day after the iron dose but by the third day they are back to normal levels. Altered mitochondrial respiration and DNA damage are not observed (38, 39).
- iii) In non-pregnant women supplemented with 120 and 98.5 mg of iron for 4 and 6 weeks, respectively, ethane exhalation rates and plasma MDA levels are also elevated, as are % saturation of transferrin and plasma ferritin levels (40,41). In weekly supplemented women with 120 mg of iron, ethane exhalation rates are elevated the day after the ingestion of the dose but by the second day most are back to non-supplementation levels. Plasma MDA is also elevated the day after the iron dose, but by the seventh day is back to pre supplementation levels, as are the % saturation of TIBC levels. Serum ferritin is not elevated in these women (40).
- iv) In field trials, a significant number of women and children supplemented daily exhibit serum ferritin levels that are beyond the levels corresponding to the 80th percentile of normal populations. This phenomenon is not observed in the same population groups receiving weekly iron supplements and where serum ferritin distributions have been analyzed, they are superimposable to those observed in normal populations (42).
- v) Several studies, but not all, demonstrate that undesirable side effects are higher in daily supplemented groups, that adherence to the supplementation regimen is lower among those with side effects and that rejection of the regimen is higher among those receiving daily iron (43,44).

## CONCLUSIONS

Iron supplementation, should be conceived as a targeted, long-term, safe preventive measure that must be differentiated from iron therapy. In the long-term it should correct mild-moderate iron deficiency and ferropenic anemia and should increase iron reserves without producing early iron overload.

Preventive iron supplementation should be conceived as another strategy for the control of iron deficiency and should be complementary to other interventions aimed at controlling iron deficiency, including iron therapy when this is indicated.

Daily iron supplements at doses of 120 mg/d, consumed away from meals, is absorbed by iron deficient subjects at levels which are therapeutic in the short term, even for pregnant women. Weekly iron supplementation at doses of 60 and 120 mg/d can provide enough iron to correct iron deficiency in a medium term and to prevent and correct mild-moderate iron deficiency even in pregnant women, if administered from early pregnancy.

Field trials demonstrate that long term, weekly iron supplementation is efficacious in improving iron nutrition of vulnerable groups.

Animal studies demonstrate that daily iron supplementation produces constant oxidative stress while this stress is less and of short duration when iron is administered intermittently. Studies in humans reach the same conclusion.

Extended population-based studies should be undertaken to determine if well designed community-based programs are sustainable and effective.

## REFERENCES

- Hallberg L, Harwerth HG and Vannotti A. Editors. Iron deficiency. Academic press. London. 1970;pp 531-616.
- Sood SK, Ramachandran K, Mathur M, Gupta K, Ramalingaswami V, Swarnabai C, Ponniah J, Mathan VI and Baker SJ. WHO sponsored collaborative studies on nutritional anaemia in India. I. The effects of supplemental oral iron administration to pregnant women. *Qtrly J Med*, 1975;174: 241-258.
- World Health Organization (WHO). Report of a WHO group of experts on nutritional anaemias. Technical report series N° 503. WHO. 1972. Geneva, Switzerland.
- American Academy of Pediatrics. Iron supplementation for Infants. *Pediatrics*, 1976;58:765-768.
- INACG/WHO/UNICEF. Guidelines for the use fo iron supplements to prevent and treat iron deficiency anemia. INACG. Washington, DC. 1998.
- DeMaeyer EM (Ed.). Preventing and controlling iron deficiency anaemia through primary health care. W.H.O., Geneva. 1989. 58 pages.
- Viteri FE. Prevention of iron deficiency. In: *Micronutrient Deficiencies: A Toolkit for Policymakers and Public Health Workers*. Eds. CP Howson, E Kennedy, A. Horwitz. Institute of Medicine, National Academy Press, Washington, D.C. 1998. pp 45-102.
- ACC/SCN. Third report of the world nutrition situation. ACC/SCN. Geneva. 1997;34 -42.
- California's Childhood Health and Disabilities Prevention Program (CHDP), 1996.
- Viteri FE, Ali F and Tujague J. Weekly iron supplementation improves and sustains women's long-term iron status as well or better than currently recommended short-term daily supplementation. *J Nutr*. In Press, 1999.
- International Conference on Nutrition. Rome. 1992.
- Viteri FE, Alvarez E, Batres R, Torún B, Pineda O, Mejía L. and Sylvi J. Fortification of sugar with NaFeEDTA improves iron status in semi-rural populations in Guatemala. *Am J Clin Nutr*, 1995;61:1153-1163.
- ACC/SCN. Controlling iron deficiency. A Report Based on an ACC/SCN Workshop. S. Gillespie, J. Kevany and J. Mason. Eds. ACC/SCN State of the Art Series. Nutriti on Policy Discussion Paper N° 9. ACC/SCN c/o WHO, Geneva, Switzerland. 1991. 93 pages.
- Galloway R and McGuire J. Determinants of compliance with iron supplementation: supplies, side effects or psychology ? *Soc Sci Med*, 1994;39: 381-390.
- World Health Organization (WHO). Maternal Health And Safe Motherhood Programme, Nutrition Programme. The prevalence of anaemia in women: a tabulation of available information. W.H.O., Geneva, Switzerland. 1992. 100 pages.
- World Health Organization (WHO). Iron supplementation during pregnancy: why aren't women complying ? A review of available information. Maternal Health And Safe Motherhood Programme, Division of Family Health. World Health Organization. Geneva, Switzerland. 1990.
- Viteri FE. Summary results of a survey on nutritional anemias, iron deficiency, and their control. In: Viteri FE, Gueri M, and Calvo E. (Eds). Report of the I Subregional workshop on the control of nutritional anemias and iron deficiency. (UNU. PAHO/WHO, And CESNI). English and Spanish versions. INCAP publication. 1996. pp 132-177.
- UNDP. Human Development Report. UNDP/Oxford University Press. Oxford, England. 1991. Table 17
- Cook JD, Carriaga M, Kahn SG, Schalch W and Skikne BS. Gastric Delivery System for Iron Supplementation. *Lancet*, 1990;335:1136-1139.
- Simmons KW, Cook JD, Bingham KC, Thomas M, Jackson J, Jackson M, Ahluwalia N, Kahn SG and Patterson AW. Evaluation of a gastric delivery system for iron supplementation in pregnancy. *Am J Clin Nutr*, 1993;58:622-626.
- Viteri FE, Liu X-N, Martin A and Tolomei K. True absorption and retention of supplemental iron is more efficient when administered every-three-days rather than daily to iron-normal and iron-deficient rats. *J Nutr*, 1995;125: 82-91.
- Grebe G, Martinez-Torres C and Layrisse M. Effect of meals and ascorbic acid on the absorption of a therapeutic dose of iron as ferrous and ferric salts. *Current Therap Res*, 1975;17: 382-397.
- Cook JD and Reddy MB. Efficacy of weekly compared with daily iron supplementation. *Am J Clin Nutr*, 1995;62:117-120.
- Hallberg L. Use of daily compared with weekly iron supplementation: apples and pears. *Am J Clin Nutr*, 1999;69:740- 742 (letter).

25. Viteri FE, Guiro A, Galán P, Mendoza C and Hercberg H. Absorption of daily and weekly supplemental iron in iron normal and iron deficient populations. *FASEB J*, 1999;13:A16742.
26. Murphy JF, O'Riordan J, Newcombe RG, Coles EC and Pearson JF. Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet*, i: 1996;992-995.
27. Kaufer M, Casanueva E. Relation of prepregnancy ferritin levels to hemoglobin levels throughout pregnancy. *Europ J Clin Nutr*, 1990;44: 709-715.
28. Sloan NL, Jordan EA, and Winikoff B. Does iron supplementation make a difference? Mother Care Project, Working Paper 15. Arlington, Virginia. 1992. 50 pages.
29. Viteri FE. Effective iron supplementation does not happen in isolation. *Am J Clin Nutr*, 1997;65:889 - 890 (Letter).
30. Viteri FE. A new concept in the control of iron deficiency (ID): community-based preventive supplementation (PS) of at-risk groups by weekly intake of iron supplements. *Biomedical and Environmental Science*, 1998;11: 46-60.
31. Viteri FE. Iron supplementation for the control of iron deficiency in populations at risk. *Nutr Rev*, 1997;55:195-209.
32. Viteri FE. Suplementación con hierro para el control de la deficiencia de hierro en poblaciones a riesgo. En: O'Donnell A, Viteri FE, and Carmuega E. (Eds.). *Deficiencia de hierro. Desnutrición oculta en América Latina*. CESNI, Buenos Aires, Argentina. 1997 pp231-258.
33. Gutteridge JMC. Iron and free radicals. In *Iron Nutrition in Health and Disease*. L. Hallberg and N. G. Asp., Editors. John Libbey & Co. Ltd. London. 1996; pp239-246.
34. Lauffer RB. *Iron and Human Disease*. CRC Press, Boca Raton, FL. 1992.
35. Knutson MD, Viteri FE. Concentrating breath samples using liquid nitrogen: a reliable method for the simultaneous determination of ethane and pentane. *Anal. Biochem*. 1996;242:129-35.
36. Knutson MD, Lim AK and Viteri FE. A practical and reliable method for measuring ethane and pentane in expired air from humans. *Free Radical BioL. and Med*. In press, 1999.
37. Knutson MD, Walter PB, Viteri FE and BN Ames. Factors influencing the determination of tissue malondialdehyde levels. 4th Annual Meeting of the Oxygen Society. San Francisco, CA, 1997. p. 123 *Oxygen '97 Book of Abstracts*. 1997.
38. Knutson MD, Walter PB, Ames BN and FE Viteri. Daily oral iron supplementation causes sustained iron accumulation and oxidative damage which are mitigated by intermittent iron supplementation. *International Congress of Nutrition*. Montreal, Canada. p. 63 *Book of Abstracts*. 1997.
39. Walter PB, Knutson MD, Viteri FE, and Ames BN. Iron supplements, mitochondrial function, and DNA damage in iron-normal and deficient rats. 4th Annual Meeting of the Oxygen Society. San Francisco, CA. p. 106 *Oxygen '97 Book of Abstracts*. 1997
40. Knutson MD, Walter P, Mendoza C, Ames BN, Viteri FE. Effects of daily and weekly oral iron supplements on iron status and lipid peroxidation in women. *FASEB J*. 1999;13:A1738.
41. Mertz SD, Woodhouse LR, Donangelo CM, Knutson MD, Walter PB, Ames BN, King JC and Viteri FE. Breath ethane excretion rate in young women is increased by daily iron but not by daily zinc supplementation. *FASEB J*. 1999;13: A876.
42. Liu X - N, Kang J, Zhao L and Viteri FE. Intermittent iron supplementation is efficient and safe in controlling iron deficiency and anemia in preschool children. *Food And Nutrition Bulletin*. 1995;16:139-146.
43. Ridwan E, Schultink W, Dillon D and Gross R. Effects of weekly iron supplementation on pregnant Indonesian women are similar to those of daily supplementation. *Am J Clin Nutr*. 1996;63:884-890.
44. Liu X-N, Liu P-Y and Viteri FE. Weekly iron-folate supplementation to pregnant women in China is as efficacious as daily supplementation in controlling ferropenic anemia and iron deficiency. *J Nutr In Press*. 1999.