ANAEMIA IN PREGNANCY ON MATERNAL HEALTH, THE FOETUS AND THE INFANT

by Fernando E. Viteri, M.D., ScD., FACN, Professor, Department of Nutritional Sciences, University of California at Berkeley.

The health-conscious world community has come to realize that anemia, the majority of which is due to iron deficiency, has serious health and functional consequences (1), is widespread especially among tropical-low income populations and that most of its nutritional component is controllable with a very high benefit/cost ratio. Women of fertile age and pregnant-lactating as well as their infants and young children are particularly affected (2,3).

In response to the overwhelming evidence to this effect, world authorities have agreed that a minimal goal is that by the end of this century, anemia in pregnant women must be reduced by 1/3. The more aggressive groups believe that with new approaches for the control of iron deficiency a reachable goal is to reduce iron deficiency anemia to overall levels below 10% in most populations.

Background

It is estimated that about 2,150 million people are iron deficient (4), and that this deficiency is severe enough to cause anemia in 1,200 million people globally. About 90% of all anemias have an iron deficiency component. In the developing world nearly 1/2 of the population is iron deficient. However the industrial world is not free from it: 11% of its population has iron deficiency.

Roughly 47% of non-pregnant women and 60% of pregnant women have anemia worldwide, and including iron deficiency without anaemia the figures may approach 60 and 90% respectively. In the industrial world as a whole, anemia prevalence during pregnancy averages 18%, and over 30% of these populations suffer from iron deficiency. The poor are more affected.

The high risk of women of fertile age and pregnant women for incurring negative balance and iron deficiency is due to their increased iron needs because of menstruation and the substantial iron demands of pregnancy. Median requirements of absorbed iron are estimated to be 1.36 and 1.73 mg per day among adult and teen-age menstruating females. However, 15% of adult menstruating women require more than 2.0 mg per day, and 5% require as much as 2.84 mg per day. The superimposition of menstrual losses and growth in menstruating teenage girls increases the demands for absorbed iron; 30% need to absorb more than 2.0 mg of iron per day; 10% as much as 2.65 mg, and 5% 3.21 mg. These requirements are very difficult, if not impossible to satisfy even with good quality, iron-fortified diets.

Birth spacing favours iron nutrition among fertile-age women because each pregnancy has a high cost in terms of iron (see below). However, the use of intrauterine devices almost doubles the iron menstrual loss while women using anovulatory contraceptive methods reduce it by almost half. Importantly, multiparous women tend to have greater menstrual losses that increase with parity.

The following table shows the total iron requirements during pregnancy (5).

Iron Costs of Pregnancy

Factor	Milligrams of iron	
	Range	Median
Fetal iron	200-450	270
Placental iron	30-170	80
Partum and puerperium losses	90-310	250
Hemoglobin and tissue expansion	130-430	200*
Maintenance during amenorrhea	160-220	190
Subtotal 1 (total iron costs)	610-1580	990
Postpartum involution iron	130-430	200
Total	480-1150	790

*Iron-unsupplemented women. For iron-supplemented women this value is 450mg.

Iron needs exhibit a marked increase during the second and especially during the third trimesters when median daily needs increase up to an average of 5.6 mg per day (that is, 4.1 mg above median pre-pregnancy needs). The approximate range would be 3.54 and 8.80 mg per day. This amount of absorbed iron needs cannot be met from food iron even if iron fortification is in place. Thus the importance of two factors: pre-pregnancy iron reserves upon which to draw; and iron supplementation during pregnancy.

Iron deficiency during lactation is mostly a residual from that resulting from pregnancy and delivery and can be partially alleviated because of lactational amenorrhea. However, once menstruation returns, if lactation continues, iron requirements become higher to reach a median of about 1.81 mg/day. Dietary iron absorption in most populations of the developing world may not be sufficient to fulfil these needs.

In conclusion, iron deficiency during pregnancy is extremely common even among otherwise well nourished populations because of the reasons reviewed above. The risk of iron deficiency in pregnancy and lactation begins with inadequate pre-pregnancy iron reserves among women of fertile age.

Folate deficiency has also been documented during pregnancy, often leading to a combined iron-folate deficiency anemia, particularly among lower socio-economic groups consuming mostly cereal-based diets (poor in folate) aggravated by prolonged cooking and food reheating of liquid preparations. Folate requirements double in the second half of pregnancy and are markedly increased by processes that involve hemolysis, such as malaria and hemoglobinopathies. Malabsorption processes, common among tropical, low socio-economic groups, impair folate absorption.

Negative Effects on the Mother During Pregnancy and the Perinatal Period.

a) Reproduction-related mortality.
It has been clearly demonstrated that the anemic pregnant woman is at greater risk of death during the perinatal period. Close to 500,000 maternal deaths ascribed to childbirth or early post-partum occur every year, the vast majority taking place in the developing world. Anemia is the major contributory or sole cause in 20-40% of such deaths (6). In many regions anemia is a factor in almost all maternal deaths, and it poses a 5 fold increase in the overall risk of maternal death related to pregnancy and delivery. The risk of death increases dramatically in severe anemia. In Zaria, Nigeria, Harrison (7) reported that mortality for women during delivery or shortly after was 20% if their haemoglobin (Hb) concentration was <50g/L. Mortality decreased as Hb concentration rose: 4.5% for Hb levels between 60 and 50 g/L. Average figures of 12.8% applied for Hb concentrations <60g/L in contrast to 2.9% among women whose Hb level was between 80 and 60 g/L. Overall maternal mortality was 1%, not very different from that in many parts of Africa, Asia and among certain Latin American populations. These rates of maternal deaths, mostly associated with pregnancy and delivery, contrast with those in the industrial world where maternal mortality is near 100 times less and severe anaemia is very rare. It is important to realize that severe anaemia is associated with very poor overall socioeconomic and health conditions in certain countries and regions of the developing world. As a rule malaria, other infections, and multiple nutritional deficiencies, including folate and vitamin A are also endemic in these populations. Iron deficiency, however, is responsible for, or contributes significantly to, the majority of anaemia cases during pregnancy.

The risk of complications during birth, including fetal mortality, is higher among stunted populations who also exhibit poor pelvic development. General undernutrition and specifically iron and folate deficiencies during childhood and adolescence impair physical growth. Both iron and folate supplementation can result in improved growth in children and in pregnant teenage girls.

b) Performance during pregnancy and delivery.
Iron deficient anemic women have shorter pregnancies than non-anemic, or even anemic but not iron deficient pregnant women. An elegant prospective study showed that all anemic pregnant women had a higher risk of pre-term delivery in relation to non-anemic women (8). The iron-deficient, anemic group had twice the risk of those with anemia in general. However, iron-deficient, non-anemics did not differ from other non-anemics. These results were obtained after controlling for maternal age, parity, ethnicity, prior low birth-weight or pre-term delivery, bleeding at entry to health care, gestational age at initial blood draw, number of cigarettes smoked per day, and pre-pregnancy body mass index (Wt/Ht-squared). Inadequate gestational weight gain (for gestational age) was significantly higher for all anemic cases, particularly among those that were iron-deficient. Inadequate weight gain has also been associated with pre-term delivery.

In some tropical populations, folate supplementation also resulted in improved hematological status, birth weight and reduced incidence of premature deliveries, suggesting a deficiency of this nutrient.

These results confirm and clarify other retrospective studies or provide indirect evidence that better nutrition, including lesser prevalence of anemia, was associated with better newborn weights and lower rates of pre-term deliveries, and that anemia was associated with increased risk of pre-term delivery. The more severe the anemia the greater the risk of low-birth weight. It must be mentioned here that *elevated* hemoglobin levels because of poor plasma expansion due to other pathological conditions are also associated with poor pregnancy outcomes.

Delivery demands endurance and severe physical effort and physically fit women (almost an impossibility in the face of severe anemia) perform better and have less complications during delivery when contrasted with less fit women. In severe anemia, cardiac failure during labour is a major cause of death.

c) Lactation performance.
There is no evidence that iron deficient or anemic mothers are less competent than their normal counterparts in the process of lactation, and milk composition, both in terms of macro and micro-nutrients is essentially unaltered.

However even under the best of circumstances, breast milk iron has been proven insufficient to maintain an adequate iron nutrition in infants beyond 4 to 6 months of age.

d) Working capacity and general well-being.
Even though there are no direct data on the effect of anemia and iron deficiency on the capacity of pregnant women to perform physical work in relation to non-anemic-iron-sufficient pregnant women, the negative relationship between anemia and working capacity is well established in both men and women. The impact of pregnancy anemia and its residual anemia and iron deficiency surely affects the woman as a mother, as a worker and as a person in general.

e) Immunity status.
Two studies in India demonstrate that severely anemic as well as iron deficient pregnant women have impaired cell mediated immunity that is reversible with iron treatment. An important control variable lacking in these studies is documentation of folate nutrition.

Negative Effects on the Infant.

a) Health and development.
Two large studies in the industrial world involving over 100,000 pregnancies clearly indicate that favourable pregnancy outcomes are less frequent among anemic mothers (9,10). Both studies found higher rates of fetal deaths and abnormalities, premature deaths, and low birth weight newborns among anemic mothers. These risks were evident even among mothers who had anemia only in the first half of pregnancy. Significant correlations between the severity of anemia, premature birth, and low birth weight were very evident.

The causality of anemia in these undesirable pregnancy outcomes has been established further by studies that show the positive results obtained in birth weights and perinatal deaths by the successful treatment of anemia with iron and folic acid. For example, low birth weight (<2,000g) was reduced from 50% to 7% and perinatal mortality dropped from 38% to 4% in a study in Nigeria (11).

In terms of infant health and development, the low birth weight child is at a disadvantage particularly in the developing world where the risk of malnutrition, infection and death are markedly increased. An additional risk to the infant may come from the fact that iron deficiency and anemia in children, as well as in adults, produce alterations in brain function that may result in poor mother-child interactions and impaired schooling later. There is mounting evidence that in infants iron deficiency anaemia may produce long-lasting defects in mental development and performance that my further impair the child's learning capacity..

b) Hematological status and iron nutrition.
Mild maternal iron deficiency and anemia have little significant repercussions on the hematological status of newborns. It has been suggested that placental transferrin receptors protect the fetus. However, it appears that the capacity of iron to transfer from placenta to fetus is limited by a threshold mechanism so that fetal iron deficiency exists in severe maternal iron deficiency and anemia. Also, the fetus of iron deficient mothers accumulates less iron reserves, and has smaller hemoglobin mass than their normal counterparts. This has been termed "hidden iron deficit" and is further magnified by low birth weight, mainly due to preterm delivery.

Further evidence of "hidden iron deficiency" at birth comes from studies that showed that maternal and cord serum ferritin levels were lower in the presence of maternal iron deficiency and that this difference with children from non-anemic mothers was magnified when the children were again studied at 2 months of age. This may account for the well documented higher prevalence of iron deficiency and anemia in late infancy among populations where anemia of pregnancy is highly prevalent. This situation increases the risk of long term and even permanent impairments in mental and physical development among such children.

A Call for Action

In the developing world, current strategies to prevent and correct iron deficiency and anemia in pregnant women have met with little success (12). Also, there are no concerted efforts to control these conditions in the populations of fertile age women and in infants and toddlers.

Food-based strategies, including general or targeted food fortification with iron, are very difficult to implement in many developing regions. Iron fortification of salt, sugar and other foods and condiments with iron alone or combined with vitamin A and iodine appear promising in certain regions, but even then, about 20% of women do enter pregnancy in a state of iron deficiency and most women will not have adequate reserves (13). The need for targeted iron supplementation during pregnancy is evident and has been the accepted practice. However its effectiveness has been frustratingly poor. There is a need to explore new approaches that modify current practices by seeking greater effectiveness and safety as well as means to increase coverage (14). New information that supports new approaches to iron supplementation is becoming available. Based on this emerging data I believe that current practices of iron supplementation to targeted groups must be modified as follows:

1 - The target for iron supplementation should be expanded to cover all women of fertile age who might become pregnant, with a different philosophy and practice of iron supplementation so they enter pregnancy with iron reserves.

2 - Current philosophy of iron supplementation is basically therapeutically oriented, dominated by the aim of correcting established iron deficiency: short courses, large daily doses, rigid schedule and centred in the health network. This philosophy must be changed to one that is primarily oriented to prevent iron deficiency: longer courses, smaller doses possibly administered intermittently, flexible schedules and centred in community organisations. Preventive supplementation should increase coverage (47% of the rural population in the developing world has no access to established health care networks). In all cases, the adequate supply and distribution of tablets and motivation of suppliers and recipients are essential.

3 - New supplementation practices must be explored. Two recent developments are important in this regard: a) The development of gastric release systems that improve iron absorption by prolonging the period of iron presentation to the gut and reduce side-effects. A single 50 mg iron tablet a day appears at least as effective as two of the ferrous sulfate tablets currently in use that provided 60mg of iron each in a recent study in Tanzania (15). This study also showed that smaller supplemental iron doses than those currently recommended are effective. b) The development of schemes that provide relatively higher doses of iron on a weekly basis (14). This new approach has proven very safe and effective in pre-school children in China and is essentially devoid of undesirable side effects (16). Preliminary results from a study by the same investigators (17) show that pregnant women in China supplemented once weekly for four months at a dose of 120 mg of iron as ferrous sulfate have the same Hb concentration at term to that obtained by the supervised intake of 120 and 60mg of iron daily also as ferrous sulfate. The three groups also achieve a similar reduction (16%) in the prevalence of anaemia at term, while unsupplemented women (following the established policy in Xinjiang province of not providing iron supplements to women with Hb levels above 80 g/L) present a rise of 26% in anaemia prevalence at term. Side effects among weekly supplemented women are nearly absent (no rejections), while those induced by the 60 and 120 mg daily iron doses lead to 9 and 19% rejection rates to those supplementation schemes. Thus, in practical terms the weekly dose appears more effective than both daily doses evaluated. c) Theory would support a single weekly iron dose of 60 mg consumed by fertile-age women as an effective scheme to cover menstrual losses in the vast majority of women, who would enter pregnancy with improved iron nutritional status. Once this practice is established, as soon as pregnancy is detected the weekly dose would be doubled. This scheme is more economical, could be handled by community organisations and the weekly dose of iron should not interfere with the daily absorption of other micronutrients in foods (i.e. zinc).

Currently the International Iron Nutrition Program (IINP) of the United Nations University (UNU) in coordination with WHO, UNICEF, IDRC (Canada), the Micro Nutrient Initiative (Canada), USAID and local organisations is conducting a series of field studies to test further the effectiveness of weekly iron doses in different population groups (children, adolescent girls, women of fertile age and pregnant women) in various countries. A list of projects and their stages of development is provided in a following section of this publication.

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IMPACT OF MATERNAL INFECTION ON FOETAL GROWTH AND NUTRITION

by Andrew Tomkins, Susan Murray, Patricia Rondo and Suzanne Filteau, Centre for International Child Health, Institute of Child Health, University of London, United Kingdom.

The Disadvantages of Being Born Small

Fetal growth and birth weight are increasingly being considered as crucial markers of future health status during infancy, childhood and adult life. For many years it has been recognised that children with a low birth weight (<2.5 kgs) have an increased risk of infection and death during the neonatal period and infancy. There are broadly two types of low birth weight (LBW) - those babies that are prematurely born (pre-term) and those that are small for their gestational age, often termed IUGR (intrauterine growth retarded). Most published population data on the prevalence of LBW in developing countries does not distinguish between pre-term babies and babies with IUGR. Where studies have separated the two types, it appears that IUGR is by far the commoner form of LBW. Those babies which are born prematurely and are also small for their gestational age have the worst prognosis. Several studies have also emphasised the importance of low birth weight on cognitive function, psycho-motor development and physical growth in childhood. There is now increasing evidence that LBW is associated with an increased prevalence of diseases such as diabetes, hypertension, ischaemic heart disease and stroke in adult life.

The Multiple Causes of IUGR

Many studies have been performed comparing the characteristics of mothers whose babies have IUGR with those whose babies have appropriate weights for their gestational age (AGA). The relative importance of the various risk markers in determining birth weight varies between populations and communities, and there is a considerable problem of 'confounding'. Nevertheless there are certain key groups of maternal risk markers which require consideration in making policies and plans to reduce the prevalence of IUGR.

Table of Maternal Risk Markers for IUGR

1. Anthropometry (e.g, maternal height, body mass index, pre-pregnancy weight)