Iron Balance in Pregnancy

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The only period of life in which daily iron requirements per unit of body-weight attain magnitudes approaching those of pregnancy is from the sixth to the twelfth month of infancy. Evaluation of iron balance is facilitated by critical analysis of the factors determining the iron requirements, the absorption of dietary iron, and the physiological adaptations relating to iron balance.

IRON REQUIREMENTS IN PREGNANCY

Iron is required for the fetus, the placenta, the increase of the maternal red cell mass, and for covering basal iron losses by the mother (1). Assuming that basal iron losses due to the exfoliation of cells from external and internal surfaces are unchanged in pregnancy, they can be estimated at 0.8 mg/day × 300; i.e., 240 mg for the whole period of pregnancy.

The term infant contains about 300 mg iron; the placenta, together with the umbilical cord, about 50 mg. The iron content of the fetus is determined by its size (Fig. 1). The amount of blood in the placenta at delivery depends very much on the technique used.

The plasma volume of the mother starts to increase early in pregnancy, probably at the sixth to eighth week. It then continues to increase during pregnancy, but at a slower rate. The mean increase from a large number of series was 42% (2,3). The red cell mass starts to increase at the end of the fourth month. A rather sudden doubling of reticulocytes is then observed, which continues throughout pregnancy (4). Provided that iron is available, this corresponds to an almost linear increase of the red cell mass (4,5). The increase in the red cell mass corresponds in turn to a 450-mg increase in circulating hemoglobin iron. The total iron requirements during a normal pregnancy are thus about 1000 mg (Table 1).

In peripheral blood, the increase in plasma volume and red cell mass is
reflected in an initial parallel decrease in hemoglobin (Hb) concentrations and hematocrit (4,5). In women with no iron stores and not supplemented with iron, Hb continues to decrease almost throughout pregnancy. In women with iron stores and in those given adequate iron supplementation, the Hb decrease stops at about the sixteenth week, remains constant for about 2 months, and then increases, but not to nonpregnant levels. The same is valid for hematocrit (4).

The main problem for iron balance in pregnancy is that iron need is not equally distributed over its duration. The exponential growth of the fetus

### TABLE 1. Iron requirements in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Gross loss Fe (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td>300</td>
</tr>
<tr>
<td>Placenta</td>
<td>50</td>
</tr>
<tr>
<td>Expansion of maternal red cell mass</td>
<td>450</td>
</tr>
<tr>
<td>Basal iron losses</td>
<td>240</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>1,040</td>
</tr>
<tr>
<td>At delivery:</td>
<td></td>
</tr>
<tr>
<td>Contraction of maternal red cell mass</td>
<td>+450</td>
</tr>
<tr>
<td>Maternal blood loss</td>
<td>−250</td>
</tr>
<tr>
<td>Net gain</td>
<td>+200</td>
</tr>
<tr>
<td><strong>Net total losses:</strong></td>
<td>840</td>
</tr>
</tbody>
</table>
FIG. 2. Daily iron requirements in pregnancy.

implies that fetal and placental iron requirements in the first trimester are almost negligible and that more than 80% of these requirements relate to the last trimester (6).

The increase in the red cell mass (hemoglobin iron) is almost linear from about the twentieth week and requires 3.2 mg iron daily (450 mg/140 day) (4,5). As shown in Fig. 2, the daily iron requirements in pregnancy increase from 0.8 mg (after cessation of menstruation) to about 10 to 12 mg in the last month of pregnancy.

In the balance calculations the iron loss due to bleeding at delivery and in the puerperium must also be considered. Several studies have been made to measure these losses (7–9). They were probably underestimated in earlier studies. In an extensive study with an adequate sampling technique, the mean blood loss in primiparas was 691 ml and in multiparas 494 ml, corresponding to an iron loss of about 300 mg and 200 mg iron, respectively (9). These iron losses are balanced by the return of iron from the gradually declining maternal red cell mass (450 mg) (Table 1).

In lactating women, iron requirements consist of daily basal iron losses (0.8 mg) and daily secretion of about 0.3 mg iron into breast milk (10), i.e., a total of 1.1 mg/day. This is thus less than the average iron requirements in menstruating women (0.8 + 0.6 mg = 1.4 mg/day).

IRON ABSORPTION IN PREGNANCY

Dietary iron absorption in pregnancy is determined by the following: (a) the amount of iron in the diet; (b) the meal composition, i.e., the bioavailability of the dietary iron determined by the balance between factors enhancing and inhibiting iron absorption; and (c) the changes in iron absorption during pregnancy. Several studies show that there are no systematic changes in the diet during pregnancy. In a study from our laboratory (11) using re-
peated 4-day dietary records from the 11th to the 37th week of gestation in 94 pregnant women, no change in the intake of energy or iron was observed. A study on the distribution of energy by groups of foodstuffs during pregnancy also showed that there was no change in the composition of the diet during pregnancy, and no difference was seen on comparing pregnant and nonpregnant women.

Iron absorption, however, changes during pregnancy. In an extensive study by Hahn et al. (12) in 466 pregnant women, it was observed that iron absorption increased. An iron salt was given at different times during pregnancy, the dose levels of elemental iron ranging from 1.8 to 120 mg. At dose levels between 1.8 and 9.0 mg, there was a fourfold increase in absorption. In another study (13), also using an iron salt (0.56 mg Fe), there was a doubling of the iron absorption from the fourth to the last month of pregnancy. In both studies the absorption was measured once in each woman. In a longitudinal study (14) on 22 healthy pregnant women, four measurements of nonheme iron absorption from a standardized meal were taken using an extremely sensitive whole-body counter. When compared with nonpregnant iron-replete women (3.1%), there was observed to be a 50% increase at the 24th week (4.5%) and a threefold increase at the 36th week (13.5%). At 9 weeks postpartum the absorption was double (6.5%) that of the control group of nonpregnant women given the same meal. An unexpected finding was a marked decrease of iron absorption in early pregnancy (0.8%). This observation was confirmed in 17 pregnant women who had been granted legal abortion. The abortion was measured both before the twelfth week of gestation and 2 months after abortion. A 50% lower absorption of iron was seen in early pregnancy from both a standard meal and a small dose of inorganic iron (3 mg Fe), despite the iron status being almost the same at both times. The only significant difference was the lower level of Hb 122 g/liter in early pregnancy compared with that of 133 g/liter 2 months after abortion (15). The absorption noted at the 24th week probably corresponds roughly to the absorption seen in borderline iron-deficient subjects, whereas the absorption seen at the 36th week probably represents maximal absorption, which is two and one-half to three times higher. This is the same degree of absorption as that seen in patients with iron-deficiency anemia.

A study in young Swedish men rendered anemic by repeated phlebotomy showed over some months a hemoglobin regeneration that corresponded to a dietary iron absorption of 4.8 mg from a similar diet containing an average of 2,675 kcal. At an intake of 2,000 kcal this corresponds to a daily iron absorption of 3.6 mg (16). Since the iron absorption in borderline iron-deficient subjects is about half of this, it is estimated that at the 24th week of pregnancy the average absorption from a similar diet would be about 1.8 mg/day, and three times higher at the end, i.e., 5.4 mg/day. Based on these considerations, a curve was drawn in Fig. 3 corresponding to the assumed iron absorption from the average Swedish diet. The main point of this graph
Iron requirements in pregnancy are too high to be covered by absorption from diet alone. It is obvious that nature has not tried to solve the critical iron balance situation in pregnancy by increasing iron absorption in the first half of pregnancy, when iron requirements are low. The only natural or fully physiological solution to filling iron requirements in pregnancy would thus be to use iron stores. As seen from the above calculations, about 500 mg
would be needed. The problem today, however, is that very few women, if any, have iron stores of this magnitude.

According to bone marrow examinations and serum ferritin measurements, about 30% of young women in Sweden have no iron stores at all (17). A similar figure is reported from Finland (18). No iron stores (subnormal serum ferritin) were observed in 16% of continental Frenchwomen, but in migrant women this figure was 40.5% (19). In the recent NHANES II study in the United States subnormal serum ferritin values were seen in 14.2% of girls aged 15 to 19 years and in 9.6% of women aged 20 to 44 years (20). Phlebotomy studies in college women in the United States showed that the average amount of stored iron in this socioeconomically privileged group was about 250 to 300 mg (21). Calculations based on serum ferritin measurements in U.S. women give an average figure for iron stores around 250 mg (22).

Present knowledge about the amount of stored iron implies that considerable numbers of pregnant women in many populations of highly developed industrialized countries, at least in Europe, have deficits of iron that cannot be covered by diet. These range from 400 to 500 mg. As previously mentioned, the deficits are mainly related to the second half of pregnancy and thus correspond to a deficit of about 3 mg/day.

At first glance, it may seem biologically unreasonable that nature has not made better provision for the iron balance situation in pregnant women. It should be remembered, however, that in early humans, the diet had probably not only a higher iron content but also a higher bioavailability of this element. This would have been due to a much higher intake of foods enhancing iron absorption, such as meat, vegetables, and fruits with a high content of ascorbic acid. It has been estimated that meat supplied some 35% of the energy and that about 400 mg ascorbic acid were included in meals. A “guesstimate” of the iron absorption from such a diet would be that the iron deficit is reduced to 300 mg. After delivery the reduction of the maternal red cell mass supplies 450 mg iron from which the blood loss at delivery and in the puerperium should be subtracted (average 250 mg). This gives a net supply after delivery of about 200 mg to the iron stores of the mother.

In the early days of the human race, restitution of iron stores to a magnitude of about 300 mg could probably be easily achieved during the lactation period; only 100 mg extra iron had to be absorbed during a period of, for example, 6 months, or 200 days, i.e., 0.5 mg iron more had to be absorbed than the 1.1 mg needed to cover basal iron losses (0.8 mg) and iron lost in milk (0.3 mg), i.e., a total of 1.6 mg/d. These calculations are not to illustrate that nature is “unwise,” but rather that nature has had neither the chance nor the time to adjust the regulatory mechanisms of iron absorption in women to our present way of living. The word “present” in this context may represent merely the last 10,000 years, or even the last few hundred years, of the several million years of our evolution.
Furthermore, in present-day woman, 200 mg iron are returned to the iron stores after delivery, provided that she is iron replete at term. In order to achieve the 400 to 500 mg storage iron needed at the start of the next pregnancy, several months or even years are required with our present kind of diet. For women with very low menstrual blood losses it may be achieved within a year or two; for those with more marked menstrual losses, iron stores of this magnitude are unattainable with the present diet and low energy expenditure.

Physiological Adaptations in Pregnancy Related to the Iron Balance Situation

There is no obvious explanation for the marked plasma volume changes in pregnancy. It is not known if hormonal factors in early pregnancy change peripheral vascular tone and directly or indirectly affect receptors for blood volume regulation. The development of the so-called physiological anemia of pregnancy (even in iron-replete women over the first 5 months) has always been explained by this plasma volume increase, which at 5 months amounts to more than 40%. This is more of a description than an explanation. A decrease in hematocrit lowers the viscosity of the blood but also reduces the oxygen-carrying capacity per volume of blood. Both clinical and experimental studies on the effect of hypervolemia on oxygen transport have shown that the optimal hematocrit for oxygen transport is clearly higher than normal in hypervolemic states (24,25). Moreover, the oxygen need of the fetus is low in early pregnancy. It is thus improbable that the initial increase of the plasma volume and the resulting dilution anemia is a physiological adaptation to improve oxygen transfer to the fetus. It is also a puzzle why the reduction of the hemoglobin concentration induced by the plasma volume increase is not counterbalanced by erythropoiesis. Normally, a lowering of the hemoglobin concentration leads to increased erythropoiesis; however, a careful longitudinal study in 45 pregnant women (44) showed that the red cell mass at 12 weeks gestation is reduced by about 100 ml (9%), indicating a suppression of erythropoiesis in early pregnancy. This observation cannot explain the more marked anemia, but it is interesting in relation to the reduction observed in iron absorption in early pregnancy.

There may be different explanations for the decrease in Hb levels in early pregnancy:

1. A shift of the oxygen dissociation curve of Hb by an increased level of 2,3-diglycerophosphate (DGP) in the red cells.
2. A change in the setting of the cells in the kidney, translating oxygen pressure into erythropoietin synthesis, a possible hormonal effect.

It is well documented that in the second half of pregnancy there is increased
erythropoietic activity, and raised levels of reticulocytes (4,26) and erythropoietin (26,27) have also been observed. In normal subjects there is a very good linear relationship between the basal oxygen consumption and the red cell mass. In pregnancy there is a significant downward displacement of this regression line, implying that the same oxygen transport can be achieved with a red cell mass that is on average smaller by 168 ml (28) (Fig. 4). This suggests that the delivery of oxygen to the periphery is in some way facilitated in pregnancy. As previously mentioned, this improvement cannot be explained by the physiological reduction of hematocrit, which is also observed in iron-replete, iron-supplemented women at this stage of pregnancy. This implies that the oxygen delivery to the tissues from hemoglobin is facilitated either by the Bohr effect (e.g., an increased $P_{CO_2}$ in placenta), or by a higher content of 2,3 DPG in red cells. The lowered hemoglobin level and the improved oxygen delivery in pregnancy can both be explained by an increased content of 2,3 DPG per mole hemoglobin in the red cells. Such an increase has been reported by several investigators (29,30), and in one extensive study a significant rise was observed early in pregnancy (30). The increase of 2,3 DPG may partly or fully explain the initial "physiological anemia" of pregnancy. The cause of the 2,3 DPG increase is unknown, but it is most likely a hormonal effect. It should be mentioned that there is a rapid drop in the 2,3-DPG level after delivery. This adjustment must be considered as a rational measure of nature to facilitate oxygen delivery to the fetus. Another advantage is that less extra iron is needed to achieve an optimal increase of the red cell mass.

**FIG. 4.** Relationship between basal oxygen consumption and red cell mass in pregnant and nonpregnant women. Pregnant women need 168 ml less red cells to transport the same amount of oxygen. [Adapted from Flanagan et al. (28).]
As previously mentioned, the adaptation of iron absorption to the needs of pregnancy is insufficient for present-day requirements and modern diet, but it was probably quite adequate in early humans. There was then a good margin of safety to ensure iron supply to both mother and fetus. This adaptation might have been adequate until recently. Changes in life style in the past few generations, however, with marked reduction in energy expenditure, lead to a lower intake of energy and nutrients. These are often below the physiological needs of the human body.

It is interesting to note how the present calculations show that early humans also needed the ferritin molecule in order to store iron and to ensure an adequate iron balance in pregnancy. The difference, however, was that early humans needed only about 300 mg in iron stores (but had probably more), whereas women today need about 500 mg but have less because of the different diet.

IRON SUPPLEMENTATION

Few women in industrialized countries today have iron stores of such magnitude that iron requirements in pregnancy can be met by the diet and iron stores. Supplementation with iron is therefore needed. The following questions then arise: Should all pregnant women be given iron or only those who develop signs of iron deficiency? Do we have good laboratory methods to identify all those who are, or will become, borderline iron-deficient cases? Is iron supplementation of advantage to such women, or are risks involved?

In one study (31) on more than 50,000 consecutive pregnancies, a U-shaped relationship was found between maternal hemoglobin levels and outcome of pregnancy (medical abnormalities, fetal death, low birthweight, and prematurity). Hematocrits below 29% and above 39% were especially disadvantageous. A simple division of the subjects into smokers and nonsmokers did not explain the results.

In another study (32) on 54,383 pregnancies it was also found that both low hemoglobin levels (<104 g/liter) and high concentrations (>132 g/liter) were associated with an adverse outcome. In U-shaped relationships there are always reasons to assume that various factors act at both ends. At the lower hemoglobin end it is reasonable to assume that deficiencies in iron and folate play a role. Chronic infections may also be considered. At the high end a clear relation was found between hemoglobin levels and hypertension. It has been reported by others that there is a less marked increase in plasma volume in those who are hypertensive (2).

Reduced plasma volume is also seen in essential hypertension (33). In a population sample of 1,152 women a significant relationship \( (P < 0.001) \) was found between blood pressure and hemoglobin level (C. Bengtsson and L. Lapidus, personal communication). It is reasonable to assume that factors
causing hypertension and eclampsia also influence the size of the vascular bed, i.e., the plasma volume. It is thus improbable that it is the higher hemoglobin level per se that is deleterious, but rather its cause. It should be noted that the high hemoglobin levels associated with increased risk of complications are mainly within the normal range of hemoglobin levels in women and that such hemoglobin levels per se improve rather than impair oxygen transfer to the fetus. Several studies have shown a clear relation between hemoglobin levels and smoking, especially heavy smoking (34–37). In the two epidemiological studies mentioned above, a simple division of the material into smokers and nonsmokers did not explain the results. There are good reasons to believe that the cause of hemoglobin increase in smokers is related to the concentration of carbon monoxide hemoglobin, which is in turn related to the degree of smoking. That heavy smoking might be one contributory factor to the association between higher hemoglobin levels and pregnancy outcome cannot be excluded. Other such factors, not examined in the two studies, are the presence of chronic bronchitis and the intake of drugs such as diuretics.

Another problem relating to the question of whether or not all pregnant women should be given iron is the accuracy in identifying those who are borderline iron deficient. It is well known that in all laboratory methods used to study iron status, there is considerable overlap between normal and iron-deficient subjects. This is even more valid in pregnancy. For example, there is an early increase in the total iron-binding capacity in serum that makes determinations of TIBC and serum iron more difficult to evaluate.

It has been suggested that serum ferritin could be used to identify pregnant women who need iron supplementation (38), particularly by making repeated determinations at regular intervals in the second half of pregnancy (39); however, all studies show considerable overlap in ferritin levels between those who develop anemia and those who remain within the normal hemoglobin range (40,41). Explanations may be that the hemoglobin level per se is a poor indicator of iron status; that the correlation between iron stores and serum ferritin is not sufficiently high in the normal range and is thus not a good predictor of iron status in the single individual; and that serum ferritin may often provide misleading information about iron status in a non-steady-state iron balance situation such as pregnancy.

Taking these facts into consideration, it would seem unreasonable to give iron supplementation only to those who show clear evidence of iron deficiency. Such management of pregnant women would actually imply that iron supplementation would be withheld from many women with true, if undetectable, iron deficiency. I would consider this less safe, and thus less ethical, than giving extra iron to a few women who might not need it, especially since the iron requirement of women during the fertile age is high.

It is understandable, however, that there are those who are of the opinion that it is unnecessary, or even unphysiological, to give supplements to
healthy women in the physiological state of pregnancy (42), and that iron should not be given "unless there is a clear and specific clinical indication" (43). It has even been questioned whether the increase in red cell mass in pregnancy corresponding to about 450 mg iron really is a physiological response and not a pharmacological effect of high doses of iron supplements. There is, however, no support for the view that in iron-replete subjects administration of an iron supplement or parenteral iron would stimulate erythropoiesis and increase the red cell mass (45). The previously mentioned close relationship between the increase in basal oxygen consumption and red cell mass in pregnant women is one of the strong arguments that the increase of the red cell mass in pregnancy is a truly physiological adaptation.

Seen in the light of the longer time perspective of human development, iron supplementation in pregnancy should be regarded as a necessary measure to compensate for the nutritional consequences of our present low-energy life style and choice of food. Moreover, it is unreasonable to believe that it would be dangerous to give extra iron in the last half of pregnancy in order to achieve the iron balance normal in our ancestors. My firm conclusion is thus that all pregnant women should be given iron supplementation.

REFERENCES


