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## THE CONSEQUENCES OF IRON DEFICIENCY AND ANEMIA IN PREGNANCY\*

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### THE NATURE OF THE PROBLEM

Iron deficiency and its consequent anemia is recognized as the most prevalent specific nutrient deficiency in the world. It is estimated that about 2.15 billion people are iron deficient (WHO, 1991) and that this deficiency is severe enough to cause anemia in 1.2 billion people globally (Viteri, 1991). About 90% of all anemias are due to lack of iron, affecting mostly the developing world where nearly 1/3 of the population is iron deficient. However, the industrial world is not free from it: 11% of its population has iron deficiency (WHO, 1991; Viteri, 1991).

Roughly 47% of non-pregnant women and 60% of pregnant women are anemic worldwide (Royston, 1982). In the industrial world as a whole anemia prevalence during pregnancy oscillates between 9 and 14% for the same age-sex categories, although the poor among these societies are more affected.

Focusing on women of fertile age and pregnant women, their vulnerability for incurring negative iron balance is due to their increased iron needs because of menstruation and the substantial iron demands of pregnancy (INACG, 1981). Median iron requirements 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/day, and 5% require as much as 2.84 mg/day. In menstruating teen-age girls, the superimposition of menstrual losses and growth increases the demands for absorbed iron to keep a balance; 30% of these girls require more than 2.0 mg of iron, 20% require 2.23 mg, 10% as much as 2.65 mg, and 5% 3.21 mg. There is a small proportion of women and girls that "normally" requires as much as 5.0 mg of iron per day. These requirements are very difficult to satisfy even with good quality diets.

\* This presentation cannot be an exhaustive review of the physiological changes in pregnancy and the repercussions that iron deficiency and anemia have on such functions and on the outcome of pregnancy. It intends to present areas of controversy and tries to suggest important areas of needed research. Some difficult choices had to be made in selecting references for the topics covered. The author apologizes for not always quoting all the significant work done by excellent investigators in this complex field.

While intrauterine device users almost double their iron menstrual loss (Guillebaud et al., 1976), women using anovulatory contraceptive methods reduce it by almost half (Nilsson et al., 1967). Importantly, multiparous women tend to have greater menstrual losses that increase with parity (Rybo, 1973).

Total iron requirements during pregnancy have been estimated by the factorial method, where iron needs are the sum of the iron contents of the baby and the placenta at term, the maintenance needs in the absence of menstruation, the physiological expansion of the total circulating hemoglobin mass, and the total losses through intrapartum hemorrhage and lochia (INACG, 1981; Hytten and Leitch, 1971). The iron demands during the first trimester of pregnancy are actually lower than they are prior to pregnancy, but they markedly increase during the second trimester mainly due to the expansion of blood volume and hemoglobin mass that normally begins at the 16th week of pregnancy and progresses almost linearly up to term. Feto-placental deposition of iron increases markedly during the third trimester (Hytten and Leitch, 1971). Approximate estimates of the total iron costs of pregnancy range from 480 to 1150 mg above those pre-pregnancy depending on the amounts assigned to the different factors contributing to the calculation shown in Table 1.

Many of these amounts are approximations based on estimations or actual determinations of iron contents of the different factors in the above equation (Hytten and Leitch, 1971; Widdowson et al., 1951; Singla et al., 1985; Hallberg, 1988). If these added needs are distributed equally throughout the 280 days of a normal pregnancy, a daily extra iron absorption of 1.28 mg (for a total daily iron absorption of 2.82 mg) would cover all the median needs of pregnancy. However, as was seen before, iron needs evolve throughout pregnancy so that during the second and third trimesters of pregnancy, median daily needs increase up to an average of 5.6 mg/day (that is, 4.1 mg above median pre-pregnancy needs). The approximate range would be 3.54 and 8.80 mg/day.

The question that arises from this brief summary of iron needs during pregnancy is: can women go through pregnancy without becoming iron deficient? The answer is yes but under the following conditions:

a) That dietary iron is abundant and highly absorbable. The diet needs to be rich in heme iron, animal protein and ascorbic acid, and low in inhibitors of iron absorption (Hallberg, 1988; FAO/WHO, 1988). Iron-fortified staples would also contribute.

Svanberg et al. (1975) reported mean non-heme-iron absorption levels between 12 and 14% in 3rd trimester pregnant women ingesting a mixed Swedish diet containing 17 mg of

Table 1. 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 450 mg.

## Consequences of Iron Deficiency and Anemia

iron of which 1-2 mg were heme iron. The upper quartile of absorption in this situation would be around 395 mg in the last trimester that period would be near 566 mg. This would be even greater.

b) That pre-pregnancy iron stores are negative iron balance. Close to 40% have these levels of iron stores (Cocroft). Estimates of iron stores among women who disclose that only a minority have adequate iron during pregnancy (Franzetti et al., 1971) in Scandinavia about 30% of fertile women.

In conclusion, iron deficiency is common in malnourished populations because of the fact that pregnancy begins with inadequate iron stores.

Iron deficiency during lactation and delivery. Iron in breast milk and nursing (Lonnnerdal, 1984). If breast-feeding amenorrhea lasts about 4 months, iron stores will reach some alleviation of the existing iron deficiency. If lactation continues, iron stores will reach a median of about 1.81 mg/c. In a developing world may not be sufficient.

## CONSEQUENCES OF IRON DEFICIENCY

When iron deficiency and anemia are documented negative effects to the mother will be considered in that order.

### 1. Negative Effects on the Mother

a) **Reproduction-Related Mortality**—The risk of death during the perinatal period as a result of iron deficiency (1962). It has been estimated that child deaths during puerperium occur every year, the vast majority of which are contributory or sole cause of death. The severity of the problem are statistically significant: almost all maternal deaths (Alauddin, 1965) increase in the risk of maternal death (Llewellyn-Jones, 1965).

The risk of death in the perinatal period (hemoglobin concentration below 40 g/L) among women whose anemia is not corrected will point out that severe anemia is generally a health condition in the developing world.

iron menstrual loss (Guillebaud et al., 1988). It is possible to reduce it by almost half (Nilsson et al., 1988). The greater menstrual losses that increase

are estimated by the factorial method, the needs of the baby and the placenta at term, the physiological expansion of the total blood volume during the first trimester of pregnancy, but they markedly increase during the second trimester and the third trimester (Hyttén and Leitch, 1971; Nilsson et al., 1988). The needs of pregnancy range from 480 to 900 mg of iron assigned to the different factors

are estimations or actual determinations of iron needs during pregnancy is: can it be sufficient? The answer is yes but under certain conditions. The diet needs to be rich in heme iron and iron absorption (Hallberg, 1988; Nilsson et al., 1988). If these added needs are met during pregnancy, a daily extra iron absorption would cover all the median needs of pregnancy throughout pregnancy so that the median daily needs increase up to an amount (2-3 times pregnancy needs). The approximate

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of iron needs during pregnancy is: can it be sufficient? The answer is yes but under

pregnancy

grams of iron
Median
270
80
250
200*
190
990
200
790

\*women this value is 450 mg.

iron of which 1-2 mg were heme iron. Importantly, 25% of the women absorbed more than 20% of the non-heme dietary iron. Total iron absorption could be as high as 5 mg/day in the upper quartile of absorption in this study, considering also heme iron absorption. In the second trimester mean non-heme iron absorption was 5.8%. With these data, mean iron absorption would be around 395 mg in the last two trimesters of pregnancy, and median iron balance for that period would be near -566 mg. If the diet is of poor quality, the negative balance would be even greater.

b) That pre-pregnancy iron stores approach 500 mg to buffer the previously estimated negative iron balance. Close to 40% of the U. S. population of women of reproductive age have these levels of iron stores (Cook et al., 1986), while the average is about 250-300 mg. Estimates of iron stores among women of reproductive age in different parts of the world disclose that only a minority have adequate iron reserves to protect them from iron deficiency during pregnancy (Franzetti et al., 1984; Calvo and Sosa, 1991; Hercberg et al., 1990). Even in Scandinavia about 30% of fertile age women have no iron stores (Rybo, 1985).

In conclusion, iron deficiency during pregnancy is common even among otherwise well nourished populations because of the reasons reviewed above. The risk of iron deficiency in pregnancy begins with inadequate iron reserves prior to pregnancy.

Iron deficiency during lactation is mostly a residual from that resulting from pregnancy and delivery. Iron in breast milk amounts to between 0.20 and 0.40 mg/day during optimal nursing (Lonnerdal, 1984). If breast feeding is exclusive for 6 months and postpartum amenorrhea lasts about 4 months, iron requirements are between 1 and 1.2 mg/day, permitting some alleviation of the existing iron deficit simply by dietary means. However, once menstruation returns, if lactation continues, iron requirements become higher (by about 0.3 mg/day) 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 fulfill these needs (FAO/WHO, 1988).

## CONSEQUENCES OF IRON DEFICIENCY AND ANEMIA IN PREGNANCY

When iron deficiency and anemia are prevalent among pregnant populations several well documented negative effects to the mother and her offspring have been documented. These will be considered in that order.

### 1. Negative Effects on the Mother during Pregnancy and the Perinatal Period

a) **Reproduction-Related Mortality.** The anemic pregnant woman is at greater risk of death during the perinatal period as has been clearly shown by the World Health Organization (1962). It has been estimated that close to 500,000 maternal deaths ascribed to childbirth and puerperium occur every year, the vast majority in the developing world. Anemia is the major contributory or sole cause of death in 20-40% of such deaths. Alarming examples of the severity of the problem are statistics from rural Bangladesh that show anemia as a factor in almost all maternal deaths (Alauddin, 1986) and studies in Malaysia that point out a 5-fold increase in the risk of maternal death related to pregnancy and delivery among anemic women (Llewellyn-Jones, 1965).

The risk of death in the perinatal period increases dramatically in severe anemia (hemoglobin concentration below 40 g/L) reaching average figures of 11.25% in contrast to 4.6% among women whose anemia is not severe (Hughes, 1991; Harrison, 1982). It is important to point out that severe anemia is generally associated with very poor overall socioeconomic and health conditions in the developing world. As a rule malaria, other infections, and multiple

nutritional deficiencies, including folate and vitamin A are also endemic (Fleming, 1981 & 1986). However, even in the British Isles moderate anemia (hemoglobin below 89 g/L) doubled the risk of perinatal deaths as recently as 1958 (Butler and Bonham, 1963).

**b) Performance during Pregnancy and Delivery.** There is now convincing evidence that iron-deficient anemic women have shorter pregnancies than non-anemic or even anemic but not iron-deficient pregnant women. In an elegant prospective study by Scholl et al. (1992) anemic pregnant women had an adjusted odds ratio (AOR) of 1.3 [95% confidence interval (CI) 0.86–2.24] for preterm delivery in relation to non-anemic women. The iron-deficient anemic group had an AOR of 2.66, CI 1.15–6.17; 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 preterm 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 (weight/height-squared). The effects of bleeding and anemia were additive for preterm delivery only, reaching an AOR of 4.98 (CI 2.92–8.48) among iron-deficient anemics. There was no increase in risk of small for gestational age babies, although the AOR for inadequate gestational weight gain (for gestational age) was significantly higher for all anemic cases particularly those that were iron deficient (AOR = 2.67, CI = 1.13–6.30). Possible confoundings still left after adjusting for the variables listed above were those of inadequate weight gain and lower overall intakes (reflected in lower energy and iron intakes) among the iron-deficient anemics. Inadequate weight gain has also been associated with preterm delivery (Abrams, 1989).

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 preterm deliveries (Rush, 1988) and that anemia, irrespective of cause, as well as elevated hemoglobin levels were associated with increased risk of preterm delivery (Garn et al., 1981b; Murphy et al., 1986). The more severe the anemia the greater the risk of low-birth-weight (Harrison et al., 1973).

Delivery demands severe physical effort and most often a great deal of endurance; yet, to my knowledge, there is no direct information on the effect of anemia on performance during delivery. There is indirect evidence that physically fit women (almost an impossibility in the face of severe anemia) perform better and have fewer complications during delivery than do less fit women (Erkkola, 1976). In severe anemia, cardiac failure during labor, which reflects an overpowering burden on physiological reserves, is a major cause of death (Hughes, 1991).

**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 even milk composition, both in terms of macro- and micronutrients (including iron and its physicochemical status) appears to be fundamentally preserved (Murray et al., 1978; Lonnerdal et al., 1976). There is some degree of controversy regarding this last point, but even where evidence for reduced milk iron among iron-deficient mothers is found, the level of reduction is small and iron supplementation produces small changes, if any (Mbofung and Atinmo, 1986).

**d) Working Capacity.** There are no 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. This lack of information is particularly worrisome when it is realized that in many parts of the world women, pregnant or not, are routinely engaged in labor-intensive activities, such as agricultural work, gathering fuel and water for home

consumption, etc. (IOM, 1992). Pre decrements in maximal aerobic capac:

There is evidence that, except for half of pregnancy expends more energy whether pregnancy decreases, does not physical activity. Most data show that daily physical activity than before. T work-related activities or only "disc decline in spontaneous activity is di advanced pregnancy, is open to debat

**e) Immunological Competence** tation of the immune system to acc structure rather than rejecting it. T "suppression" of immunity: i) local mechanisms, and ii) hormone-media their actions at tissue antigen/receptor tissue and humoral defense mechanism There are indications, however, that and that pregnant serum is able to alt al., 1972).

Locally, hormone-sensitive ute immuno globulins including secreto cervical inflammatory infiltrates may cervical infections are more common cycle (Carroll et al., 1973). Also, gn infections during pregnancy has been However, the lack of information on severity of different infections during

Two studies in India (Prema et al.: anemic as well as iron deficient preg is reversible with iron treatment. A documentation of folate nutrition.

## 2. Negative Effects on the Concept

**a) Health and Development.** normal (Wingard et al., 1976), an associated with malaria. Larger plac same phenomenon is seen in smoker

Favorable pregnancy outcomes studies, one in the U. S. involving Project, and the other in Cardiff, Wal over 54,000 pregnancies. Both studi premature deaths, and low birth wei mothers with hemoglobin and hematc among mothers who had anemia in t Previously, significant correlations t birth weight had been found but wer

are also endemic (Fleming, 1981 & a (hemoglobin below 89 g/L) doubled and Bonham, 1963).

There is now convincing evidence that iron deficiency is more common in anemic women than non-anemic or even anemic women. A prospective study by Scholl et al. (1992) found an OR of 1.3 [95% confidence interval 1.1-1.5] for iron-deficient non-anemic women. The iron-deficient non-anemics did not differ from the controls after controlling for maternal age, parity, gestational age at entry to health care, gestational weight gain, and pre-pregnancy body mass index. Iron deficiency and anemia were additive for OR of 1.8 (95% CI 1.3-2.4) among iron-deficient anemics. Iron deficiency was also additive for OR of 1.8 (95% CI 1.3-2.4) among iron-deficient anemic women. The AOR for iron deficiency was significantly higher for all anemic women (OR = 2.67, CI = 1.13-6.30). Possible reasons for the findings listed above were those of inadequate iron intake (low iron energy and iron intakes) among the iron-deficient women. It has been associated with preterm delivery

and low birth weight. In a study by Odeh et al. (1988), iron deficiency was associated with better newborn weight (OR = 1.3, 95% CI 1.1-1.5) and that anemia, irrespective of iron deficiency, was associated with increased risk of preterm delivery (OR = 1.3, 95% CI 1.1-1.5). The more severe the anemia the greater the risk of preterm delivery.

Iron deficiency is most often a great deal of endurance; iron deficiency has the effect of anemia on performance. Iron deficiency in physically fit women (almost an impossibility) results in fewer complications during delivery. Iron deficiency, cardiac failure during labor, and low iron reserves, is a major cause of death during pregnancy.

It is clear that iron-deficient or anemic mothers have a greater risk in the process of lactation, and even milk production (including iron and its physicochemistry) is affected (Lonnerdal et al., 1978; Lonnerdal et al., 1976). At this point, but even where evidence for iron deficiency, the level of reduction is small and iron deficiency (Aboung and Atinmo, 1986).

The effect of anemia and iron deficiency on work in relation to non-anemic, iron deficiency is particularly worrisome when it is iron deficiency or not, are routinely engaged in gathering fuel and water for home

consumption, etc. (IOM, 1992). Pregnant women in the third trimester have consistent decrements in maximal aerobic capacity (Artal and Wiswell, 1986).

There is evidence that, except for upper body activity, the pregnant woman in the second half of pregnancy expends more energy in performing work, but there is lack of agreement on whether pregnancy decreases, does not modify, or increases the efficiency of movement and physical activity. Most data show that women in advanced pregnancy expend less energy in daily physical activity than before. The question is whether this decline in activity includes work-related activities or only "discretionary" activities (IOM, 1992). How much of that decline in spontaneous activity is due to anemia, besides the logical cumbersomeness of advanced pregnancy, is open to debate.

**e) Immunological Competence.** Pregnancy is characterized by an extraordinary adaptation of the immune system to accept the conceptus with its unique genetic and antigenic structure rather than rejecting it. Two types of mechanisms have been implicated in this "suppression" of immunity: i) local ovum (trophoectoderm)-uterus (endometrium)-placental mechanisms, and ii) hormone-mediated systemic effects. Both mechanisms appear to exert their actions at tissue antigen/receptor mechanisms that have only minor effects on the general tissue and humoral defense mechanisms against viral and bacterial infections (Finn et al., 1972). There are indications, however, that during pregnancy cell-mediated immunity is depressed and that pregnant serum is able to alter lymphocyte receptors to mutagenic agents (Purtilo et al., 1972).

Locally, hormone-sensitive uterine defense mechanisms (production of a variety of immunoglobulins including secretory IgA by cervical epithelium and endometrium) and cervical inflammatory infiltrates may protect against topical infections. However, vaginal and cervical infections are more common during pregnancy than at other times in the reproductive cycle (Carroll et al., 1973). Also, greater susceptibility to tuberculosis, urinary and malarial infections during pregnancy has been well documented (McGregor, 1984; Lichtenstein, 1942). However, the lack of information on the impact of anemia and/or iron deficiency on rates and severity of different infections during pregnancy is appalling.

Two studies in India (Prema et al., 1982; Kandoi et al., 1991) demonstrate that severely 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.

## 2. Negative Effects on the Conceptus and the Infant

**a) Health and Development.** Placental weight at term in anemic women is higher than normal (Wingerd et al., 1976), and placental infarcted areas are seen in severe anemia associated with malaria. Larger placentae are viewed as compensatory for hypoxia, since the same phenomenon is seen in smokers and in populations residing at high altitudes.

Favorable pregnancy outcomes were less frequent among anemic mothers in two large studies, one in the U. S. involving over 59,000 pregnancies in the Collaborative Perinatal Project, and the other in Cardiff, Wales (Garn et al., 1981a & b; Murphy et al., 1986) involving over 54,000 pregnancies. Both studies found higher rates of fetal deaths and abnormalities, premature deaths, and low birth weight newborns among anemic mothers, as well as among mothers with hemoglobin and hematocrit levels above "normal." These risks were evident even among mothers who had anemia in the 1st or 2nd trimesters (before 24 weeks of pregnancy). Previously, significant correlations between the severity of anemia, premature birth, and low birth weight had been found but were far from definitive.

Still, the fact that iron deficiency anemia is more prevalent among the underprivileged and poorly nourished populations leaves some doubt about the magnitude of causality that can be attributed to iron deficiency and anemia, or the relative contribution of these interrelated variables, on preterm birth and low birth weight.

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 (Tucker et al., 1984; Pollitt, et al., 1989) that may result in poor mother-child interactions.

**b) Hematological Status and Iron Nutrition.** There is little evidence that mild maternal iron deficiency and anemia have significant repercussions on the hematological status of newborns. It has been suggested that the placenta with its avidity for maternal circulating iron through its richness in transferrin receptors (Huebers and Finch, 1987) protects 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 (Finch et al., 1983). Also, there is evidence that the fetus of an iron-deficient mother accumulates less iron reserves (Strauss, 1933) and has smaller circulating hemoglobin mass than its normal counterpart (Sisson and Lund, 1958; Ahmad et al., 1983). This "hidden iron deficit" is further magnified by the higher frequency of low birth weight mainly due to preterm delivery.

Important new evidence of "hidden iron deficiency" at birth is provided by de Benaze et al. (1989) who showed that maternal and cord serum ferritin levels were lower in the presence of maternal iron deficiency (a finding in agreement with several studies and in disagreement with several others), but more importantly, this difference was magnified when the children were again studied at two months of age. This observation strengthens the well documented higher prevalence of iron deficiency and anemia in late infancy among populations where anemia of pregnancy is highly prevalent, and raises the issue of increased risk of long term and even permanent impairments in mental and physical development among such children (Chwang et al., 1988; Lozoff et al., 1991).

I believe, with Rosso (1990), that the evidence for a negative repercussion of maternal iron status on the iron reserves of the fetus, the newborn and the infant is much stronger than the evidence to the contrary.

## PHYSIOLOGICAL ADAPTATIONS DURING PREGNANCY AND THE POSSIBLE EFFECTS OF IRON DEFICIENCY AND ANEMIA

### 1. Hematological Adaptations

Blood volume begins to increase slowly early in pregnancy because of expansion of the plasma volume and a reduction in circulating red cell mass. However, by the 15th-20th week both plasma and circulating red cell mass are increasing rapidly, the former reaching about 150% of pre-pregnancy plasma volume by the 30th-35th gestational week. Circulating red cell mass follows closely plasma expansion but is normally of lesser magnitude (maximum expansion is about 35-40%). During the last 5-10 weeks of pregnancy there is very little additional change in either of the two blood components (Chesley, 1972). These phenomena account for the well recognized drop in hemoglobin concentration and hematocrit during pregnancy ("physiological or dilutional anemia"). The exact mechanisms and signals that regulate these changes are not yet fully known.

The superimposition of fer results, as would be expected, in a diminution of all hematological parameters. It must be remembered that infection and hemoglobinopathies in alterations of biochemical indicators.

### 2. Cardio-respiratory Function:

The progesterone surge during pregnancy centers to  $P-CO_2$  and in increased ventilation by using inspiratory reserve volume. Residual volume is also decreased. In ventilation is as high as 40% above normal in oxygen consumption; therefore during pregnancy, a pattern of respiratory alkalosis (because of excess lactic acid production) and aerobic capacity and endurance to hypoxia (Hyttén and Leitner).

Maternal hemoglobin oxygen affinity (fetal hemoglobin's oxygen affinity to the left). Theoretical estimates indicate that they are relatively small in relation to the decrease in  $P-CO_2$  (Table 2).

Placental oxygen transfer in the environment regarding partial gas pressure in placenta in maternal anemia may result in hypoxia for the fetus. However, women (Anon, 1974).

In terms of gas exchange, transfer in pregnancy mostly due to arterio-venous fistulae (Boe, 1954).

Pregnancy is also characterized by a decrease in non-pregnant state) and in visceral (decreased over the whole vascular system) responsible for the increase in output,

Table 2. Estimated Changes in Hemoglobin Concentration at Different Hemoglobin Concentrations

[Hb, g/dL]
13
12
11
10
9
8
7
6

(Based on G.G. Power and P.S.)

ivalent among the underprivileged the magnitude of causality that can contribute of these interrelated

th weight child is at a disadvantage malnutrition, infection and death are due to the fact that iron deficiency affects brain function (Tucker et al., 1983) and child interactions.

There is little evidence that mild maternal iron deficiency on the hematological status of the fetus (Finch, 1987) protects the fetus. Fetal iron transfer from placenta to fetus is limited by a severe maternal iron deficiency and the fetus of an iron-deficient mother has a smaller circulating hemoglobin mass (Mead et al., 1983). This "hidden iron deficiency" is mainly due to preterm

at birth is provided by de Benaze et al. In several studies and in disagreement with the well documented increase in iron deficiency among populations where there is an increased risk of long term developmental delay among such children

a negative repercussion of maternal iron deficiency and the infant is much stronger than

## PREGNANCY AND THE CONSEQUENCES OF ANEMIA

Pregnancy because of expansion of the blood volume. However, by the 15th-20th week of pregnancy, rapidly, the former reaching about 50% of gestational week. Circulating red cell mass is of lesser magnitude (maximum increase during pregnancy there is very little increase) (Chesley, 1972). These phenomena affect hemoglobin concentration and hematocrit during pregnancy. The exact mechanisms and signals that

The superimposition of ferropenic anemia on the "adaptive" hematological changes results, as would be expected, in a limitation of red cell mass expansion and a more profound diminution of all hematological parameters with the typical characteristics associated with iron deficiency. It must be remembered that folate and other nutritional deficiencies as well as infection and hemoglobinopathies can alter the classical picture of ferropenic anemia or result in alterations of biochemical indicators mimicking iron deficiency.

### 2. Cardio-respiratory Functions and Physical Working Capacity

The progesterone surge during pregnancy results in enhanced sensitivity of the respiratory centers to  $P\text{-CO}_2$  and in increased ventilation by means of higher tidal volumes achieved mostly by using inspiratory reserve volumes as well as by lowering expiratory reserve volume. Residual volume is also decreased, possibly due to larger central blood volume. The increase in ventilation is as high as 40% above pre-pregnancy values and almost doubles the increase in oxygen consumption; therefore the oxygen extraction ratio and blood  $P\text{-CO}_2$  are lowered during pregnancy, a pattern of respiratory alkalosis. At near maximal exercise, acidosis ensues (because of excess lactic acid production and use of fat as energy substrate), reducing maximal aerobic capacity and endurance to anaerobic exercise. This may be a protective mechanism against hypoxia (Hyttén and Leitch, 1971; Artal and Wiswell, 1986).

Maternal hemoglobin oxygen dissociation changes little if at all during pregnancy, but fetal hemoglobin's oxygen affinity is higher (hemoglobin oxygen dissociation curve is shifted to the left). Theoretical estimates indicate that fractional changes in transplacental  $O_2$  transfer are relatively small in relation to fractional changes in hemoglobin concentration but increase as the latter decrease (Table 2).

Placental oxygen transfer also depends on placental blood flow and on local placental environment regarding partial gas pressures and blood pH (Longo et al., 1972). A larger placenta in maternal anemia may result in an increased surface area, thus reducing the danger of hypoxia for the fetus. However, partial  $O_2$  pressure in amniotic fluid is lower among anemic women (Anon, 1974).

In terms of gas exchange, trans-uterine and overall arterio-venous differences are reduced in pregnancy mostly due to arterio-venous pooling and mixing at the placental level that mimics a-v fistulae (Boe, 1954).

Pregnancy is also characterized by increments in cardiac output (about 30% above the non-pregnant state) and in visceral (primarily uterine) blood flow, although peripheral resistance is decreased over the whole vascular system thus increasing overall blood flow. Stroke volume is more responsible for the increase in output, rather than heart rate, primarily in early pregnancy (Hyttén and

Table 2. Estimated Changes in Transplacental Oxygen Transfer with Different Hemoglobin Concentrations

[Hb, g/dL]	% change in Hb	% change in $O_2$
13	+18	+3.5
12	+9	+1.9
11	0	0
10	-9	-2.3
9	-18	-5.2
8	-27	-8.7
7	-36	-12.9
6	-45	-18.0

(Based on G.G. Power and P.S. Dale's model, see Artal and Wiswell, 1986, p. 172)

Leitch, 1971; Ueland et al., 1969). This increase in overall cardiac performance does not seem to limit cardiac reserve for performing physical activity, until late in gestation, where physical working capacity decreases as manifested by a clearly reduced maximal aerobic capacity (Artal and Wiswell, 1986). The sympathetic response to hypoxia and physical activity, resulting mostly in norepinephrine release, plays an important role in maintaining adequate oxygen transport during exercise by inducing spleen contraction with the consequent increase in hematocrit, and by diverting splanchnic blood flow without impairing uterine blood flow.

Even if these safety mechanisms are in place, babies born of anemic women or at higher altitudes or from smoking mothers tend to be of lower weight, suggesting that, among several mechanisms responsible, even relatively mild hypoxic conditions negatively affect fetal growth (Meyer, 1977). In a study performed in Guatemala among pregnant women at term living at 2,360 m above sea level, and their newborns, Matute (1977) and Viteri (1973) found higher hemoglobin concentrations in the mothers (141 g/L, sd 11 g/L) as well as in cord blood (170 g/L, sd 19 g/L) than among similar women and cord blood at 1650 m above sea level (128 g/L, sd 12 g/L, and 156 g/L, sd 22 g/L respectively). This finding was interpreted as evidence for incomplete maternal compensation to the low partial oxygen pressure of altitude that resulted in chronic fetal hypoxia that in turn triggered fetal polycythemia.

Iron deficiency and anemia most probably alter many of these functions during pregnancy, due to the multiple roles iron-enzymes and other iron compounds have in oxygen transport and in many redox reactions particularly those that involve molecular oxygen (Comrack et al., 1990). These reactions are the backbone of the respiratory chain.

In non-pregnant experimental animals and humans, clear derangements in energy metabolism that include diminished oxidative capacity at the mitochondrial level, altered mitochondrial structure, impaired alpha-glycerophosphate shuttle, lactic acid accumulation, and restricted blood oxygen transport even with mild anemia have been documented (Viteri, 1989; Celsing, 1987). These alterations are responsible for impaired physical work of many types (maximal, sub maximal, endurance, and spontaneous) among iron-deficient and anemic experimental animals and humans.

### 3. Digestive and Absorptive Functions

The relevant aspects of these functions for the topic of this paper are mainly gastric acid secretion, intestinal motility and iron absorption.

Overall evidence is that there is little change in gastric acid secretion until the last trimester of pregnancy when it seems to increase (Rooney et al., 1975). Gastric and intestinal motilities are sluggish in pregnancy (Wald et al., 1982) and non-heme iron absorption is increased particularly during the second and third trimesters, when iron stores are reduced and iron deficiency is common. There is no convincing evidence that heme or non-heme iron absorptive capacity is enhanced beyond the expected response to "iron deficiency" during pregnancy. However, given the apparently exaggerated plasma biochemical responses in indicators of iron deficiency during pregnancy (elevated transferrin, depressed iron and ferritin) even when iron deficiency is not truly present, signals may be conveyed to the mucosa to increase iron uptake and transfer it from the cell to the plasma. The mucosa could then be "more efficient" in absorbing iron. This possibility has not been fully answered yet.

### 4. Endocrine and Metabolic Functions

The endocrine and metabolic functions that take place during pregnancy are vast and complex, and are beyond this review. The interested reader is referred to Tulchinsky and Ryan (1980).

The following is only a very brief place during pregnancy and their per research on iron deficient and anemic at the same time surprising to note the metabolic alterations due to iron deficiency.

Changes in the regulation of the hypothalamus for successful pregnancy and lactation: TRH-like substance, and Chor Thyrotrophin (TSH) effect that essentially on the other hand, estrogens increase the levels of circulating thyroxin (T4) remain within the normal limits for normal reverse T3 and TSH are, however, often a hypothyroid state even in the face of a normal thyroid gland.

Impaired response to TRH stimulus: T3 peripheral conversion and T3 turnover deficiency and anemia (Beard et al., 1988). Higher sympathetic activity through increased turnover of this sympathetic hormone (norepinephrine) capacity to react to stressful situations.

Epinephrine (E), nor-epinephrine (NE) very much involved in endometrial ar (Parvez et al., 1988). Free- and bound during pregnancy, cortisol reaching the fetus is one is important for the initiation of myometrium. Estrogen sensitizes the uterus (Chalis, 1980). Near term, phenylethylamine is reduced, thus favoring NE accumulation in the myometrium decreases as pregnancy progresses. Estrogens on this enzyme. This also favors the release of NE.

In addition, oxytocin also inhibits (COMT) favoring again NE accumulation. These have an agonistic effect on NE metabolism.

At the endometrial level, oxytocin that strengthens uterine contractions, steroid metabolism, cytochrome P450, and leukotrienes, prostaglandins, through these mechanisms iron deficiency may be exacerbated.

At the mammary level E and COMT of oxytocin and inhibit its release. Iron deficiency may have some impact on these mechanisms.

Lastly, some mention must be made of the metabolism of several amino acids, nucleotides and purine nucleotides. Glucocorticoid anabolic activity, iron deficiency may be exacerbated.

### 5. Immunology and Defense Mechanisms

As indicated previously, pregnancy theoretically could make the pregnant

diac performance does not seem to be affected during pregnancy, where physical working capacity (Artal and Wiswell, 1989) and aerobic activity, resulting mostly in no change in oxygen transport during pregnancy, decrease in hematocrit, and by diverting

energy from iron-deficient women or at higher altitudes, suggesting that, among several factors, iron deficiency negatively affects fetal growth. Viteri (1973) and Viteri (1973) found higher hemoglobin (Hb) (170 g/L) and iron (1650 mg) in cord blood (170 g/L) at 1650 m above sea level (128 g/L), which was interpreted as evidence for iron deficiency anemia.

These changes during pregnancy, which are associated with iron deficiency, have in common a decrease in oxygen transport and molecular oxygen (Commack et al., 1989) and a decrease in energy chain.

Other derangements in energy metabolism include mitochondrial level, altered mitochondrial membrane, lactic acid accumulation, and decreased physical work of many types among iron-deficient and anemic women.

Some of the findings of this paper are mainly gastric acid

secretion until the last trimester (Viteri, 1985). Gastric and intestinal motilities are decreased. Iron absorption is increased and iron stores are reduced and iron deficiency anemia or non-heme iron absorptive iron deficiency during pregnancy. Physiological responses in indicators of iron deficiency (iron and ferritin) even when iron stores are low could then be "more efficient" in iron absorption.

Changes during pregnancy are vast and are referred to Tulchinsky and Ryan

The following is only a very brief account of endocrine and metabolic functions that take place during pregnancy and their possible alterations because of iron deficiency, based on research on iron deficient and anemic non-pregnant animals and humans. It is important and at the same time surprising to note that there are no direct experimental data on endocrine and metabolic alterations due to iron deficiency and anemia in pregnancy.

Changes in the regulation of the hypothalamic-hypophyseal-thyroidal function are essential for successful pregnancy and lactation. The placenta produces a Thyrotrophin Releasing Hormone (TRH)-like substance, and Chorionic Gonadotrophic Hormone (CGH) has a demonstrable Thyrotrophin (TSH) effect that essentially substitutes TSH function in early pregnancy. On the other hand, estrogens increase the levels of circulating thyroglobulins and in this fashion modify the levels of circulating thyroxin (T4) and T3, although the circulating levels of free T4 and T3 remain within the normal limits for non-pregnant women. The ratio of T3/T4 and the levels of reverse T3 and TSH are, however, often elevated as is thyrotoxic volume, suggesting a functional hypothyroid state even in the face of adequate iodine intake (Radunovic et al., 1991).

Impaired response to TRH stimulation, low T4 and T3 circulating levels, diminished T4 to T3 peripheral conversion and T3 turnover, and increased reversed T3 have been described in iron deficiency and anemia (Beard et al., 1989). These thyroidal dysfunctions are associated with higher sympathetic activity through elevations of circulating and urinary NE, and increased turnover of this sympathetic hormone (Beard et al., 1990). These functional alterations reduce the capacity to react to stressful situations such as hypothermia (Lukaski et al., 1990).

Epinephrine (E), nor-epinephrine (NE), estrogens, progesterone, and adrenal steroids are very much involved in endometrial and myometrial physiology during pregnancy and delivery (Parvez et al., 1988). Free- and bound-adrenal steroid circulating levels are markedly increased during pregnancy, cortisol reaching near Cushingoid levels. A high ratio of estrogen to progesterone is important for the initiation of labor, together with increased levels of NE in the myometrium. Estrogen sensitizes the uterus for NE beta-adrenergic action, which is opposed by E (Chalis, 1980). Near term, phenylethanolamine-N-methyl transferase (PNMT) activity is reduced, thus favoring NE accumulation. In several animal studies, monoamine oxidase (MAO) in the myometrium decreases as pregnancy progresses, possibly due to an inhibitory action of estrogens on this enzyme. This also favors NE accumulation near term (Hobel et al., 1981).

In addition, oxytocin also inhibits MAO and catecholamine-O-methyl transferase (COMT) favoring again NE accumulation in the myometrium. Iron deficiency may very well have an agonistic effect on NE metabolism and action during pregnancy.

At the endometrial level, oxytocin enhances the production of prostaglandin f2 (PGF2) that strengthens uterine contractions during the expulsion phase. Hydroxylation reactions in steroid metabolism, cytochrome P450 detoxification processes and conversion of arachidonate to leukotrienes, prostaglandins, thromboxanes and prostacyclin are iron dependent and through these mechanisms iron deficiency may alter uterine function.

At the mammary level E and corticoids desensitize the myoepithelial cells to the action of oxytocin and inhibit its release from the posterior pituitary (Cross, 1955). Thus, iron deficiency may have some impact on mammary gland function.

Lastly, some mention must be made of the role of iron in many enzymes that regulate the metabolism of several amino acids and nucleic acids through production of deoxyribonucleotides and purine nucleotides. Given that pregnancy and lactation are periods of large anabolic activity, iron deficiency may have negative effects.

## 5. Immunology and Defense Mechanisms

As indicated previously, pregnancy requires a series of immunological adaptations that theoretically could make the pregnant woman more susceptible to infection. Iron deficiency

and anemia affect defense mechanisms (Chandra and Saraya, 1975; Farthing, 1989): in leukocytes through a reduction in myeloperoxidase and the formation of chloramine, hypochlorite and singlet oxygen that intervene in bacterial killing; in milk through diminished activity of lactoperoxidase that acts by the oxidation of chloride and thiocyanate anti-infectious properties; and through impaired cell-mediated immunity, including cell replication in response to mitogenic stimuli and lower levels of DNA and RNA in bone marrow cells. Diminished cutaneous delayed hypersensitivity is also present in iron deficient subjects (Bhaskaram and Reddy, 1975).

In spite of reservations due to flaws in experimental design, the overwhelming evidence indicates that the severity and duration of an infectious episode (i.e. diarrhea, mucocutaneous candidiasis), and the rates of respiratory and urinary tract infections are enhanced in iron deficiency (Dhur et al., 1989; Giles and Brown, 1962). Thus, iron deficiency may lower further the suppressed immunological capacity of pregnant women.

## CONCLUSIONS

Even though anemia and iron deficiency are highly prevalent during pregnancy and lactation, many of the functional limitations that can occur, based on known effects of iron deficiency and anemia among non-pregnant individuals, remain to be properly explored.

Several "adaptive" physiological changes that normally occur during different phases of pregnancy are similar to those observed among iron deficient and anemic non-pregnant subjects. These changes are particularly evident in the case of cardio-respiratory, immune and beta adrenergic functions at term. The similarity of these changes may actually result in a potentiation of functional effects in anemic, iron-deficient pregnant women that may: further limit oxygen transport and metabolism with enhanced lactic acid production, hampering physical working capacity; enhance susceptibility to infections; and increase the sensitivity to the triggering mechanisms of uterine contractions near term.

There are other "adaptive" functions that are opposite to what is observed in the presence of iron deficiency and anemia. Particularly evident are nucleic acid synthesis that increases in pregnancy and is reduced in iron deficiency, and thyroidal function, which is enhanced in pregnancy with higher TRH and TSH activity levels as well as elevated T3/T4 ratios, contrary to what is observed in iron deficiency and anemia.

The complex and dynamic functional relationships that are normal during pregnancy in its different phases make the study of possible alterations due to iron deficiency and anemia more difficult. In spite of these difficulties there are clearly demonstrated negative effects of iron deficiency and anemia both in terms of the mother and the newborn child. The repercussions of anemia and iron deficiency on lactation performance, however, are not clear.

The available evidence is enough to warrant a major effort in controlling iron deficiency and anemia during pregnancy and lactation, keeping in mind not only the health and welfare of the baby but the continued health and welfare of the mother in all her social and productive roles before, during and after pregnancy and lactation.

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