NUTRITIONAL ANEMIA IN PREGNANCY

by

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to my Parents

TABLE OF CONTENTS

INTRODUCTION

Anemia is the most common single objective finding in medical practice. It is indicated by a lower than normal level of hemoglobin in the circulating blood. It may be caused by a reduced number of red blood cells or by a lowered quantity of hemoglobin in the cells or both. Normal hemoglobin levels vary with age, sex, weight, physiological status, and altitude (1). During growth as well as pregnancy, blood volume is increased. During these growth periods a need occurs for an increased iron intake as well as several other nutrients required for synthesis of hemoglobin. When nutrient needs do not meet these requirements, anemia occurs.

Diagnosis of anemia is usually based on some measure of hemoglobin or red cell mass per unit volume of peripheral blood. It is necessary therefore to have an understanding of the physiologic changes that occur in blood during pregnancy.

Physiologic changes in plasma, red cells, and total blood volume occur during pregnancy. Determination of a precise hemoglobin level during pregnancy that can be called "anemia" is often difficult to assess. The WHO (World Health Organization), however, has established normal blood values for pregnant women. For persons with values below these, a diagnosis of anemia is made (2,3). Blood values indicative of anemia are contained in Table 1.

Nutritional anemia is the result of a deficiency of iron and folic acid (4,5,6). Deficiency of vitamin B-12 also produces anemia. This deficiency may be secondary to the lack of an intrinsic factor, a substance essential for the absorption of vitamin B-12 (7). Most of this paper deals with the former type of anemia, i.e., resulting from an iron and folic acid deficiency.

Table 1: Blood values indicative of anemia during pregnancy

Hemoglobin	11 g per 100 ml of blood
Red Blood Cell	3.3 million per cu mm of blood
Packed Cell Volume	29 mg per 100 ml of blood
Mean Capsular Hemoglobin	87 mg per 100 ml of blood
Mean Cell Hemoglobin Concentrate	34 mg per 100 ml of blood

World Health Organization Scientific Group: Nutritional Anemia, World Health Organization Techn. Rep. Ser., 1959 & 1968.

Persistent anemia in pregnancy is associated with increased infant morbidity and mortality. Severe anemia often causes maternal complications, and in some instances is the cause of death (8,9,10). Prevention of anemia is an essential part of prenatal care.

CLASSIFICATION

(A) Hypochromic Anemia is caused by an iron deficiency. As a result of this anemia, blood cells are pale. In the normal red blood cell, iron is a structural component of the hemoglobin molecule. During a 24 hour period as much as 6.3 g of hemoglobin, containing 21 mg of iron, can be synthesized and degraded (7). An inadequate supply of iron for the developing erythroid cells becomes apparent in a short time. Erythropoiesis is diminished and small erythrocytes having decreased hemoglobin concentration are formed. The erythrocyte is pale, misshaped, and has a shortened survival time (11).

(B) Megaloblastic Anemia is caused by a folic acid deficiency. The erythrocytes are larger than normal, have an excessive amount of

cytoplasm and a disproportionate aging of the nucleus (11). Folic acid is necessary for erythrocyte maturation which occurs in the bone marrow. Lack of this vitamin interferes with the synthesis of both nucleic acids and nucleo-proteins. Hence, large nucleated red cells (megaloblasts) are formed and are discharged into the blood. Usually these cells contain normal or increased amounts of hemoglobin. However, the number of cells produced is sharply reduced so that total hemoglobin is less than normal. The survival time of these cells is decreased (11).

(C) Pernicious Anemia is caused by a vitamin B-12 deficiency. It is a megaloblastic type of anemia. It produces many of the same symptoms which occur in a folic acid deficiency, such as fatigue, pallor, shortness of breath and gastrointestinal discomfort (11). Deficiency of vitamin B-12 is associated with abnormalities in nucleic acid metabolism (12). Erythrocyte precursors, normoblasts and reticulotytes, are larger than normal. Mature red cells also are large (macrocytes) but contain normal or even higher concentrations of hemoglobin. The total red cell count however is decreased (11).

INCIDENCE

Numerous investigations of nutritional anemia of pregnancy have been conducted around the world. These studies conclude: all types of nutritional anemia are prevalent in (1) low-income, low socioeconomic groups; (2) women who have had successive pregnancies; (3) women giving birth to twins; (4) women engaged in prolonged breast feeding prior to their pregnancy; and (5) adolescent mothers with inadequate dietary patterns (6,8,13).

Anemia is a relatively late manifestation of a nutritional deficiency state. Therefore, large groups of women suffer from a more moderate degree of this nutritional deficiency, but do not manifest the symptoms of anemia (11). The sequence of defective hemoglobin formation and a subsequent anemia is: (1) nutrient deficiency; (2) depletion of nutrient storage; (3) decreased delivery of nutrients to the erythroid cell; and (4) impaired hemoglobin synthesis (14).

The frequency of anemia among pregnant women in the less-developed countries is greater than among pregnant women residing in the more developed countries. In India, it has been estimated that 30-50% of women in lower income groups have hemoglobin levels under 10 g/100 ml during late pregnancy. A higher prevalence of anemia exists among rural Indian pregnant women. Scarce medical facilities, infection, poor sanitation, malnutrition and ignorance contribute to the high incidence of this condition (16).

In comparing two localities in India, one rural and one urban, a WHO study found 470 of 1,000 pregnant villagers with hemoglobin levels under 10 g/100 ml as compared to 297 of 850 city dwellers. Data indicate that those having hemoglobin levels between 11 and 10 g/100 ml of blood were 800 and 476 respectively (3). Not only is the incidence of gestational anemia high in developing countries, but much of it is of a severe form. In a study conducted in Malaysia of approximately 73,000 mothers who were receiving prenatal care between the years of 1952-1962, 3.1% were found to have hemoglobin levels under 6.5 g/100 ml. The incidence of severe anemia among pregnant women (hemoglobin less than 8 g/100 ml) in more developed countries is far less. It is in the range of 0.5 to 1% for pregnant women (3). Usually a higher proportion of women in the developed countries receive

prenatal care. In the developing countries many women do not seek medical care until labor ensues (7,18,19).

In the first trimester of pregnancy anemia is usually mild. A decrease in the hemoglobin level is more common during the second trimester, and still more common during the third trimester (9,13,17).

In 1962, Emerson reported that 14% of all babies born in the United States were born to mothers nineteen years of age or younger. Complications such as toxemia, premature delivery, and anemia were prevalent in this age group (20). A study by Milder and Audery on 114 pregnant teen-agers showed that hemoglobin levels, iron and serum folic acid levels were significantly low (21).

Iron deficiency is considered the most common cause of anemia in the world today. Many studies show a higher incidence of an iron deficiency rather than a folic acid deficiency anemia. In countries such as India, iron deficiency anemia poses a major public health problem (3). However, anemia is not confined to underdeveloped areas. It also occurs in western societies. A report by Scott and Pritcherd found scanty or absent marrow iron stores in 2 out of 3 healthy American college women who had never been pregnant and denied heavy menstrual flows (22). The Ten-State Nutrition Survey indicated that an iron deficiency occurs in both high and low-income groups in the United States (23). Thus, an iron deficiency, although more common among the poor and during pregnancy, frequently exists among women of all economic levels prior to pregnancy.

Folic acid deficiency during pregnancy is world-wide. This is the result of a high maternal and fetal requirement for this vitamin. Many investigators suggest a high incidence of folic acid deficiency among economically disadvantaged people of the world, especially pregnant women (24).

In well-developed countries, a substantial number of women will show laboratory evidence of folic acid deficiency during pregnancy. Megaloblastic anemia however is uncommon (13). In developing countries folic acid deficiency exists among a majority of mothers (18,24). In Nigeria, megaloblastic anemia was found to be common (18). In Latin America, however, there is a low prevalence of this condition and it is rare among the Chinese (25).

The incidence of folic acid deficiency tends to be high during the first trimester of pregnancy and then again at close to term (6). It is markedly increased with the common complications of pregnancy, especially toxemia; in successive pregnancies; and during pregnancy involving twins (26).

NORMAL ERYTHROPOIESIS AND BLOOD CHANGE DURING PREGNANCY

A. Normal Erythropoiesis:

Formation of blood cells occurs principally in bone marrow. In the early stages of development, the immature cell contains a large nucleus. Maturation occurs by cell division and differentiation. During this process the nucleus becomes progressively smaller, hemoglobin appears within the cytoplasm, ribonucleic acid lessens in amount, and the cell decreases in size (11).

Erythrocytes are continuously produced at a rate sufficient to replace the aged cells that are removed from the circulation. Approximately one per cent of the body's red cells are regenerated each day. The balance between red cell production and red cell destruction in the normal adult is precisely maintained. Rate of destruction of red cells depends upon the life-span of the erythrocytes which in healthy people is approximately 120 days (27).

Biosynthesis of Hemoglobin:

Hemoglobin is a conjugated protein, with a prosthetic group, heme, united to the protein, globin.

The pathway of hemoglobin formation can be outlined as requiring prophyrin biosynthesis to form heme and protein biosynthesis to form globin. In the final stage of heme formation, iron is introduced into protoporphyrin. The hemoglobin molecule of a normal adult contains four heme groups and two pairs of polypeptide chains (28).

Erythrocyte Maturation:

The primary function of the erythrocyte is to synthesize and transport hemoglobin. The size of the red blood cell mass controls the concentration of hemoglobin in circulation. Its regulation is responsive to the body's need for oxygen (27). A series of cell divisions take the original cell through four stages of maturation. During stage I, the cell starts synthesizing hemoglobin and undergoes cell division. In stage II, the cell is divided and decreases in size. This cell is called a polychromatic normoblast. In stage III, the cell loses its capacity for further division, and a loss of its nucleus. In stage IV, the cell is a marrow reticulocyte, and is finally released into the circulatory system and with maturation becomes an erythrocyte (27).

A schematic summary of erythropoiesis and substances required for erythropoiesis is shown on page 8 in Figure 1.

B. Blood Change in Pregnancy

In general, normal physiologic processes during pregnancy are increased (29). Cardiovascular changes are observed. These include an increase in heart rate, pulse pressure, cardiac output, O_2 saturation, central

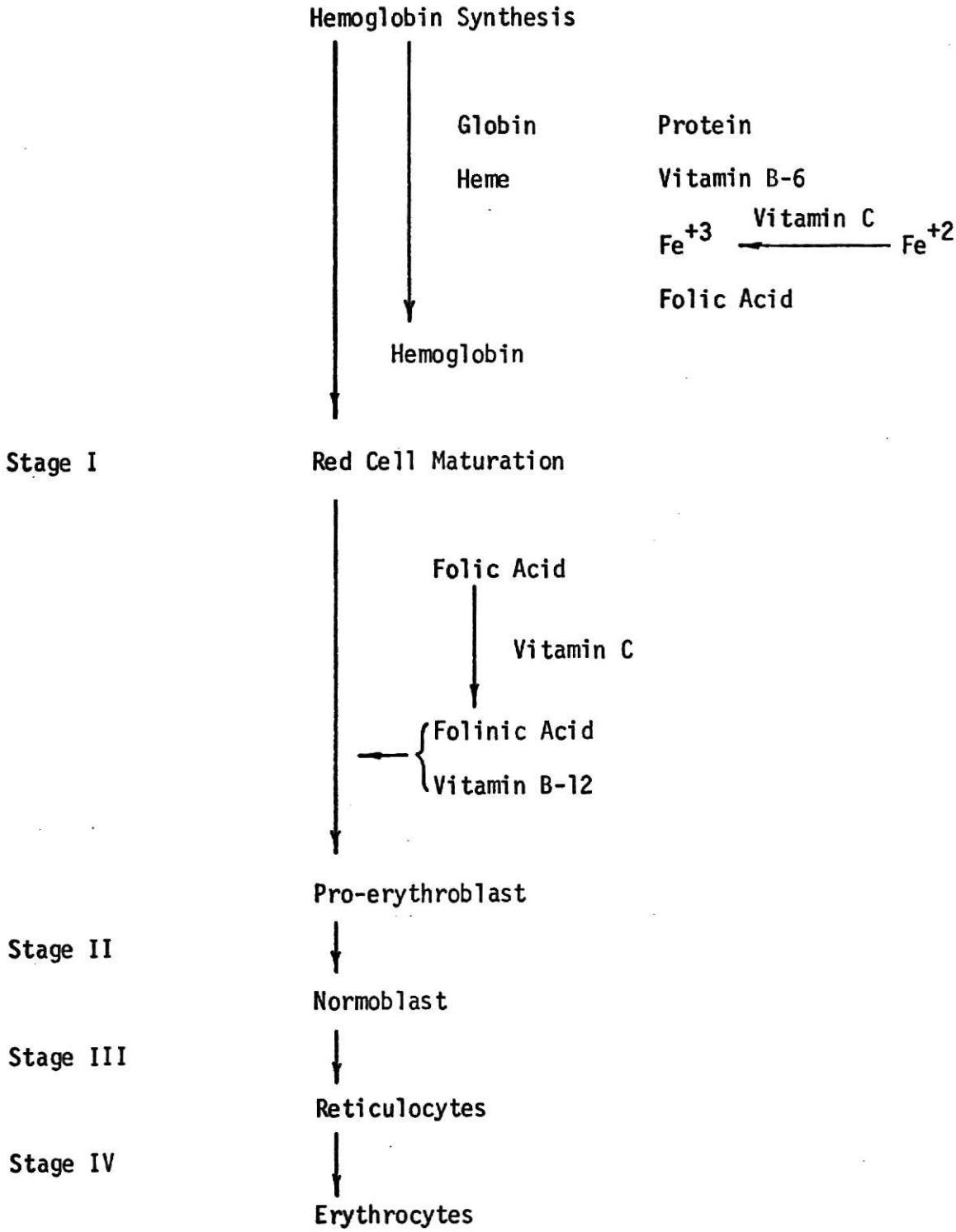

Figure 1: Schematic Summary of Erythropoiesis

arteriovenous O_2 difference, and blood volume (30). The marked increase in blood volume during pregnancy involves a larger increase in plasma volume than in red cell mass (31). This is especially true during the first half of pregnancy whereas the reverse is true in the later stages of pregnancy (31).

Plasma volume increases progressively throughout pregnancy, reaching a maximum in the 9th month and decreasing from this peak slightly before term. The peak increment in plasma volume probably occurs at about the 34th week of gestation (32). The cause of hypervolumia is at present unknown. It probably results from a retention of sodium and water (32). It is also known that in primary aldosteronism there is a marked increase in blood volume. Pregnancy is accompanied by an increase in aldosteron production, and it may be that the increased production of this hormone is responsible for the plasma volume increase (33). Blood volume is also increased by administration of large doses of estrogen. Pregnancy is a hyperestrogen state (34).

An increase in red cell mass may be due to consumption of an iron supplement. Red cell mass increases are less in women whose diets are not fortified with an iron supplement than those who receive an iron supplement during pregnancy (35).

The maximum plasma volume increase is on the order of 40%. The red cell mass increase is approximately 30%. This plasma volume increase accompanied by a smaller red cell mass increase leads to a "physiological anemia of pregnancy", a condition which is a reflection of the disproportionate increase in plasma volume rather than a true anemia (31). A diagnosis of anemia during pregnancy therefore requires the measurement of the serum iron or folic acid level of the blood.

IRON AND FOLIC ACID METABOLISM RELATED TO PREGNANCY

Iron and folic acid are nutrients required for erythropoiesis. The metabolism of these two nutrients determines their availability for this purpose. During pregnancy both iron and folic acid requirements are increased due to a blood expansion in the mother and a high demand for these nutrients by the fetus. Iron absorption is increased during pregnancy, but no change occurs in the absorption of folic acid (31,36,37).

(A) Iron Metabolism: The role of iron in the body is closely associated with that of hemoglobin formation. Body storage of iron is 3 to 5 grams; approximately two-thirds of which is present in hemoglobin (38). This small amount of iron is used over and over again. Normally very little iron is lost from the body. Iron loss from the body occurs through bleeding and the birth process (39).

Iron metabolism is controlled through absorption from the gastrointestinal tract (14). As the ingested iron passes through the gastrointestinal tract, it is reduced from the ferric to the ferrous state, if it is not already in this form. This transformation occurs in the presence of gastric acidity, -SH groups, ascorbic acid, or other reducing agents in food and secretions. Ferrous iron is oxidized, combined with phosphate and united with "apoferitin" to form ferritin, a storage form of iron. Ferritin is stored in the mucosal cells of the body. The amount of ferrous iron moving into the cell depends upon the level of ferrous iron in the cells and indirectly upon its ferritin concentration. After iron has been delivered by mucosal cells to the blood it is bound and transported by transferrin, a beta-globulin. One molecule of transferrin is capable of binding two atoms

of ferrous iron. This transferrin-iron complex is attached to the developing red blood cell, gives up its iron to receptor sites and then recirculates as a carrier protein (14). The average transferrin content of normal plasma is about 0.24 to 0.28 gm per 100 ml of blood. However, transferrin concentration of the blood is ordinarily stated in terms of its iron-binding capacity, roughly 280 to 400 ug per cent.

The amount of iron utilized for hemoglobin synthesis per day in a normal adult is approximately 20 to 25 mg (38). Most of this iron comes from the transferrin in blood plasma.

The major pathway of iron loss from the body is the result of hemorrhage, caused by disease or accident, blood letting and the normal physiologic process of menstruation. Urinary iron excretion is small with a mean value of approximately 0.1 mg or less per day. The iron in feces is derived from blood lost into the alimentary canal, from unabsorbed ingested iron, biliary iron, and from intestinal mucosal cells (37). Iron losses during menstruation vary widely; the upper normal limit is approximately 2.5 mg per period (39).

In pregnancy, the pregnant woman transfers iron to the fetus through the placenta and cord. The bulk of this transfer occurs during the third trimester (36). The fetus has a highly effective acceptor system for assimilating iron. Maternal transferrin passes through the placenta to the fetal tissues. This pathway seems to be a one-way street, capable of operating effectively against increased maternal requirements for iron and even in the face of maternal iron deficiency. During the last trimester of pregnancy, 3 to 4 mg of iron are transferred to the fetus per day (36).

Blood loss at the time of delivery averages 507 ± 308 ml for primipara and 280 ± 293 ml for multipara (29). Lactation causes an additional drain of

iron, approximately 0.5 to 1.9 mg per day. The total iron "cost" of a normal pregnancy and breast feeding for a six month period is estimated to vary from 435 to 970 mg. Most of this iron "cost" of a pregnancy occurs during the third trimester and at the time of delivery (29). Table 2 gives the estimate of the total iron cost of a normal pregnancy and breast feeding.

Table 2: Total iron cost of a normal pregnancy

	mg
Iron contributed to fetus	230-370
Iron content of placenta and cord	35-170
Iron loss at delivery	100-250
Total	365-790

Moore, C.V.: Iron nutrition and requirements. Scand. J. of Haematol. Ser. *Haematolo. 6:1*, 1965.

(B) Folic Acid Metabolism: Folic acid is readily absorbed from both upper and lower portions of the gastrointestinal tract (40). This intake occurs in foods primarily as conjugates of glutamic acid. These conjugates are broken down in the body by enzyme systems found in the tissue (40). An average diet selected from a wide variety of foods supplies 150 to 200 ug of "folic acid activity" material of which 65 ug is unconjugated. The term "folic acid activity" is defined as the growth promoting effects of folic acid glutamates used in a biologic assay (41).

Once folic acid is absorbed, it undergoes further metabolic conversions to its coenzymatic form, tetrahydrofolic acid, via a series of reduction reactions (40). Tetrahydrofolic acid plays a central cofactor role in the

various metabolic chemical reactions which folic acid catalyzes. It is important for the transport of one-carbon units essential for the biosynthesis of purine and pyrimidines and for certain methylation reactions (42). Folic acid is also involved in the formation of the porphyrin ring and therefore in hemoglobin metabolism.

It is believed that there is no change in the absorption of folic acid during pregnancy. A study by Iyenger indicated that the absorption of folic acid during the first 28 weeks of pregnancy is no different from that of a non-pregnant state. The percentage of folic acid retained in body tissues was found to be similar in both groups (37). No evidence exists to indicate a change in folic acid metabolism during pregnancy.

PATHOPHYSIOLOGY

A. Laboratory Findings:

a. Iron Deficiency Anemia: Iron deficiency anemia does not appear until iron stores are exhausted (14). The sequence is as follows: (1) depletion of iron stores; (2) rise in transferrin levels; (3) fall in serum iron; (4) decrease in hemoglobin concentration; and (5) appearance of hypochromic anemia (11). These changes usually, but not always, result in decreased mean corpuscular hemoglobin levels and mean cell hemoglobin concentrate values. Measurement of mean cell hemoglobin concentration for diagnosis is more reliable, as deviation from normal values of this index is not dependent on red cell count (43). A low serum iron level, i.e., a value below 60 ug/100 ml suggests iron deficiency (44). In this state the iron binding capacity is high, usually above 400 ug/100 ml (44). In pregnancy, the iron-binding capacity normally increases. This is a measure of transferrin, the

iron-binding transport protein. It, like many other binding proteins, is increased during a normal pregnancy (29).

The bone marrow is hyperplastic in an iron-deficiency anemia. Most of the nucleated red blood cells are mature normoblasts. In addition, microcytosis, considerable variation in the size and shape of the red cell, and total hemoglobin concentration occur (11).

b. Folic Acid Deficiency Anemia: The diagnosis of folic acid deficiency anemia is based on biochemical measurements and ultimately on a bone marrow examination. During the development of this anemia the following conditions appear, in this order: (1) decrease in blood serum folic acid levels; (2) hypersegmentation of neutrophil nuclei in peripheral blood; (3) increased urinary FIGLU (Formiminoglutamic Acid) excretion; (4) decreased folic acid concentration of erythrocytes; (5) macro-ovalocytosis; and (6) megaloblastic anemia (45). This sequence of events as shown in Table 3 involves about 19 weeks but may be accelerated if a deficiency of folic acid exists prior to the pregnancy or if complicating factors exist (45).

The FIGLU excretion test is not a reliable measure for the diagnosis of megaloblastic anemia as 90% of all pregnant women with a megaloblastic anemia have a normal FIGLU excretion (46). Non-anemic pregnant women have megaloblastic bone marrow changes in the last trimester of pregnancy. These changes are almost completely absent when subjects are treated with 500 ug folic acid daily (46). Thus bone marrow examination seems to be a precise measure of the occurrence of folic acid deficiency in pregnancy.

In folic acid deficiency anemia, many of the red cells are oval macrocytes, with marked variations in size and shape. These range from small irregular red cells to large oval macrocytes (11).

Table 3: Sequence of development of megaloblastic anemia due to folic acid deficiency

Laboratory findings	Time span in weeks
Low serum folic acid	3
Hypersegmentation of neutrophil nuclei	7
High FIGLU excretion	13
Low RBC folic acid	17
Macro-ovalocytosis	18
Megaloblastic cells in bone marrow	19
Beginning anemia	19

Ktay, D.Z.: Folic acid deficiency in pregnancy. Amer. J. Obstet. Gynecol., 98:393, 1967.

B. Clinical Manifestation:

a. Iron Deficiency Anemia: Hypochromic anemia is a relatively late manifestation of iron deficiency. When iron stores have been totally depleted, anemia develops (14). The time required for symptoms to occur may vary from months to years, depending on the initial level of iron stores and the degree of the negative balance.

The clinical significance of mild iron deficiency is not clear, as it often causes no clearly recognizable disturbance in the individual's sense of well-being (11).

Symptoms are insidious in their onset. The anemia may develop so gradually that it interferes only moderately with work efficiency. Complaints of weakness, fatigability, pallor, dyspnea on exertion, palpitation, headache and a feeling of "dead-tiredness" often occur. These,

however, are symptoms common to all types of anemia. Approximately one-third of all patients with this condition complain of a sore tongue or sore mouth. The discomfort, however, is rarely as great as it is in pernicious anemia. Pallor of the skin, mucous membranes, and nail beds is proportional to the reduction in hemoglobin. The heart may be slightly enlarged as well as the liver. These conditions are often accompanied by edema. Neurological examination findings are almost always normal. The finger nails in many patients are brittle and show a longitudinal ridging and flattening (38).

b. Folic Acid Deficiency Anemia: It is difficult to give an accurate general description of the typical patient suffering from folic acid deficiency anemia. This condition has some symptoms common to other anemias, such as fatigue and pallor (38). In severe cases, shortness of breath and congestive failure develop. In addition, glossitis, gastrointestinal discomfort and diarrhea often occur but mostly in severe deficiency states (38).

Smears from the vaginal mucosa, as well as biopsies of the small intestine show morphological changes characteristic of megaloblastic anemia (11).

C. Anemia in Pregnancy:

Many pregnant women are prevented from enjoying their pregnancies because of weakness, headache, dizziness, palpitation, shortness of breath, and fatigue to the point of exhaustion. These are all symptoms caused by anemia (8,47). Results of a study conducted in India during 1971 on 210 pregnant women with anemia are shown in Table 4 on page 17.

Reduced O_2 tension in the amniotic fluid, hypertrophy of the placenta and low estriol excretion have been shown by many studies to be the result of

an anemia (48,49). Evidence also suggests an association between folic acid deficiency anemia and spontaneous abortion in early pregnancy, habitual abortion, abruption of placenta, toxemia of pregnancy, premature deliveries, and fetal abnormalities (50).

Table 4: Symptoms occurring in 210 anemic pregnant Indian women

Symptoms	%	Symptoms	%
weakness	79	headache	38
fatigue	73	bodyache	37
excretional dyspnea	64	insomnia	36
giddiness	61	anorexia	28
palpitations	56	diarrhea	12
		nausea	11

Metha, B.C.: Anemia in pregnancy. India J. Med. Sci. 25:101, 1971.

Effects of Anemia on the Mother

Cardiac Failure: The most disastrous maternal effect of anemia results from circulatory alterations, including cardiac failure. As hemoglobin levels drop, compensatory changes occur in order to maintain adequate peripheral tissue oxygenation. Plasma volume, cardiac output and velocity of blood flow increase. In severe anemias total blood volume sometimes drops. As time passes, a level of hemoglobin is reached where further compensatory changes are no longer feasible and cardiac failure results. In the absence of other complications this usually occurs during pregnancy at a hemoglobin level of 4 - 5 g/100 ml. If other complications, such as infection, toxemia or the stress of labor exist, cardiac failure may develop at higher hemoglobin

levels. Hemorrhage may cause further shock and often precipitates death (17,48,51).

Inability to Withstand Hemorrhage: The most common serious maternal consequence of anemia is an inability to withstand significant hemorrhage. As previously stated there is an increased blood volume in pregnancy but a low red cell volume. This is accentuated in anemia and results in a reduced oxygenating capacity of the blood. Significant blood losses are apt to reduce peripheral oxygenation and produce shock more quickly. Anemia is responsible for or contributes toward an estimated 20-30% of maternal deaths in many developing countries where the prevalence of severe anemia is high (16,17,48,52).

Association with Toxemia: Several surveys indicate that anemic pregnant women have a higher incidence of toxemia. Chaudhrui in India evaluated this association from several points of view. Of 500 consecutive patients seen in his clinic beyond the 32nd week, 56% had hemoglobin values below 10 g/100 ml; 25% of these subjects subsequently developed toxemia while only 11% of the non-anemic group did so. In comparing toxemic subjects with non-anemic subjects, hemoglobin and serum iron levels were significantly lower in toxemic subjects (53).

In a study in which supplementary iron and vitamins were prescribed, the incidence of toxemia dropped from 14.6% to 4.8%. Although anemia cannot be said to cause toxemia, the two frequently coexist. The same deficits which lead to anemia may also cause toxemia. Poor nutrition of persons with anemia is no doubt important in the etiology of toxemia (54).

Relationship of Anemia to Infection: It is believed that anemia of pregnancy leads to diminished resistance to infection and to a higher incidence of puerperal infection. Years ago, Bickerstaff investigated the relationship between hemoglobin levels of multiparas during the last month of pregnancy and postpartum febrile morbidity. This investigator found that 20% of his subjects with hemoglobin levels less than 9 g/100 ml had elevated body temperatures. This is 5 to 6 times that of persons with hemoglobin levels of 10.5 g/100 ml and over (55).

Scott observed a higher incidence of postpartum morbidity in patients with severe (hemoglobin less than 8 g/100 ml) untreated antepartum anemia than in normal patients (56). Chronic anemia, if it is associated with severe malnutrition or protein lack, can lead to an increased susceptibility to infection. This is also true of anemia following acute blood loss especially if accompanied by an uncorrected hypovolumia (56).

Effects of Maternal Anemia on Fetal Development

Maternal anemia may directly affect the growth and development of the fetus. The fetus may also be affected by complications which are the result of anemia in mothers (50). High mortality rates and premature births have been associated with a maternal prenatal hemoglobin level below 10 g/100 ml (10). A study by Flemming found that maternal anemia causes fetal hypoxia. This is followed by compensatory placental hypertrophy, a condition which interferes with fetal development (9).

Higher Perinatal Mortality and Low Birth Weight Infants: Infants born to anemic mothers generally suffer a higher perinatal morbidity. Reports from different parts of the world have shown an increased number of premature and

low birth weight infants associated with anemia (9,10). Results of a survey in Malaysia indicate that the birth of infants weighing 500-2000 g occurs three times more frequently of mothers with hemoglobins less than 6.5 g/100 ml than of those with normal hemoglobin levels (17). A study in Kenya showed a direct relationship between birth weights and hemoglobin levels. Forty-two per cent of subjects with hemoglobins under 7.5 g/100 ml delivered underweight infants whereas only 12.7% of infants of low birth weight were born to mothers with hemoglobin levels over 9 g/100 ml (54).

Perinatal mortality rates are higher in children born to anemic mothers. In Kenya neonatal deaths and stillbirth rates are 2-3 times higher in children born to mothers suffering from anemia during their pregnancy. Most of these neonatal deaths occur to premature infants (54).

Intrauterine Hypoxia: A report of several hundred subjects with hemoglobin levels under 9.2 g/100 ml indicated that 24% of these women had subnormal estriol levels during late pregnancy. This occurs more commonly as the severity of the anemia increases. Fetal distress during labor occurs twice as frequently in anemic subjects with reduced estriol levels as it does in normal subjects (13). Perinatal data on children born of anemic mothers are often clouded by the coexistence of other disease conditions. Common abnormalities with this effect are hypertension, renal disorders, antepartum hemorrhage and successive pregnancies (26,49).

Anemia causing intrauterine hypoxia may precipitate prelabor intrauterine death. This is the result of inadequate placental perfusion and oxygenation. Anemia may also cause fetal distress during labor, which may result in birth asphyxia or intrapartum death. It is thought that some

infants of anemic mothers are born prematurely as a mechanism of escape from a progressively hypoxic intrauterine environment (57).

PATHOGENESIS

Several common factors contribute to iron and folic acid deficiency anemia. These include an increased demand; disorders caused by pregnancy, such as gastrointestinal disturbances; successive pregnancies; twin pregnancies; prolonged breast feeding prior to pregnancy; and insufficient dietary intake (3,4,13,21,24,47,48).

Successive pregnancies as well as prolonged breast feeding cause depletion of body stores of iron and vitamins. These depletions contribute toward the development of anemia. In twin pregnancies, iron and vitamin demands for both mother and fetus are significantly increased (11).

During pregnancy mechanical activity of the gastrointestinal tract and the production of gastric juice may be decreased (49). Loss of appetite, vomiting, and other gastrointestinal disturbances frequently occur. These may adversely affect dietary intake, the absorption of iron and other nutrients (49).

Iron Deficiency Anemia: Iron deficiency anemia is caused by a dietary iron lack, chronic blood loss or increased iron demands during pregnancy. The iron requirement for a single pregnancy averages 800 mg, of which 300 mg is utilized by the fetus and placenta and 500 mg is used for the expanded maternal hemoglobin mass (43). In addition, there is a normal obligatory iron loss of about 250 mg. A mean quantity of 1050 mg of iron is therefore required during the period of gestation. This requirement frequently exceeds the iron which is available from the diet and body stores.

A normal adult woman has 3.5 to 4.0 gm of body iron. She excretes 0.5 to 1.5 mg daily in feces, urine and sweat. An equivalent amount is lost during normal menstruation (58). The dietary intake of iron is usually not adequate to compensate for these normal losses. The iron content of typical diets adequate in all other nutrients is estimated at 6 mg per 1000 calories (59). With a caloric intake of 2100-2300 calories, it is difficult to meet the recommended dietary allowance of 18 mg or more of iron daily. Consequently, many women are deficient in iron at the time of conception. Increased iron needs of pregnancy precipitate an anemic condition. Anemia during the first half of pregnancy has been shown to indicate a pre-existing state of iron deficiency.

The World Health Organization found daily dietary intakes of iron by women substantially below 10 mg in many less-developed countries. Higher levels of iron are consumed by women in Europe and the United States (60). In the developing countries, iron rich foods, particularly meat, are unavailable. The amount of iron consumed depends not only upon the iron content of the foods consumed but also upon the availability of the iron. Other dietary factors also limit the amount of iron assimilated. In India, where the daily dietary iron is adequate (15-30 mg), there is also a large intake of phytates, derived from their cereal-based diet. This, coupled with a lack of calcium and vitamin C may result in a markedly decreased level of iron absorption. The ingestion of starch, clay and other forms of pica are also associated with low dietary iron and anemia (57).

In many tropical areas hookworm infestation plays a major role in iron deficiency anemia. This parasite sucks blood from the intestinal wall. Heavy infestations result in a daily blood loss up to 150 cc (3,61,62). The

effect of hookworm infestation on the mucosa of the gastrointestinal tract and consequent blood loss is related to the severity of the infestation and dietary factors.

There is no evidence showing that iron absorption and metabolism are affected during pregnancy. But as activity in the gastrointestinal tract during pregnancy is depressed, there is a decreased ability to convert the ferric iron of food into the ferrous form, the form in which iron is absorbed (14).

Folic Acid Deficiency Anemia: The cause of a folic acid deficiency in pregnancy appears to be a combination of increased fetal demand and inadequate maternal intake (5,19). The daily adult requirement for folic acid is approximately 50 ug. During late pregnancy it is increased to 300 to 400 ug daily (63). Failure to meet this requirement results in anemia.

The fetus has a high demand for folic acid. A folic acid gradient is maintained between the fetus and mother. This occurs through the rapid transfer of folic acid from the mother to the fetus. Because of this, a maternal deficiency can readily occur (5,19,63,64).

Folic acid is present in many foods yet dietary deficiency occurs. Rich sources are meats, liver and green vegetables. In countries where such foods are unavailable or when foods are cooked for prolonged periods, a folic acid deficiency often occurs.

Factors other than diet may contribute to a folic acid deficiency in pregnancy. Both vomiting and increased needs for erythropoiesis play a role. The folic acid requirement is increased during treatment of an iron deficiency (65). It is also increased in successive pregnancies. Acute infection and the use of anticonvulsant drugs have been implicated as factors

which increase the need for folic acid during pregnancy (66). In addition, women taking birth control pills often manifest a folic acid deficiency when measured by serum and red cell folic acid levels, and FIGLU excretion in the urine (67,68).

If a megaloblastic anemia occurs due to an iron deficiency, this condition will be corrected by iron therapy. This treatment may make for better utilization of the folic acid in the diet.

TREATMENT

Iron: The choice of therapy in iron deficiency anemia in pregnancy is an individual matter. Most investigators agree that the oral route is preferred in amounts of 200 mg of elemental iron daily. Continuation of oral therapy is recommended for a 4 to 6 month period following the correction of the anemia. This insures the repletion of iron stores (70,71). A dose of 300 mg of ferrous sulfate three times a day supplies 180 mg of elemental iron. This amount is usually well tolerated and is inexpensive. Intolerance can be decreased if the dose is taken with milk or with meals.

Parenteral iron is used only when an individual can not tolerate iron orally or when a rapid therapeutic response to a severe iron deficiency is indicated (70).

Free ionic iron is toxic. When the amount of iron exceeds the binding capacity of transferrin, toxicity occurs (14). In efforts to overcome toxicity, various forms of iron have been tried parenterally. Inferon, an iron-dextran complex has been widely used for years (72,73). The recommended dosage is no more than 2 ml per day (73). Intramuscular injection of this substance during pregnancy has been found to be safe (72).

Folic Acid: Treatment of megaloblastic anemia consists of the administration of folic acid. The minimum daily requirement of folic acid for the adult is between 50-100 ug. For the pregnant female it is 300-400 ug per day (63). Doses in excess of this quantity are used for therapeutic purposes. In the treatment of a folic acid deficiency, sufficient folic acid must be supplied to replenish body stores and to meet daily needs.

Usually, the dose for treating a mild folic acid deficiency anemia is 1 mg per day. Daily doses of 5 mg of folic acid provided orally for a period of 4 weeks are sufficient to treat a severe folic acid deficiency anemia and restore tissue stores to normal (74,75).

PREVENTION

Promotion of maternal and child health is of prime public health concern. Effectiveness needs to be evaluated not only in terms of the immediate influence on health and physical status, but also on the productivity of an individual's life.

The most effective way to prevent a nutritional deficiency is to provide adequate nutrients and eliminate those factors which interfere with adequacy. Iron supplementation for pregnant women is recommended (76). Iron enrichment of food can prevent iron deficiency anemia especially in those areas of the world where iron rich foods are consumed in inadequate quantities. In addition, maternal care and nutrition education are essential for insuring the health of mother and child.

A. Nutrient Supplementation in Pregnancy:

Iron: As previously indicated most pregnant women cannot meet their daily needs of 18 mg of iron by diet alone. On the basis of recommended dietary allowances for energy, an adult female will ingest 9-12 mg of iron (14,39). If the diet does not contain large amounts of meat or other iron rich foods, problems associated with inadequate iron intake occur (77). Thus, it is recommended that iron supplementation be provided to all pregnant women.

The World Health Organization recommends a daily dose of a ferrous salt containing 30-60 mg of elemental iron for women with adequate iron stores and a daily dose of 120-240 mg for women with inadequate iron stores. Iron supplementation is recommended during the second trimester of pregnancy and during the first 6 months of lactation.

Folic Acid: The recommended dietary allowances of folic acid for an adult is 50 ug (41). During pregnancy this quantity is increased to 400 ug per day (63,75). For the mother who breast-feeds her infant, an additional 200 ug of total folic acid per day is recommended. This value is based on an estimated absorption efficiency of 25% and a daily secretion of 50 ug in milk (75).

It is not difficult to meet this requirement if the pregnant woman consumes adequate amounts of food, selected from a wide variety. Supplementation with this vitamin is ordinarily not necessary.

B. Food Enrichment:

Because of a lack of iron-rich foods and difficulty in meeting the requirement of 18 or more mg per day, iron fortification of foods is practiced in the United States to reduce the incidence of iron deficiency anemia. Table 5 provides the Federal Standards of Identity for iron enriched foods.

Table 5: Federal Standards of Identity for iron enriched foods

Food	Minimum mg iron per pound	Maximum mg iron per pound
Bread, rolls and other baked foods	8.0	12.5
Flour	13.0	16.5
Farina	13.0	not established
Macaroni, noodle paste products	13.0	16.5
Corn meal	13.0	26.0
Rice	13.0	26.0

Robinson, C.H.: Tabular Materials in Normal and Therapeutic Nutrition, 13th ed. Pa., Lea & Febiger, 1970.

C. Supplemental Food Program in Pregnancy:

Many mothers and infants constitute a "nutritional risk" because of inadequate nutrition due to inadequate income. The government has established a supplemental food program to provide adequate nutrients to low-income pregnant women in this country.

The WIC (Women, Infants and Children) Program has been developed to provide maternal care and supplemental foods for mothers and their offspring. The addition of essential foods has beneficial effects on the health of these mothers and their children.

D. Improved Food Preparation:

Inadequate dietary intake may be caused by improper methods of food preparation. Highly nutritious foods are seriously reduced in nutritive value when improper methods of preparation are used. Folic acid, a water

soluble, heat sensitive vitamin is lost or destroyed during the usual methods of cooking. Prolonged heating in large amounts of water and discarding the liquid in which the food is cooked increase the destruction and loss of folic acid as well as a number of other nutrients (40).

Foods providing liberal amounts of iron and folic acid are listed in Table 6.

Table 6: Food sources of iron and folic acid

Nutrients	Food sources
Iron	Best: liver Good: meat, egg yolk, enriched bread and cereals, peaches, apricots, prunes, raisins, dark green vegetables, molasses and legumes Poor: milk, cheese
Folic Acid	Best: liver, kidney, yeast, deep green vegetables Good: lean beef, veal, wheat cereals Poor: root vegetables, dairy foods, pork, light green vegetables

Robinson, C.H.: Normal and Therapeutic Nutrition, 13th ed. Pa., Lea & Febiger, 1970.

E. Sanitary Improvement:

In areas where hookworm infection is the principal cause of iron deficiency anemia, the best preventive measure is obviously the eradication of these parasites. Sanitation programs are closely linked to improved standards of living.

F. Maternal Care:

The outcome of the pregnancy for both mother and child is directly related to the nutritional status of the mother prior to conception,

nutritional intake during pregnancy and a host of environmental factors including sanitation.

Routine examination of urine, blood pressure, hemoglobin level and body weight permit treatment necessary for maintaining the health of mother and child.

G. Nutrition Education for the Public:

Large segments of the population do not appreciate the importance of diet and health. Little knowledge of nutrition often leads to the acceptance of false or misleading information. Therefore, it is important for community services providing health care for pregnant women, mothers and young children to give high priority to nutrition education in a form which can readily be applied.

CONCLUSION

Anemia is a world-wide problem. It is more common during pregnancy than in the non-pregnant state. Anemia is a general indicator of an individual's health state. It is closely linked to malnutrition and many disease conditions. Complications during pregnancy often develop in the anemic mother. These may result in high risk situations for both mother and child.

Nutritional anemia in pregnancy, caused by an iron and/or folic acid deficiency, is a common problem, world-wide. Its incidence is high among women of low socioeconomic status; those who have had successive pregnancies or multiple births; those engaged in prolonged breast feeding prior to their present pregnancy; and during adolescence.

The marked increase in blood volume which occurs during pregnancy involves larger increases in plasma volume than red cell mass. The peak

increment in plasma volume occurs at approximately the 34th week of gestation and decreases slightly before term. This physiological characteristic of pregnancy increases the body's need for iron. In addition, 3 to 4 mg of iron are transferred to the fetus per day during the last trimester. Total iron cost of a normal pregnancy is 365 to 790 mg.

Laboratory findings of iron deficiency anemia include: depletion of iron stores, rise in transferrin levels, fall in serum iron, decrease in hemoglobin concentration, and the appearance of hypochromic anemia. Erythrocytes are small and pale.

No change in the absorption and metabolism of folic acid occurs during pregnancy. A deficiency of this substance, however, produces decreased blood folic acid levels, hypersegmentation of neutrophil nuclei in peripheral blood, increased urinary FIGLU excretion, decreased folic acid concentration of erythrocytes, macro-ovalocytosis and megaloblastic anemia. Cells are oval with marked variations in size and shape.

Nutritional anemia is caused by an increased demand, gastrointestinal disturbances, impaired absorption, and insufficient dietary intake. Anemia in pregnancy produces symptoms of weakness, easy fatigability, pallor, palpitation, headache, bodyache and nausea. If the anemia is not treated, cardiac failure, inability to withstand hemorrhage, and a decreased resistance to infection may occur.

Maternal anemia may also have adverse effects on fetal development. These include an increase in mortality rate, fetal hypoxia, premature birth and low birth weight.

Customary treatment of anemia includes the oral administration of 300 mg of ferrous sulfate three times a day or the intramuscular injection of 2 ml

of inferon. Folic acid deficiency anemia is treated by supplementing the diet with 1 to 5 mg of folic acid per day depending upon the severity of the condition.

Nutritional anemia in pregnancy may be prevented by nutrient supplementation, food enrichment, supplemental food programs, improved food preparation techniques, sanitation and maternal care. A wide-spread and effective program of nutrition education for all persons is currently needed to prevent and combat nutritional anemia.

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NUTRITIONAL ANEMIA IN PREGNANCY

by

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AN ABSTRACT OF A MASTER'S REPORT

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ABSTRACT

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