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Iron deficiency anemia in pregnancy : with emphasis on the metabolism of iron and therapy (includes studies using FE59 in pregnant albino rats)

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IRON DEFICIENCY ANEMIA IN PREGNANCY
WITH EMPHASIS ON THE METABOLISM OF IRON AND THERAPY

Includes Studies Using Fe^{59} in Pregnant Albino Rats

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I. INTRODUCTION

Iron and its role in body metabolism, enzymes, and hemopoiesis has been studied extensively for the past half-century. However, only in the last 25 years have most of the current concepts been postulated. The present state of knowledge is in an endless flux which makes this field of investigation stimulating to the investigator. Those, who, in times past, have advocated the Blaud pill, those proposing the "physiologic anemia of pregnancy" and those refuting it, those for and those against intramuscular and intravenous iron therapy, and the champions of the "mucosal block" theory and those opposing it----all these conflicts in one area of medicine have kept active the research in this field.

With these varied concepts, the literature is abundant with writings in the area of iron metabolism associated with iron deficiency anemia of pregnancy. This paper will correlate some of the aspects of this topic into one presentation. Special emphasis will be placed on iron metabolism and the treatment of iron deficiency anemia in pregnancy. Also included is data and discussion of experiments using Fe^{59} intravenously in pregnant rats to study various aspects of iron metabolism in pregnancy.

II. HISTORICAL REVIEW

As in almost every subject in medicine the history of iron and its theraputic uses is intriguing and enlightening. Long before the true Iron Age, which began approximately 1000 B.C., the element

iron was known and used in medicine. There was meteoric iron which was recognized of celestial origin and emphasized the superstitious and supernatural side of medicine. One such superstition was that a wound could only be healed by the metal inflicting the wound. (1,2)

Dioscorides, Galen, Celsus, and Aetius advocated the use of iron in cases of splenic enlargement, dysentery, and menorrhagia which suggests early recognition of the value of iron in secondary anemias. (2)

Avicenna recognized that iron was of no therapeutic value unless it was a salt. He prescribed an acetate salt of iron but warned against gastrointestinal upsets with prolonged or excessive use. He also described chlorosis and its treatment. Lange (1554) is also commonly given credit for describing this extreme form of iron deficiency anemia. The classic description of chlorosis, however, was by Sydenham (1661) and he also prescribed a dosage of 0.5 to 1.0 Gm. iron per day for treatment. (2)

Paracelsus of the Renaissance era came from a family of Swiss miners. He was familiar with the new process of acid digestion and blended this with the older distillation techniques in an attempt to isolate iron. Unfortunately, he became preoccupied with the distillate rather than the residues of the acid digestion and hence threw "the baby out with the bath water". (2)

It was inevitable that experiments should turn to human blood since it was known that iron in the diet in some manner made a

person feel better. Menghenni (1746) showed that iron in the blood could be increased by feeding animals iron containing foods. Both Sydenham and Willis expressed the belief that iron could impart its color to blood. Iron therapy was in vogue at this time for all people with pale complexion. (2)

Pierre Blaud (1813) introduced the immortal Blaud pill which was a combination of ferrous sulphate and potassium carbonate with approximately 300 mgm. ferrous sulphate in each pill. He advocated increasing the dosage to maximum toleration taking from two to twelve pills per day. This was effective by subjective evaluation but from 1890 to 1920 iron therapy fell into disrepute partly due to the intolerance to ferrous sulphate. This intolerance to ferrous sulphate has since been questioned. (1)

About the same time Bunge stressed the use of organic iron salts because, he thought, inorganic iron was converted to sulphide in the stomach and intestines thus not absorbed. This erroneous theory was immediately refuted by MacCallum and Stochman but the damage was done. Now a second reason developed for the discontinuance of ferrous sulphate as a form of therapy. (3)

Williamson and Ets (1925) proported to show that inorganic iron was not incorporated into hemoglobin, so why use it? Haden (1938) reviewed the whole field and once again suggested the dosage level of the Blaud pill of a century earlier. (3)

Whipple began making his experiments in iron metabolism and his ideas for iron usage were presented. This work and other which was to follow won for him the Nobel Prize. (4)

Present investigators as Hallberg, Lund, Nylander, Cartwright, Holly, Wintrobe, and others have now organized the current concepts of iron metabolism and iron therapy in deficiency states. From this point in our knowledge the intercelluar iron utilization, placental transport of iron, and bone marrow assimilation of iron must be discovered.

The history if iron is one that illustrates how closely progress and methods are associated in science. Initially the methods were too speculative but eventually they became more scientific and advances in the knowledge of iron in medicine were forthcoming. Now we are awaiting better methods of studying cellular metabolism for the next phase of the history of iron.

III. IRON METABOLISM

A. General Aspects

Ionic iron is one of the most essential yet potentially most toxic minerals in mammalian physiology. It not only acts as an enzyme cofactor but is an important component of intracellular respiratory enzymes. Yet iron in massive doses may cause death. Iron containing compounds may be divided into two general categories. The porphyrin group is represented by hemoglobin, myoglobin, and the heme enzymes (e.g. cytochromes, peroxidase, and catalase). (5) Secondly, the non-porphyrin group is represented by ferritin, transferrin (siderophilin), and hemosiderin. (6)

The total iron content in the body of an adult female amounts to 3.0 to 4.0 Gm. of which 70 to 75 per cent is contained in the

hemoglobin molecules. (7,8) Myoglobin contains 5 to 10 per cent and a smaller amount is in the respiratory enzymes. Storage iron accounts for 500 to 1000 mgms. or 15 to 20 per cent and is stored primarily in the liver, spleen, and bone marrow. (7)

Josephs (9) raises the question as to the validity of the above paragraph. He states, "It is possible that the constancy of the total iron of the body is one of those convenient fictions that has been handed down from one authority to another because no one takes the trouble to find out whether it is true or not. Most people making the statement give no reference at all. Even the figure given of 4.5 Gm. or thereabouts has apparently never been actually determined."

The average diet contains 10 to 15 mgm. of iron per day (8) of which less than 10 per cent is absorbed per day. (8,10) Thus the adult female will absorb 0.5 to 1.5 mgm. of iron per day. In subjects with iron deficiency 3 to 5 mgm. of iron may be absorbed per day. (8,10)

B. Intestinal Factors Influencing Iron Absorption

Iron of both plant and animal origin must be released from its conjugates before it can be absorbed from the gastrointestinal tract. It is mainly in the ferric state and bound to such molecules as citrate, lactate, and to amino acids when ingested. Only ionic iron may be absorbed in man and the ferrous state is more readily absorbed than the ferric state. (11)

Iron absorption is mainly in the duodenum as illustrated by the accumulation of ferritin and hemosidern in the mucosa following oral administration of iron. (12) However, lesser amounts of ferritin have been found in the stomach and decreasing amounts of ferritin are found from the proximal jejunum to the distal ileum. (2,12)

Many other factors influence the absorption of iron from the intestine. Iron forms insoluble compounds with phytates of cereals (13) and with phosphates. (14) (Decreased iron absorption in rats is also seen with excessive intake of calcium, calcium carbonate, aluminum hydroxide, and magnesium trisilicate.) (15) To what extent the latter applies to man is uncertain. Decreased iron absorption is also seen with increased alkalinity of the intestinal tract and with excess bile acids which form insoluble iron salts. (19) Valuable information as to the iron content of various foods has been found by injecting radioactive iron into poultry and by adding radioactive iron to solutions applied on growing vegetables. As judged by the amount of radioactive iron incorporated into the hemoglobin and the amount excreted in the feces, less than 10 per cent was absorbed as was stated before. (10) The only way found to increase iron uptake was by adding 200 to 250 cc. of ascorbic acid to the meals. (10) Adding hydrochloric acid to patients with achlorhydria did not increase iron absorption. (10) Yet in patients with partial gastrectomies, absorption of radioactive iron from test meals was shown to be below average in 6 of 8 subjects. (16)

Hydrochloric acid given to normal patients does not increase iron absorption as long as iron is in the ferrous form. (17) These conflicting statements show that normal acid is important in iron absorption in some conditions but relatively unimportant in others. However, high body requirements for iron may need good hydrochloric acid secretion in the stomach for good absorption. (18)

The psychological aspects of iron absorption have also been partially examined. Ferrous sulphate (2 mgm. per Kg. body weight) was given in one-half glass of tap water to fasting patients. Fasting blood samples were drawn and blood samples at one, three, and five hours after ingesting the iron solution. Psychological evaluation of the 25 patients in this study revealed chiefly depression as the diagnosis. The conclusion was that serum iron levels following an oral dose were not related to the clinical condition of depression. (20)

C. Regulation of Absorption

The mechanism of iron absorption was thought to be clearly demonstrated (12,21) but prior and recent investigations have shown the mechanism to be much more complicated than originally proposed. (22-28)

The original theory held that all iron ingested must be in the ferrous form for absorption. Reduction of ferric to ferrous iron occurred in the acidic environment of the stomach and upper small intestine. The schematic presentation, modified from

Granick (21), is as follows.

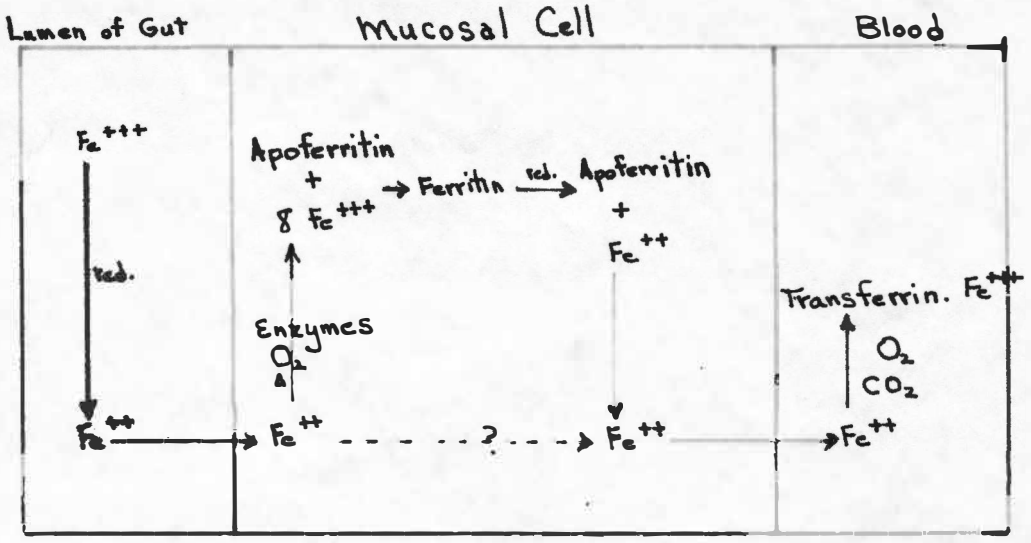

Fig. I. Schematic version of the regulation of iron absorption by the mucosal cell. Modified from Granick, S. (21)

The movement of ferrous iron into the mucosal cell and ferric iron out of the mucosal cell into the blood stream was thought to occur by the establishment of concentration gradients which depend on the ease of the conversion of ferrous to ferric iron. If one assumes that the oxidation potential is greater at the front part of the cell and the reduction potential is greater at the rear of the cell (the portion of cell away from the intestinal lumen) this might account for the movement of iron across the cell. On entering the cell, ferrous iron would be oxidized to the ferric state, thus establishing a concentration gradient, and upon leaving the cell ferric iron would be reduced to the ferrous form, thus establishing a second concentration gradient. The ferrous form would be then bound to transferrin in the blood, as the ferric state, and the concentration of free ferrous ion would remain low.

Apoferritin on combining with the ferric iron formed ferritin which supposedly is the transport mechanism across the cell. When the ferritin reached the inner aspect of the mucosal cell the iron was again reduced to the ferrous form which entered the plasma. The iron was again oxidized in the plasma to the ferric form which is bound with the protein transferrin to be transported to areas of body requirement for iron or to the storage areas. (5,29)

The above theory of iron absorption was held true until about five years ago when data appeared challenging the theory. Hailmeyer (30) was an early champion of the new concepts. He gave single doses of 15 mgm. ferrous iron orally to guinea pigs and found peak levels of ferritin in the duodenum at 20 hours and back to normal by 40 hours. However, simultaneous determinations of ferritin in the liver showed increased absorption from 20 to 40 hours. Thus absorption of iron must be continuing. Even during the highest ferritin level in the duodenum the amount of liver iron was increasing, again indication continued absorption. No indication could be found that an increase of ferritin in the intestinal mucosa reduced iron absorption. The experiments were continued by giving 15 mgm. ferrous iron per day for 28 days. An increase in liver iron could be seen for the first 14 days even though there were maximum ferritin levels in the stomach, small intestine, and duodenum, hence further absorption of iron was indicated. From the fourteenth day on no increase in liver iron was noted and there was a decrease in the ferritin of the stomach, duodenum, and small intestine.

It has been found that considerably more radioactive iron is absorbed by dogs made anemic by bleeding than in normal dogs given similar amounts of iron by mouth. (22)

Similarly, in humans during pregnancy and following repeated blood loss, the uptake of iron is increased. (31) The maximum amount of iron which can be absorbed under conditions of iron need is about 3 to 5 mgm. per day. (8)

The theory of mucosal block proposed by Granick (21) stated, in summary, the amount of iron absorption depended upon the amount of iron requirement by the body and was regulated by the intestinal mucosa. As was stated before, this theory began to falter when certain disease states were studied more carefully. For example, in pernicious anemia and familial icterus the iron stores are known to be high but very little iron is in the red blood cells. (31) Iron absorption, as measured by incorporation of radioactive iron into red blood cells, shows dereased absorption in pernicious anemia. However, this is due to decreased erythropoiesis and not to poor absorption. (24) In fact, it has been shown that there is actually more iron absorbed in pernicious anemia than is utilized for hemoglobin synthesis. (23)

It has been shown that unless iron is withheld from the diet of pyrodoxine deficient pigs, even though the plasma iron is markedly elevated, the tissues will be laden with deposited iron. (25) With alteration in the diet of humans, it has been shown that iron absorption can be increased in the absence of anemia. (26)

Increased absorption of iron has also been demonstrated in hemolytic anemias where serum iron levels are already high. (27) Hemochromatosis may develop during prolonged oral iron usage in hemolytic anemias. (28) With all of these experiments and the accumulation of data showing increased iron absorption in the face of elevated iron stores and/or plasma iron, it is evident that the mucosal block theory is not the entire mechanism for the control of iron absorption. Just exactly what the mechanism of iron absorption entails is not known at present. The rule adopted by Moore (32) that iron requirements are regulated by absorption and not excretion still holds but must be modified to fit these new concepts. Thus the theory of mucosal block may play a part in iron absorption but certainly is not the entire solution to this problem. Perhaps the plasma iron transport mechanism mediates the iron demand of the body to the absorptive area. (33)

Hallberg (33) in his recent work has demonstrated some very interesting factors of iron absorption which further illustrates that if a mucosal block is present, it is definitely not the entire control of iron absorption. Iron concentrations given orally to human volunteers varied from 4 to 150 mgm. but absorption rates were the same. However, the more iron given the higher the total amount absorbed. The amount of iron stored in the mucosa seemed to be independent of the total amount absorbed but was mainly determined by the magnitude of the dose administered. Absorption was shown to be rapid during the first 2 to 4 hours after oral

iron administration and then a slow phase of iron storage in the mucosal cell continued for several hours later. There was no correlation between the amount of iron absorbed and the plasma iron concentration at different times in 6 cases, with similar hematologic status, given 40 mgm. oral iron.

Patients were given constant intravenous infusions of inert iron to keep the transferrin saturated. They were then given 40 mgm. iron orally and there was marked decrease in iron absorption as compared with a similar study on the same patient three days prior without the constant intravenous infusion. A rapid decrease in absorption takes place when the plasma iron approaches the total iron binding capacity. Patients with partial saturation of transferrin have iron absorption at varying yet almost normal rates. (33)

If 5 Gm. of transferrin was given intravenously to patients, it will cause increased flow of iron from stores to plasma and decreased flow from plasma to stores. This amount is very small, however. (33)

Hallberg (33) also gave patients continuous gastric feedings of iron (50 mgm. per hour). At the point 3 to 4 hours later when the absorption began to decrease, transferrin was given intravenously and the absorption of iron once again was elevated. This demonstrates that it is not exhaustion of the mucosal cell transport system that regulates iron absorption but rather either decreased total iron binding capacity or increased plasma iron levels or both. When the patients were given single doses of iron (40 mgm.)

and then investigated as those immediately above, they showed no increase in absorption of iron. This is probably because there was very little ionized iron in the gastrointestinal tract at the time the transferrin was given. This suggests the possibility of giving more frequent doses of iron during therapy for iron deficiency. (33)

The importance of these studies lies in the conclusion that the iron-transferrin system probably mediates the iron demand of the body to the absorptive area thus forming a basis for the regulation of iron absorption.

D. Iron Transport

Iron is transported in the plasma by an iron binding protein which is a beta-1-globulin with a molecular weight of 90,000 capable of binding 1.25 gamma of iron per molecule of protein. This protein is commonly called transferrin or siderophilin. (34) It is estimated the plasma contains 2 to 4 Gm. of iron binding protein per liter capable of binding a total of 3 mgm. of iron per liter. (34)

Under normal conditions there is enough iron binding protein to bind with 9 to 10 mgm. of iron but only about one-third or 3 mgm. is bound at any one time. (5) Iron is bound to transferrin in a ration of two ferric atoms per mole. (5)

Average serum iron levels are 130 gamma per 100 cc. (35) with a range of 60 to 200 gamma per 100 cc. The average normal total iron binding capacity is 359 ± 30.8 gamma per 100 cc. (36) or 312

gamma per 100 cc. in studies by Rath and Finch. (35) The serum iron plus the iron binding capacity equals the total iron binding capacity. The iron binding capacity is increased in acute and chronic blood loss (36) and pregnancy. (37) The iron binding capacity decreases in acute and chronic infections, pernicious anemia, hemolytic anemia, cirrhosis, uremia, malignancy, and all pathological conditions with decreased proteins. (36,37)

The transport mechanism of iron may be illustrated as follows.

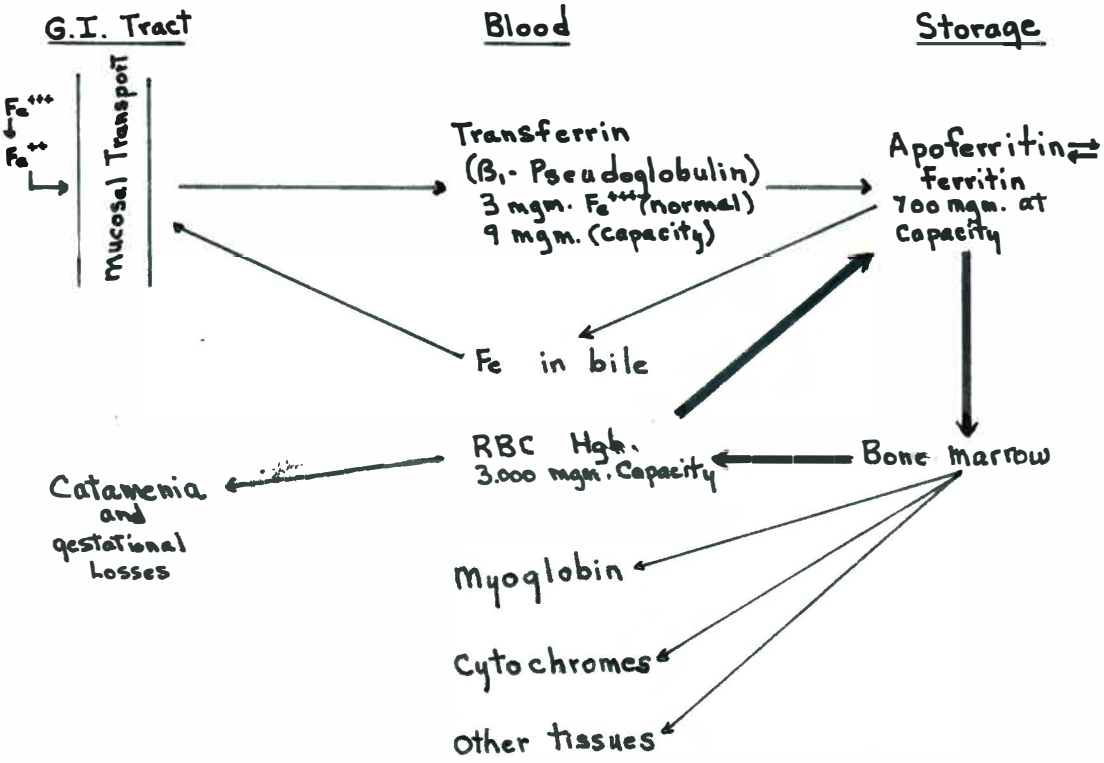

Fig. II. The metabolism of iron. The above is a schematic illustration of the cyclic movement of iron. From Drabkin, D. L., (38)

E. Iron Storage

The main sites of iron storage are in the liver, spleen, and bone marrow. (38) The adult male liver contains approximately

700 mgm. of iron present almost entirely as ferritin. (5) Iron is stored in the cells as ferritin or hemosidern. (7) Whether the hemosidern is a physiological form of iron storage or not has been questioned. Drabkin (38) suggests that hemosidern is just tissue iron in excess of the ability of apoferritin to bind the iron.

Whether ferritin or hemosidern forms depends on the amount of iron administered and the duration of cellular uptake. In large doses, iron is briefly stored as hemosiderin and then later is changed to ferritin. With small doses iron is bound to ferritin immediately. Ferritin seems to be the more differentiated and, for the cell, the more physiologic form of iron. (30)

In infections and inflammations there is a decrease in spenic and hepatic ferritin. This is probably due to the inability of the liver to synthesize apoferritin or decreased protein in the body. There is increased hemosidern in the liver at this time but the total absolute amount of iron may be the same or only slightly increased in the liver. Pure histochemical methods, which measure hemosidern, would falsely indicate a pathologic increase of iron in the liver. Thus, these methods may not be used as absolute guides to the amount of iron storage in all patients. (30)

The factors regulating the amount of stored iron are absorption and excretion of iron plus the amount of circulating hemoglobin. (7) The amount of storage iron may be estimated by staining an aspiration of the bone marrow. (7,18,40) This test may be valuable in the evaluation of the hematologic status of a patient.

Excessive amounts of hemosiderin in the tissues may be associated with a condition known as hemochromotosis. (40) However, the administration of iron, intravenous or oral, or in the form of blood transfusions does not necessarily produce hemochromatosis. (40) As many as 587 transfusions were given to one patient who was later found to have hemosiderosis but not hemochromatosis. (41) Both conditions indeed have excessive iron in the tissues but there usually is more in hemochromatosis. (42) Hemosiderosis and fibrosis, which is termed hemochromatosis, generally parallel one another but Ellis and associates (43) could find no evidence of a causal relationship between the two conditions.

If iron is not used on its initial contact with areas of utilization, it is temporarily stored (pooled). If the erythropoietic activity is not reduced and the amount of iron not too great, practically all of the iron will be utilized in the next few days. It is the speed and relative completeness of the use of this iron that has led to the designation "labile iron pool". (9)

If iron is given intravenously in colloidal form (as saccharated ferric oxide), its pathway is similar to iron derived from hemoglobin breakdown. Ferrous iron apparently goes to the tissues more readily than the ferric form when given intravenously. (43a) Thus it is taken up by the reticuloendothelial cells and is utilized in new hemoglobin formation exactly as iron is derived from hemoglobin breakdown. Iron from hemoglobin breakdown, or from any other source, is not all immediately transported to the site of

hemoglobin synthesis but enters the "labile pool" consisting of about 4 to 5 days supply. This "pool" is in equilibrium with hemoglobin synthesis on the one hand and with less labile iron stores on the other. Increased iron availability from any one source would cause an increase in the size of the "labile iron pool"; thus, utilization of labeled iron (Fe^{59}) might be reduced by diversion to non-hemopoietic tissues. This may cause error in the calculation of iron turnover by radioactive tracer methods should they be in use at the time. (9)

There are usually two storage areas for iron---parenchymal and reticuloendothelial. In general, parenchymal storage is derived from absorbed iron and iron injected in the ionic form while the reticuloendothelial storage is derived mainly from hemoglobin breakdown and injected iron in colloidin form. Reticuloendothelial iron normally is used for the synthesis of new hemoglobin on a daily basis. The parenchymal storage, largely derived from absorbed iron, is used to repair losses from hemorrhage. Eventually, iron deposited in the reticuloendothelial system is transported to parenchymous storage if it is not used in immediate hemoglobin formation. (43) Tissue hypoxia is felt to be the mobilizing factor for the parenchymous storage. (9)

The important features to stress concerning iron stores are: (1) Normal iron stores are approximately 1000 mgm. and, (2) Iron deficiency anemia does not occur until these stores have been depleted. (39) Conversely, iron stores are not replenished until

hemoglobin has reached a normal level (above 12 Gm. hemoglobin per 100 cc. whole blood). (44)

F. Excretion of Iron

The body rigidly conserves iron. Iron losses per day normally do not exceed 1.0 to 1.5 mgm. (5,7,8,45) Small amounts of iron are lost in the urin, sweating, and hair and nail exfoliation. Iron is also lost via the kidneys in small amounts (7,45,46) via sloughing of the skin (45), and via the gastrointestinal tract (7,45,46). Acute and chronic hemorrhage account for significant blood loss. Approximately one milligram of iron is lost per two cubic centimeters of blood loss. The amount of blood loss during menstruation amounts to 20 to 30 mgm. per month or approximately 40 to 60 cc. of blood. This delicate balance of iron absorption and excretion tends to keep the female in a precarious state of iron balance. A small negative balance is partially responsible for the depleted iron reserves in a majority of females. (45) Thus iron deficiency anemia is common in females. By way of contrast, iron deficiency anemia rarely occurs in males except where there is chronic blood loss or an associated malabsorption syndrome. (45)

IV. IRON REQUIREMENTS DURING PREGNANCY

The average pregnant woman has 3.0 to 4.0 Gm. iron in her body. (7,8,9) With the onset of pregnancy, new iron demands are made by

the fetus. Table 1 illustrates the iron required by a pregnant woman to maintain normal hematologic values.

Table 1
Iron Requirements of a Pregnant Woman

	Not Pregnant	Pregnant
Blood Vol.	4000 cc.	5000 cc.
Hgb. (Gm./100 cc.)	13.0	13.0
Hgb. Mass (Gm.)	520	650
Hgb. Iron (mgm.)	1768	2210
Iron Needed (mgm.)	----	442

As can be seen, the woman needs 442 mgm. of iron just to maintain a hemoglobin of 13.0 Gm. per 100 cc. of whole blood when the blood volume expands about 25 per cent as it does normally during pregnancy. (7,8,45) The woman absorbs 1.0 to 1.5 mgm. iron per day from her diet which is a total of 280 to 420 mgm. during her pregnancy. Excretion of iron during pregnancy is minimal because menstruation has ceased. Thus we find the woman 50 to 200 mgm. iron deficient to maintain her own hematologic values during pregnancy. [Iron needed (450 mgm.) minus obtained from diet (280 mgm.)].

The fetal requirements during pregnancy must now be delineated. The term fetus requires 350 to 400 mgm. of iron. (7,47) The largest amount, or about three-fourths of the fetal requirement, is during the last trimester. Table No. 2 is a summary of iron requirements in pregnancy encompassing all factors.

Table 2

Total Iron Requirements in Pregnancy

	Iron Needed	Iron Supplied
a. Iron for mother to inc. blood volume	500 mgm.	
b. Fetal iron requirements	400 mgm.	
c. Blood loss at delivery	100 mgm.	
d. Iron excreted in gestation	150 mgm.	
e. Iron absorbed via diet		420 mgm.
Total	1150 mgm.	420 mgm.
f. Deficit---iron needed	730 mgm.	
g. Maternal iron stores (ideal)		1000 mgm.
h. Total in stores during preg.	270 mgm.	
i. Iron from dec. bl. vol.	500 mgm.	
j. Total fron stores p. partum	770 mgm.	
k. NET LOSS DURING PREGNANCY		230 mgm.

The previous values are for a pregnant woman with ideal iron stores. However, many women enter pregnancy in a precarious state of iron balance. (45) Iron absorption of 15 to 45 mgm. per month and blood losses of 25 to 40 mgm. per month due to menstruation and other excretion leaves a small positive balance if any at all. Slightly elevated blood loss or, by the same token, slightly decreased absorption and the woman will be in negative iron balance. Hence, it is very conceivable that by the time the woman enters the child bearing era the iron stores may be diminished or entirely absent.

Daily iron requirements are estimated to be 1 mgm. per day the first trimester and over 2 mgm. per day the last trimester. (7) Thus the heaviest demands on the woman are during a period of about 90 days.

Holly (48) states that "normal" hemoglobin values of 10 Gm. per 100 cc. whole blood and a hematocrit of 33 per cent is too low.

The value he proposes is 11.5 to 12.0 Gm. per 100 cc. for the hemoglobin. The following reasons are cited: 1) When the hemoglobin falls below 11.5 Gm. per 100 cc., the decreases in the serum iron and increases in iron binding capacity are consistent with iron deficiency anemia, 2) storage iron is depleted as determined by bone marrow examination (8,48), and 3) administration of iron will maintain normal hematologic values during pregnancy. In summary, the statement by Holly (48) is very applicable, "Hematologic values established for the nonpregnant apply for pregnancy as well".

The normal hematologic values for pregnancy are found in Table 3 (modified from Holly). (48)

Table 3
Normal Hematologic Values for Females

	Mean	Minimum	Maximum	S.D.
Age	24	19	38	----
Gm. Hgb.	13.4	11.6	15.9	0.83
Mil. RBC/mm^3	4.44	3.67	5.47	0.38
Hematocrit %	41.5	37.5	47.0	2.00
Serum iron (Gamma %)	103	64	192	29.0
IBC (Gamma %)	181	100	285	11.0

Dietary sources of iron are not adequate to meet the iron requirements of pregnancy. (47) A good diet is of great benefit, however, in helping avoid iron deficiency. The best sources of iron are meat (esp. liver, heart, and kidney), egg yolk, fish, molasses, green vegetables, and dried fruits. (49) Cereals, although fortified

with iron, are poorly absorbed hence not a good source of iron. (49) To maintain normal hematologic values in pregnant women supplementary iron is required. (47)

Physiologic anemia of pregnancy was a term used to denote the heretofore moderate decreases in hemoglobin during pregnancy. Because of the known increase in plasma volume during pregnancy, the concept of hemodilution was suggested. This change in hemoglobin value was accepted as the normal course during pregnancy. However, recent investigators have shown that with supplemental iron during pregnancy, no anemia develops. (2,7,8,18,47,48) In reality, anemia occurs because of iron deficiency and not because of increased plasma volume. Thus, anemia in pregnancy is not physiologic but usually the result of iron deficiency. (47)

V. TYPES OF ANEMIA IN PREGNANCY

A. Classification

Anemia in pregnancy is a common complication, occurring in at least 50 to 75 per cent of pregnancies if appropriate therapy is not begun. (50) There has been a considerable amount of material published classifying and re-classifying the various types of anemia associated with pregnancy. The following classification has been adapted and modified from the presentation by Eastman and Hellman (51) and Holly. (38,50)

I. Anemia Directly Related to Pregnancy

1. Iron Deficiency
2. Megaloblastic
3. Hypoplastic or Refractory

II. Anemia not Directly Related to Pregnancy

1. Sickle-Cell (S-A, S-S, S-C)
2. Hemoglobin C Disease
3. Hemolytic Anemia
   a. Familial
   b. Acquired
4. Infection with Anemia

Only a brief discussion will be made of the anemias other than iron deficiency anemia, which will be discussed in detail.

B. Refractory Anemia

This form of anemia is often associated with granulocytopenia and thrombocytopenia but is not associated with chronic renal disease, hepatic disease, or malignancy. (52) The letter conditions may have the same signs and hematologic values but are not classified as true refractory anemias because of the prolonged course of these conditions. Several synonyms have also been used as aregenatory, hypoplastic, aplastic, and myleophthisic. The latter term is most often used to describe malignant or pathologic processes which replace bone marrow, therefore, is not an entirely correct term to be used to describe refractory anemia.

Refractory anemia is usually established by the following criteria. (52)

1. The appearance of anemia during pregnancy that does not respond to treatment other than transfusions, and that disappears after delivery.

2. Normal or increased serum iron.

3. Thrombocytopenia and granulocytopenia.

4. Normoblastic hypoplasia of the bone marrow. A few have hypercellular bone marrow for reasons unknown. The normal bone marrow has a ratio of normoblasts to leucocytes of 1:3 or 1:4 (from 16 to 24 per cent of the counted cells) however, in refractory anemia the ratio may be 1:5 or more and the percentage of normoblasts may fall to 5 per cent. The marrow apparently has an arrest of the proliferation of normoblasts. (38)

5. No response to hematinics with the possible exception of cobalt. (38)

6. Peripherial blood smear usually normocytic and normochromic.

7. Absence of any other cause of anemia.

A bone marrow examination is absolutely necessary to rule out any form of bone marrow depression. Iron, in any form, should not be given unless an associated iron deficiency can be demonstrated. The iron stores are usually not depleted and therapy with iron will only tend to cause hemosiderosis. (38)

The only treatment for this condition is blood transfusions. Transfusions are usually done just prior to delivery if the hemoglobin falls below 10 Gm. per 100 cc. If no therapy is deemed necessary, the hematologic values usually return to normal 2-3 months post partum. (38)

C. Anemia with Infection

Anemia associated with infection, especially chronic infection, is a common occurrence. The suggested etiology is depressed hemo-

globin formation due to the infection and the products of infection and the products of infection affecting the body. (52) Studies show that the hypoferremia which is associated with infection is not the result of a reduction in iron binding capacity but some other cause. (53) The serum iron is depressed proportionately more than the total iron binding capacity (53) but iron storage is adequate. (52)

The peripheral smear shows microcytic, hypochromic red blood cells, normal platlets and toxic granulations in the white blood cells. There is usually a mild to a moderate leucocytosis. Bone marrow examination reveals iron present but decreased erythropoiesis, both conditions which are not found with iron deficiency anemia. (52)

The diagnosis is usually made by the presence of anemia, leucocytosis, the presence of infection, and lack of response to iron therapy. Removal of the source of infection usually leads to prompt resolution of the anemia. (52)

Recovery can be estimated as there is a rise in the total iron binding capacity and serum iron as recovery proceeds. (53)

D. Familial and Acquired Hemolytic Anemia

This area of discussion is more extensive than any of the other causes of anemia in pregnancy. There will be no attempt to discuss this area fully but merely to list partially the causes of hemolytic anemia.

The hemolytic anemias have been classified as acute and chronic according to the clinical manifestations. This classification has

limited usefulness since fulminating symptoms may develop during the course of chronic disorders. Hence, the differentiation in to familial (congential) and acquired hemolytic anemia is much more accurate. Familial forms are the consequence of intrinsic defects in the erythrocytes wheres, as a rule, the acquired forms are due to extracorpuscular etiology.

The following classification is modified from Wintrobe (18).

I. Intracorpuscular defects

- a. Hereditary spherocytosis
- b. Congenital non-spherocytosis
- c. Hereditary leptocytosis (Thalassemia)
- d. Sickle cell disease
- e. Other hereditary hemoglobinopathies (C,D,E,G,H,I)
- f. Combinations of above (C,D,E)
- g. Paraxysmal nocturnal hemoglobinuria

II. Extracorpuscular defects

- a. Infectious agents (e.g. malaria, infectious mononucleosis, primary atypical pneumonia)
- b. Chemical agents
- c. Physical agents (e.g. heat, burns)
- d. Poisons
  1. Vegetable (e.g. fava bean, castor bean)
  2. Animal (e.g. snake venom)
- e. Iso-agglutinins
  1. Mismatched transfusions
  2. Minor group transfusion reactions (e.g. Kell, Duffy)
  3. Hemolytic disease of the newborn (e.g. Rh, ABO)
- f. Paroysmal cold hemoglobinuria
- g. Symptomatic hemolytic anemia
  1. Hemopoietic disorders (e.g. Hodgkins Disease, lymphosarcoma)
  2. Collagen disorders
  3. Miscellaneous conditions (e.g. liver disease, ovarian tumors)
  4. Thrombocytopenia purpura
- h. Idiopathic acquired hemolytic anemia

However, this classification has its limitations. Paroxysmal nocturnal hemoglobinuria seems to due to an intrinsic abnormality of the erythrocyte yet no genetic cause can be demonstrated. Also, in certain drug induced hemolytic anemias, the susceptibility to hemolysis appears to be inherited. (18)

E. Megaloblastic Anemia in Pregnancy

Megaloblastic anemia is a rare complication of pregnancy, especially in the northern areas of the United States. The incidence in the United States has been reported as 2.8 per cent of all anemias in pregnancy. (51) It apparently is more common in Europe and England than in the United States. (54) Several other terms have been used to describe this condition: pernicious anemia of pregnancy, macrocytic anemia, and nutritional anemia of pregnancy. However, the term megaloblastic anemia of pregnancy is more accurate to describe the chief feature of this condition, which is a megaloblastic bone marrow. (38,50)

Although megaloblastic anemia has been compared with pernicious anemia several key features of the latter are absent in megaloblastic anemia. Achlorhydria is rare and neurological lesions are never seen in megaloblastic anemia. (56,57) The peripherial smear is often normal in megaloblastic anemia and it does not respond to Vitamin B_{12} alone. (56)

The diagram on the next page modified from Holly (56) and Diggs (57) illustrates some of the biochemical differences between

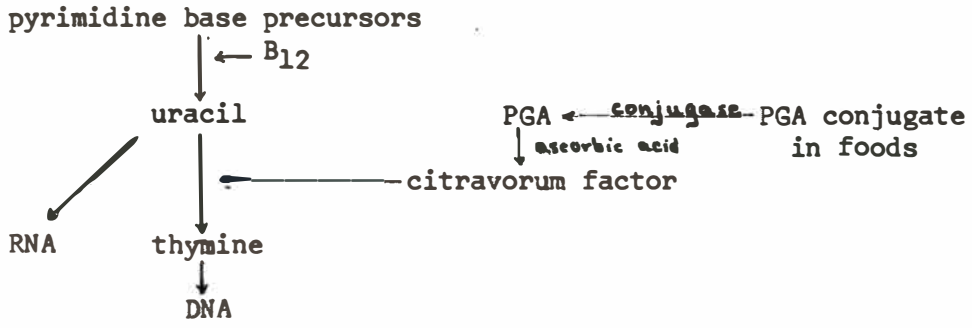

Figure III. Schematic representation of the synthesis of the nuclear materials of body cells.

pernicious anemia and megaloblastic anemia of pregnancy. In both conditions there may be a megaloblastic change in the bone marrow. Pernicious anemia is the result of a deficiency in Vitamin B_{12} and the synthesis of both RNA and DNA is affected. It is RNA which is concerned with the neurological manifestations of pernicious anemia. A satisfactory hematologic response in pernicious anemia is seen with either Vitamin B_{12} or with folic acid. However, folic acid does not alter the synthesis of RNA and will not correct the neurologic manifestations.

Megaloblastic anemia of pregnancy is primarily a folic acid deficiency thus no neurologic lesions are found. By the same reasoning used above, adequate treatment for megaloblastic anemia is folic and ascorbic acid not Vitamin B_{12}. (56,57)

Megaloblastic anemia of pregnancy is usually associated with a nutritional deficiency or a condition such as sepsis which interfered with normal bone marrow activity. (38,54) The patho-

genesis of this disease is thought to be a deficiency of ascorbic acid which ultimately leads to a deficiency of citrovorum factor. (38) Citrovorum factor, leucovorum, or folinic acid are names for a naturally occurring deriative of folic acid. (55) Maternal requirements for folic acid, citrovorum factor, and ascorbic acid are increased during pregnancy. (38,56) Megaloblastic anemia can be prevented by an adequate intake of Vitamin C. (38,56,57) Since the nutritional status of patients in the United States has improved, with subsequent increased intake in Vitamin C, megaloblastic anemia is becoming less common. (50)

Treatment of this condition consists of the administration of folic acid, 10 to 15 mgm. per day, or the combined use of ascorbic acid, 500 mgm. per day, and Vitamin B_{12}, 10 mgm. per day. Adequate prophylaxsis is 30 mgm. of ascorbic acid per day in the diet. (58) Iron therapy should be used only if the iron stores are low. (38)

F. Iron Deficiency Anemia

The most common anemia in pregnancy results from a deficiency of iron. It has been estimated that 95 per cent or more of the anemia encountered in pregnancy is due to iron deficiency. (38) However, this form of anemia is relatively easy to diagnose and to treat effectively.

The etiology of this condition has been discussed previously in this paper. Briefly, it may be again stated that the principal

cause of iron deficiency is blood loss. (59) This blood loss may be in the form of metrorrhagia, menorrhagia, previous post partum hemorrhage, frequent blood donations, peptic ulcer disease, parasitic infestation, hemorrhoids, frequent nose bleeds, tumors of the gastrointestinal tract, etc. Inadequate intake of iron in the diet has often been used to explain iron deficiency anemia. However, the normal intake of iron is usually adequate to supply the body's hematologic requirements if the simultaneous iron losses are not excessive and the woman is not pregnant. The exception to this fact is the malabsorption syndrome in which adequate iron intake may be present yet the patient has iron deficiency anemia. As an example of this, a woman with normal iron stores (1000 mgm.), a hemoglobin of 13 Gm. per 100 cc., not pregnant, a menstrual flow of 60 cc. per month, 0.5 mgm. iron per day excreted, and no dietary intake of iron will not become iron deficient (iron stores depleted and a hemoglobin of 10 Gm. per 100 cc.) for two years.

An entirely different clinical condition exists in the pregnant patient. Following the illustrations of Holly (38), three hypothetical obstetrical patients will be examined. All factors are constant in each patient except the first has 1000 mgm. of iron stores, the second 300 mgm., and the third no iron reserves at the onset of pregnancy. It is assumed that each woman excretes 0.5 mgm. of iron per day (150 mgm. for 280 days) and losses of 100 mgm. of iron via blood loss at the time of delivery are incurred. The blood volume of each patient when pregnancy begins

is 4000 cc. and this rises to 5000 cc. at 36 weeks. (60) The fetus requires 400 mgm. of iron. (9,38) Each patient begins pregnancy with a hemoglobin of 13 Gm. per 100 cc. With normal diet, iron absorption is 1.5 mgm. per day. The hemoglobin of 13 Gm. per 100 cc. is 520 grams of hemoglobin mass if the blood volume is 4000 cc. (13 Gm./100 cc. x 4000 cc. = 520 Gm. Hgb.). Since one gram of hemoglobin contains 0.0034 Gm. of iron, there is approximately 1800 mgm. total iron in 4000 cc. of blood. (0.0034 x 520 x 1000 = mgm. of iron)

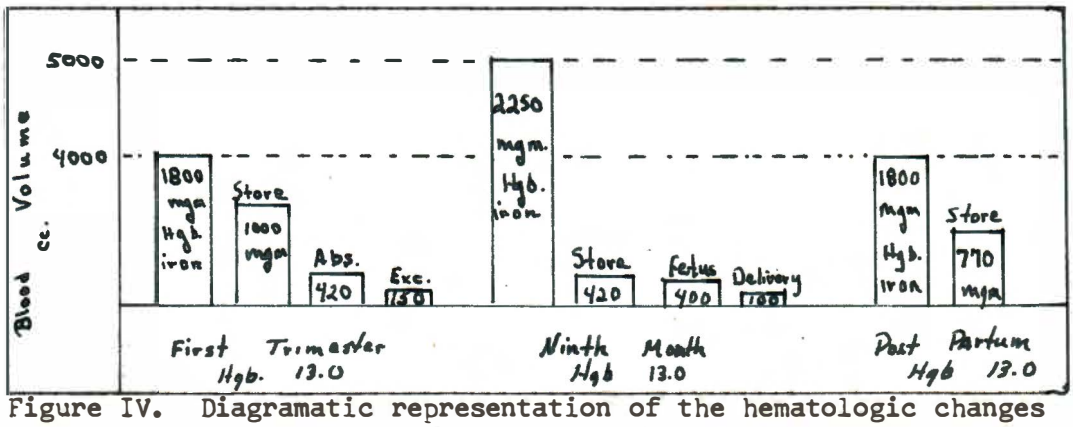

Figure IV. Diagramatic representation of the hematologic changes during pregnancy in a patient with iron stores of 1000 mgm. prior to pregnancy. (Store = iron stores; Abs. = iron absorption; Exc. = iron excretion; fetus = iron to fetus; Delivery = iron loss in blood at delivery.)

The first patient, Figure IV, starts pregnancy with 1000 mgm. storage iron, a hemoglobin of 13 Gm. per 100 cc., and a blood volume of 4000 cc. This quantity of hemoglobin contains 1800 mgm. of iron as noted above. To maintain the hemoglobin of 13 Gm. per 100 cc. when the blood volume expands to 5000 cc., the patient must increase the hemoglobin mass 130 Gm. and the hemoglobin iron 450 mgm. The net amount of absorbed iron (absorption minus excretion) is

270 mgm. Then 180 mgm. of iron are diverted from the storage areas and the hemoglobin remains at 13 Gm. per 100 cc. The fetus requires 400 mgm. of iron and 100 mgm. is lost at delivery through blood loss. Thus the post partum hemoglobin is 13 Gm. per 100 cc., total hemoglobin mass 520 Gm., hemoglobin iron 1800 mgm., and iron stores of 770 mgm. The net iron loss has been 230 mgm.

The second patient, Figure V, is exactly the same except the iron stores are now 300 mgm. at the onset of pregnancy. Since the fetus needs 100 mgm. of the net absorbed iron (270 mgm.) plus all of the storage iron the hemoglobin iron can only expand to 1970 mgm. The hemoglobin falls to 12.2 Gm. per 100 cc. and the total hemoglobin mass expands only to 610 Gm.

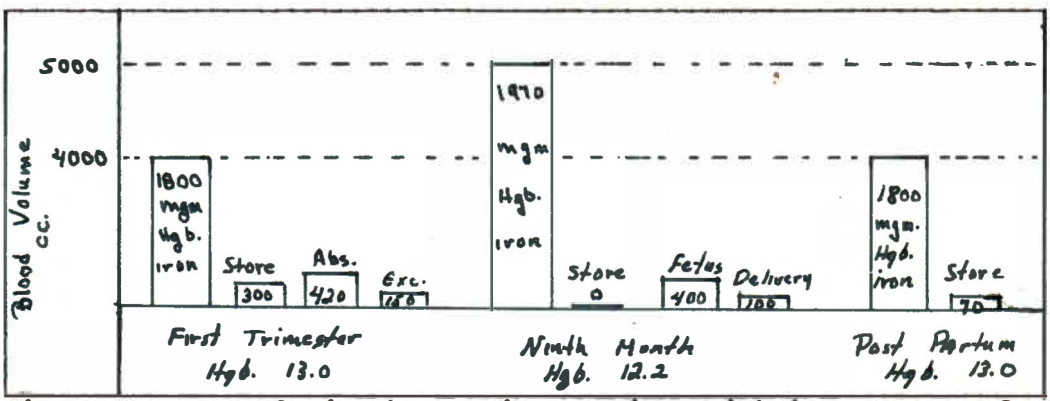

Figure V. Hematologic changes in a patient with iron stores of 300 mgm. prior to pregnancy. Captions as before.

The post partum condition of the hemopoietic system is a hemoglobin of 13 Gm. per 100 cc., total hemoglobin mass of 520 Gm., total hemoglobin iron of 1800 mgm., and iron stores are 70 mgm.

The third patient, Figure VI, with no iron stores at the beginning of pregnancy also has a hemoglobin of 13 Gm. per 100 cc.

To provide the fetus with 400 mgm. of iron, the net iron absorbed (270 mgm.) plus 130 mgm. from the hemoglobin iron must be used. The hemoglobin at the ninth month falls to 9.8 Gm. per 100 cc., the total hemoglobin mass to 490 Gm., and the total hemoglobin iron to 1670 mgm. Following delivery the final hematologic values are a hemoglobin of 10.2 Gm. per 100 cc., hemoglobin mass of 460 Gm., hemoglobin iron of 1570 mgm., and depleted iron stores.

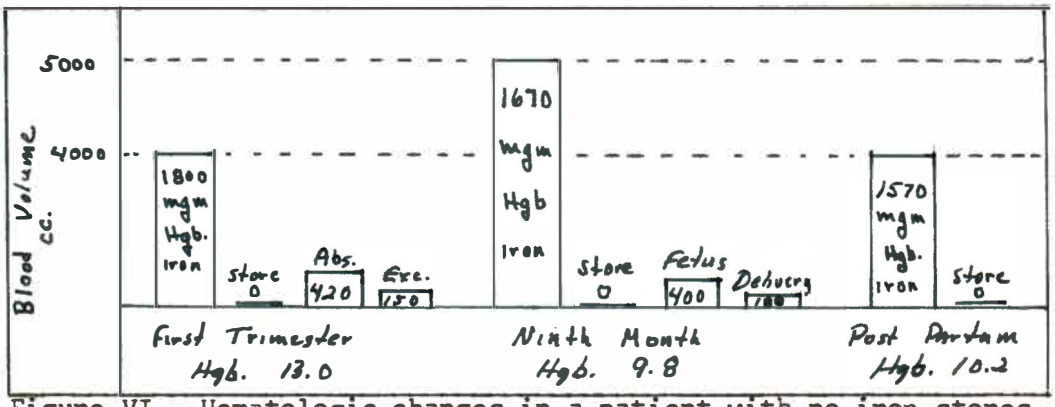

Figure VI. Hematologic changes in a patient with no iron stores prior to delivery. Note the markedly decreased hemoglobin at term. Captions as before.

The above three patients entered pregnancy with equal hematologic conditions at the initial examination but the degree of subsequent change was markedly different. Holly (38) states that approximately 20 per cent of the patients are like the first illustration, 60 per cent like the second, and 20 per cent like the third. Thus 80 per cent of the patients manifest some degree of anemia during pregnancy with 60 per cent slightly to moderately anemic and 20 per cent severely anemic.

It may be concluded from the previous discussion that a normal

hematologic status at the beginning of pregnancy in no way indicates the subsequent course which the hematologic values will take.

The classic clinical description of iron deficiency anemia includes weakness, fatigue, mucous membrane pallor, glossitis, brittle finger nails, and irritability. These are now rarely seen in pregnant patients; first, because the anemia is usually not severe enough to cause any symptoms other than fatigue and, second, the patient may attribute the fatigue to her pregnancy in general and only be aware of it after iron replacement therapy has been instituted. Finally, patients are now more often being given supplemental iron during pregnancy and post partum; consequently, anemia does not develop as readily as in former years.

The classical laboratory values in iron deficiency anemia includes decreased hemoglobin, hematocrit, serum iron, mean corpuscular volume, and mean corpuscular hemoglobin concentration. The peripheral smear appears hypochromic and microcytic. There is simultaneous elevation of the iron binding capacity and the erythrocyte protoporphyrin. The bone marrow has increased normoblastic elements and there is an increase in the myleoiderythroid ratio. (77) Most of the above changes are not definite or easy to evaluate when the anemia develops rather suddenly, as over the 9-10 month interval of pregnancy. Therefore, decreased hemoglobin, hematocrit, and serum iron are the best diagnostic tests during pregnancy. With severe, long-standing, iron deficiency anemia the other laboratory tests may be of value. More often, however,

the results from the other laboratory tests are equivocal and of little value. (38)

Kerr and Davidson (61) have complied an extensive statistical analysis of their patients evaluating the incidence, seasonal variation, age, and parity in relation to iron deficiency anemia. The incidence of anemia on the first clinical visit markedly increased with longer gestation time before the visit. The results are found in Table 4.

Patients seen in 1st. 11 wk. of preg.	2% less than 10.4 Hgb. 32% less than 12.6 Hgb.
Patients seen after 24 wk. of preg.	14% less than 10.4 Hgb. 78% less than 12.6 Hgb.

Table 4. Comparison of the hemoglobin values of patients seen for the first time at less than 11 weeks of pregnancy and those seen for the first time after 24 weeks of pregnancy.

The results in Table 4 are not entirely unexpected because of two reasons. First, iron demands are greater during the second trimester than during the first trimester and, second, the earlier that patients were seen in the clinics, the sooner definitive therapy was begun.

Pregnant women first seen in clinics during March and April had less anemia than those seen in August and September ($p < 0.001$). (61) However, Lund (62) found a lower incidence in the summer months.

The age of primagravid patients and the incidence of anemia was also evaluated by Kerr and Davidson. (61) They found no

significant difference in hemoglobin values in primagravid patients, with no previous iron therapy no matter what their age at the onset of pregnancy. This probably reflects again the fact that dietary iron is adequate to maintain normal hematologic values if the woman is not pregnant and she is not having any abonormal or excessive blood loss.

The most surprising statistics by Kerr and Davidson (61) were those concerning the effect of parity on the development of anemia. They found no significant difference in the hematologic values between 618 primagravidas and 390 parous women ($p > 0.3$). They also found no significant difference between primagravida and parous patients, pregnant with the last five years, in the degree of anemia. These results were attributed to a combination of the following: 1) Improvement in economics with simultaneous improvement in dietary intake, 2) Better doctor instruction as to the cause of anemia, and 3) Better care and treatment, both earlier and more vigorously, by the doctors. Patients treated vigorously and accurately in some clinics seldom developed anemia even with repeated pregnancies. (61)

The fact remains that all pregnant patients should receive supplemental iron therapy. Even the patient in Figure II, who had adequate iron stores, lost approximately 300 mgm. of iron during pregnancy. This iron loss should be replaced with supplemental iron.

Holly (38) reports a study of normal obstetric patients given supplemental iron as contrasted to those who did not receive iron

therapy. At delivery 66 per cent of the control group had a hemoglobin below 12.0 Gm. per 100 cc. whereas in the iron supplemented group only 17 per cent were below 12.0 Gm. per 100 cc. The dosage of iron given was not reported. Fisher and Biggs (63) report that prior to iron therapy in 92 patients, 80 per cent had hemoglobin values below 11.8 Gm. per 100 cc. at 4 months of pregnancy. After therapy 85 per cent had a hemoglobin value above 12.0 Gm. per 100 cc.

The need for iron therapy in pregnancy has been established. Now the criteria and methods of treatment must be evaluated.

VI. TREATMENT OF IRON DEFICIENCY ANEMIA

The need for iron therapy during pregnancy has been well established; however, the criteria for treatment have not been. Holly (38) states that all pregnant patients need some supplemental therapy. He does not state when therapy should begin but implies iron should be given throughout pregnancy. It has also been stated that therapy should begin any time the hemoglobin falls below 12 Gm. per 100 cc. of hemoglobin. (45) Kerr and Davidson (60) recommend iron therapy to all pregnant patients but late in pregnancy rather than early. The following reasons were given for their choice of therapy late in pregnancy: 1) The patient saves money and the inconvenience of taking iron throughout the entire pregnancy, 2) the iron is better absorbed later in pregnancy, 3) fetal demands for iron are greatest late in pregnancy, and 4) results with this method have been satisfactory. However, they routinely give iron

early in pregnancy if the hemoglobin is below 12.6 Gm. per 100 cc. or the patient is past the twenty-fourth week of gestation.

The above discussion illustrates the multiple opinions concerning iron therapy in pregnancy. There are several aspects of this problem to consider but the following general points may be used as early guides to the need for iron supplement therapy.

1. Clinical, as opposed to laboratory, diagnosis of anemia is one of the most falacious ventures in the whole practice of medicine. Hematologic status can not be evaluated adequately by the patient's symptoms, signs, or by physical examination. These may be an aid to the diagnosis if the anemia is severe but will be of little value in the mild and moderate anemias.

2. The demonstration of anemia must be followed by evaluation as to the type of anemia present. As was stated earlier, this can not be done by a single hemoglobin determination.

3. As a minimum preliminary evaluation, the hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin concentration, and a well prepared smear, carefully examined, must be preformed.

4. With very few exceptions, anemia consequent upon iron depletion will respond to adequate oral iron therapy.

5. If response is not noted with iron therapy, oral or intramuscular, the cause of the anemia must be ascertained. This means a serum iron, bone marrow examination, a search for malignant lesions, and a repeat inquiry of the patient concerning possible blood loss.

6. Iron therapy should not be used unless the cause of the anemia is iron deficiency.

The problem of therapy in iron deficiency anemia in particular must now be considered. The above general points are necessary for the treatment of all anemias but the criteria for the treatment of iron deficiency anemia should be listed. This area of the literature is very confusing to the physician determining the dosage, route, response, and time interval necessary in the use of iron preparations. The following points must be considered.

1. The calculation of the total adequate dose must be done first. The following formula may be used to estimate the total requirement for iron:

$$\frac{13.5 - \text{pt's. hgb.}}{100} \times \text{pt's. blood vol. in cc.} \times 3.4 + 500 = \text{mgm. of iron required.}$$

This formula will give the milligrams of iron required to raise the hemoglobin to 13.5 Gm. per 100 cc. The average blood volume for a non-pregnant woman is 4000 cc. and 3.4 is the conversion factor for grams of hemoglobin to milligrams of iron. The 500 mgm. is added for iron storage. One important principal is to provide enough iron for hemoglobin formation and to replace the iron stores. (38)

2. The above calculated dose must be delivered to the hemopoietic and iron storage areas of the body. (65) Intramuscular

and intravenous iron is in the body directly but only 4-10 per cent of the oral dose of iron is absorbed from the gastrointestinal tract. Thus, the total dose of oral iron must be much higher than the parenteral route.

3. The time for therapy must be determined. Oral therapy is desired but is not as rapid as intravenous or intramuscular therapy.

4. An adequate response by the parenteral route is a rise in hemoglobin of 2 Gm. per 100 cc. or a rise in the hematocrit of 5 per cent in three weeks. If the blood fails to show this response, one of the following must be considered: 1) the anemia is not due to iron deficiency, 2) complicating disease impairs the ability of the marrow to respond, 3) there is continued active blood loss. (66)

5. The response to therapy may be masked. During the second trimester plasma volume expands more than red cell volume, hence the patient may have a improving hematologic status yet it is not reflected in the laboratory values at the same time. (66)

6. Methods of therapy are oral, intravenous, or intramuscular iron, and whole blood or packed cells. (19)

7. Six per cent of iron deficiency patients given oral iron fail to respond (17) and need some form of therapy to place the iron directly into the body.

A. Oral Iron Preparations

Stevens (66) makes a statement which bears repeating, "Although it seems trite to say that the treatment of iron-deficiency anemia is iron the statement is in order, for the physician in America is offered more than 150 preparations for the treatment of hypochromic, microcytic anemias". The number surpassed 160 in 1960 and fewer than ten were simple iron medications. (67) It was stated before that the ferrous form of iron is better absorbed than the ferric form (11) but this has been challenged by Josephs. (9) However, because of the widespread acceptance of the former concept most preparations contain iron in the ferrous form. (67)

There are many ferrous iron-anion complexes but the most common are ferrous sulphate, ferrous gluconate, ferrous succinate, and ferrous carbonate. The amount of elemental iron utilized by the body from these compounds is very different. Table 5 compares the relative efficacy of several iron salts and the amount needed to furnish 25 mgm. of utilizable iron.

Table 5

Compound	Iron ingested (mgm.)
Ferrous sulphate	600 mgm.
Ferrous sulphate (exsiccated)	400 mgm.
Ferrous sulphate (anhydrous)	333 mgm.
Ferrous carbonate	800 mgm.
Ferrous gluconate	1000 mgm.
Ferrous succinate	1000 mgm.

The amount of iron necessary to be ingested to provide the body with 25 mgm. of elemental iron.

Holly (38) states the daily dose should be 100 to 200 mgm. elemental iron in divided doses. Ferrous gluconate contains about 10 to 11 per cent elemental iron by weight (38, 68), hence the gross daily capsule dose must be 1800 to 2000 mgm. of ferrous gluconate. In contrast ferrous sulphate contains 21 to 33 per cent elemental iron so the gross daily capsule dose would only have to be 600 to 1000 mgm. per day. Ferrous succinate contains about 23 per cent elemental iron so the gross daily capsule dose should be approximately 900 mgm.

Stone and others (69) recommend an iron loading test following an overnight fast to determine if the patient is a good candidate for oral iron therapy. This test has the inherent disadvantages of all measurements of iron absorption in that blood iron levels are assumed to reflect absorption. This inaccuracy was noted earlier in this paper. Secondly, the expense for the test hardly justifies submitting all patients to it in the detection of the small percentage of patients who are iron deficient yet refractory to oral iron preparations.

The cheapest preparation to use for iron replacement therapy is ferrous sulphate. However, this form of iron therapy is supposed to have the major number of side effects such as nausea, vomiting, constipation, and abdominal pain. (66,70) Sallman (71) states that these complications are due to waste digestive products combining with iron and forming insoluble compounds which act as irritants to the gastrointestinal tract. Several authors

have challenged this postulation recently. Kerr and Davidson (61) preformed a double blind study on student nurses using ferrous calcium citrate, ferrous succinate, ferrous gluconate, an "unknown" control (by the patient), and a "known" control (by the patient). All the pills contained 35 mgm. iron per tablet and the dosage was three tablets per day for a total daily dose of 105 mgm. The investigators found no significant difference between the number of complaints with any particular iron preparation or with the "unkown" control. There were significantly less complaints with the "known" control. The postulation was made that the intolerance to oral iron in normal dosage was largely of psychogenic origin. Whether this study applies to pregnant patients is not known.

Holly (38) also states the intolerance among all oral iron compounds is the same. Talaga (70) believes that intolerance to ferrous sulphate is due to the compound alone. Gatenby (68) found a greater intolerance to ferrous sulphate than to ferrous gluconate or ferrous succinate. The question remains unsolved. The explanation probably involves some intolerance, especially early in pregnancy, to all oral medication and also due to some irritating effect of ferrous sulphate.

Response to oral iron therapy is slow and gradual. (18) The reticulocyte response is never marked. (18,38) A response of 7 to 8 per cent may be seen (38) 4 to 11 days after the onset of therapy. (18)

The most commonly used forms of therapeutic iron are ferrous

gluconate. No difference in the efficacy of either has been found. (72) Kerr and Davidson (61) state that in their studies the rise in hemoglobin, red blood cell count, and packed cell volume was greater with ferrous sulphate than with ferrous gluconate. However, only the rise in red blood cell count was significant ($0.01 < p < 0.05$). This question requires further evaluation before definite conclusions are formed.

The decision as to whether oral iron therapy is adequate rests with the physician. The first question is absorption and it is usually adequate. (66) The only remaining question is whether the amount absorbed will be enough to supply the maternal and fetal hematologic requirements. If absorption is not adequate or rapid enough, other methods must be tried. (These will be subsequently discussed.) If oral iron therapy is used, it must be continued until iron stores are replenished. (38)

Adjuvants to iron are unnecessary and only add additional expense for the patient. Hydrochloric acid is not needed in the normal patient to increase iron absorption. (10,65,66) Ascorbic acid in normal amounts does not increase absorption but will in massive doses of 250 to 300 mgm. per day. (10) Cobalt with iron will not give a significant increase in hematologic response (61, 73) and may be dangerous. (74) The combination of vitamins and other minerals to the iron is of little value if the diet is adequate. Only with a known deficiency should they be added. (38) In summary it may be said:

1. Simple iron compounds should be used. (e.g. ferrous sulphate, ferrous gluconate, ferrous succinate)
2. The total elemental iron dose is 100 to 200 mgm. per day in divided doses.
3. Intolerance may exist but the psychogenic aspect must be considered.
4. The response is slow and gradual with oral therapy.
5. The response may be masked by the increasing plasma volume.
6. Therapy must be continued until the iron stores are replenished.
7. Adjuvants are not advisable unless a specific problem exists.

B. Parenteral Iron Therapy

The most common causes for failure of oral iron therapy are: 1) incorrect diagnosis, 2) complicating disease inhibiting the response, 3) concurrent blood loss, 4) medication not taken, and 5) failure of absorption, e.g. sprue. (66)

The indications for the use of parenteral therapy are as follows: [modified from Coleman, Alexander, Finch (75)]

1. Intolerance to oral iron. This is valid only if all oral regimens have been tried and have failed, and the patient would rather be anemic than take further medication.
2. Gastrointestinal diseases which would be adversely affected or would affect absorption or oral iron. (e.g. gastric ulceration, regional enteritis, ulcerative cloitis, steatorrhea, sprue)

3. Patients will not take iron of any form orally. (e.g. psychiatric, geriatric, and incompetent patients)
4. The need for rapid replacement of iron. (e.g. severe anemia, anemia late in pregnancy, continued blood loss, etc.)

Parenteral iron therapy may be in the form of 1) intramuscular iron, 2) intravenous iron, and 3) whole blood or packed cells intravenously.

1. Intramuscular iron

Intramuscular iron has been used for several years in England but only recently has it become popular in the United States. Perhaps it should be stated here that the injectable iron-dextran complex was withdrawn from the market at one time because of British intestigations stating that sarcomas were found at the site of injection in rats and mice. Only one questionable cause and effect relationship was found in man. This was in the deltoid region of a patient where iron-dextran was thought to have been injected three years prior. Since rats and mice are very susceptible to local sarcomas due to injections of many materials the withdrawal of iron-dextran was again evaluated. The American Medical Association Council on Drugs stated "---the use of iron-dextran complex does not appear to be attended by any greater hazard than does the administration of intravenous forms of iron and the transfusions which physicians must now use as substitutes." (76) After more discussion and debate the intramuscular form of iron was recently placed back on the market.

Iron-dextran is now the method of choice for parenteral iron replacement. (66) The indications for therapy are those of parenteral therapy in general.

The total dose is calculated by the same formula presented earlier for oral iron therapy. Once the total amount to be given is calculated the rate and amount per injection must be decided. The last two items depend upon 1) the severity of the iron deficiency, 2) the time available for replacement, and 3) the patient's tolerance of the medication. (66)

The dose may vary from 250 mgmg. each clinic visit to 500 mgm. every 12 hours. On an outpatient basis the dose probably should be 250 mgm. in each gluteal muscle per week if time to raise the hematologic values is available. The accelerated dose may be given if the patient is hospitalized and observed carefully. (78)

All injections should be given in the gluteal muscle using a 2 1/2 inch 20 or 21 gauge needle. A longer needle may be needed for obese patients. The skin over the gluteal region must be drawn to one side before the injection begins. The movement of the skin and to a lesser degree the deeper tissues results in a Z-shaped track. This reduces the possibility of the injected solution leaking toward the surface and staining the surface tissues. A small amount of air is injected before withdrawing the needle to clear the needle of solution, which also aids in avoiding skin stains. (78)

Goldberg (77) gives an excellent and detailed description of the absorption, diffusion, and metabolism of iron-dextran from the

site of injection. Karloefors (79) states that 66 per cent of the Fe^{59} -Dextran is absorbed rapidly from the site of injection in the buttock. In 90 to 150 minutes the serum iron is increased and by 4 to 6 hours the plasma has split the Fe^{59} -Dextran complex. The reader is referred to the above authors for a more detailed description of the fate of injected iron-dextran.

The response to therapy is best indicated by the rise in hemoglobin and hematocrit as stated before. A rise of 2 Gm. per 100 cc. of hemoglobin and 5 per cent in hematocrit in three weeks are minimum values. The reticulocyte response is about 4 to 5 per cent with the meximum 3 to 5 days after the onset of therapy. (78)

Toxic reactions to the injections have been reported. (38,78, 79,80) Menon and Willmont (79) report an incidence of 17 per cent in a series of 112 patients. The reactions most often reported are muscular and joint pain, encephalopathy, effusion into joint spaces, cerebral hemorrhage, lymphadenitis, allergic skin rashes and pyrexia. The reactions usually occur immediately after injection and may begin any time during the course of therapy. There seems to be no relation between the amount of iron given and the severity of the reaction. Reactions occur with severe or moderate anemia. When the anemia is dimorphic (hypochromic and macrocytic) the reactions are more severe. (79) The classic "iron-dextran reaction" is characterized by painful inguinal lymph nodes, high erythrocyte sedimentation rate, normal white blood cell count, and pyrexia. (81)

In summary:

1. The dose of iron-dextran depends on the time, amount, hospitalized or out-patient, and the patient's tolerance to therapy.
2. Injections should be deep in the gluteal muscle.
3. An adequate response is a hemoglobin rise of 2 Gm. per 100 cc. and a hematocrit rise of 5 per cent in three weeks.
4. Toxic reactions occur with enough frequency that all patients should be carefully watched immediately after each injection.

2. Intravenous iron therapy

The indications for parenteral therapy again apply to the intravenous administration of iron when there is a contraindication to intramuscular iron. This iron is usually in the form of saccharated iron oxide which is a negatively-charged, colloidal solution of iron oxyhydrate stablized by the absorption of alkali and sugar. (9) The one theoretical advantage of this form of therapy is the direct placement of the iron into the blood stream for more rapid utilization.

The total dose is calculated in the same manner as for oral iron therapy. Josephs (9) suggests giving 500 mgm. to the adult patient as an initial course. If an adequate response of 2 Gm. per 100 cc. hemoglobin rise occurs in three weeks, then the full course of therapy is given. The patient should be given a single injection

of iron per day, in a concentration of 20 mgm. per cc. over an interval of 3 to 5 minutes. The first dose should be 50 mgm., the second 100 mgm., and the third 200 mgm. If no symptoms have occurred, the latter dose may be repeated as often as every 24 hours until the total dose has been given. (9) This form of therapy is best executed in the hospital. (9)

The main disadvatage of intravenous saccharated iron is the high incidence of side reactions. The reported incidence varies from 5 to 35 per cent. (9, 19, 53, 82, 83, 84, 85) These reactions are theorized to occur when the iron saturates and exceeds the iron binding capacity of the beta-1-globulin of the serum. (9,37,53) Goldberg (77) has shown that serum iron levels of 1 mgm. per 100 cc. are possible without reactions. The confusion here is between ionic iron, which must not exceed the binding capacity of the plasma or reactions will develop, and complexed iron as iron-dextran, which circulates as an inert material as long as it is not metabolized into free ionic iron. Since both forms of iron are measured in the laboratory analysis for serum iron, the levels of serum iron following complexed forms of iron may be very high without causing reactions.

Among the reactions which have occurred are local vein spasm, flushing of the face, syncope, lumbar pain, abdominal cramps, nausea and vomiting, coughing, choking, sensation of constrictive chest pain, shock, and even death. In contrast to intramuscular iron reactions which are somewhat delayed, reactions to intravenous

injections are usually immediate. (9) The development of hemosiderosis or hemochromatosis, although possible, is not likely because of the excessive overdose required to produce these conditions. (9,40-43)

Intravenous iron therapy is available but not recommended because of the serious reactions. The use of this method of therapy should be only attempted when other forms have failed. Comparison of the results of intramuscular and intravenous therapy has not shown significant difference between them. (78,82) Hence, it would seem best to use intramuscular iron therapy instead of intravenous.

3. Whole blood or packed cells

The indications for the use of whole blood or packed cells are similar to that of parenteral therapy in general. However, the criteria are enough different to be listed here. They are as follows:

1. When rapid replacement of blood is required, as with hemorrhage.
2. For treatment of severe anemia prior to delivery when the response to other forms of therapy would be too slow.
3. To combat shock due to blood loss.
4. When the patient cannot tolerate parenteral iron earlier in the gestation.
5. For anemia which will not respond to iron therapy (e.g. refractory anemia).

Perhaps it should be stated here that several authors feel that if time permits other forms of therapy blood should not be given. (86,87)

When to give blood to a patient is a difficult question to answer. Obviously, if shock is present, immediate transfusion is required. When the hemorrhage is persistent blood should be given. The usual time to transfuse prenatally is when the hemoglobin falls below 10 Gm. per 100 cc. and other forms of therapy have not or will not be adequate. (86) The patient should be, if the circulatory system permits, should be transfused to 11.5 or 12.0 Gm. hemoglobin per 100 cc. (86) The total amount to transfuse may be estimated by knowing that one unit of fresh blood will raise the hemoglobin approximately 1.5 Gm. per 100 cc. (88) A repeat hemoglobin determination several hours after the last estimated unit of blood has been given is necessary for accurate knowledge of the hemoglobin. However, a patient without active bleeding should not receive more than 500 cc. of blood daily.

Serious reactions may develop with the use of blood. These reactions may be divided into four types according to Hall and Hellman. (89)

1. Pyogenic. The patient may have fever, chills, nausea, vomiting, headache, but usually not hemoglobinemia or hemoglobinuria.
2. Allergic. Uriticaria, but rarely angioneurotic edema is seen.

3. Hemolytic. This is manifested by restlessness, pain in the back, chills, fever, nausea, and vomiting. The patient may be in a shock-like state with oliguria or anuria, uremia, hemoglobinuria, and hemoglobinemia present.

4. Reaction to plasma. The patient has only chills, fever, and back pain.

Hall and Hellman (89) report a series of 18,924 deliveries in which transfusions were given in 6.2 per cent. Approximately 1 per cent of these 6.2 per cent had hemolytic reactions and 0.25 per cent died. Death was usually due to renal failure. If the basement membrane of the tubules is not totally destroyed recovery may occur. However, if the basement membrane is totally destroyed, death is inevitable. (89)

Because of the incidence and especially the seriousness of transfusion reactions, the use of blood has decreased. Pritchard (87) reports a decrease from 53 pints of blood per 100 deliveries in 1955 to 7 pints per 100 deliveries in 1957 at Parkland Memorial Hospital of The University of Texas Southwestern Medical School. The requests for cross matching remained the same during this period of time. He attributed the decreased use of blood to better prenatal care and awareness of the danger of unlimited use of blood transfusions.

In summary it may be said that whole blood for therapy of anemia has a definite place in the armamentarium of the physician but should not be used as a substitute for inadequate prenatal care.

RESEARCH STUDIES USING Fe^{59} IN PREGNANT WHITE RATS

A. Introduction

In an attempt to correlate research laboratory and clinical data several studies using the radioisotope Fe^{59} injected intravenously into pregnant, albino rats were performed. Answers to the following questions were sought: How long after the injection of Fe^{59} does the plasma become free of radioactivity? Will the plasma be free of radioactivity at any different rate following the subcutaneous injection of iron-dextran four days prior to delivery? Are pregnant white rats anemic on an ordinary diet of rat chow? With these objectives in mind the project was begun.

B. Materials and Methods

The albino rats, Sprague-Dawley strain, were obtained from Hormone Assay Laboratories of Chicago, Illinois. The date of each mating was known, confirmed by vaginal smear for sperm thus the exact gestation period was predictable. The rats were shipped by air express to our laboratory.

The rats upon arrival were placed in separate 20 x 20 x 10 cm. pens with wire bottoms and fed a diet of Purina Rat Chow and water ad lib. The animals were handled only a few times to maintain gestation as natural as possible.

When the studies using Imferon®, an iron-dextran complex obtained from Lakeside Laboratories, were in process the subcutaneous

injections were made in the dorsal neck region. A single dose of 50 mgm. was given to each rat four days prior to delivery. This time was chosen because serum iron levels following iron-dextran administration in rats were found to peak at 20 to 35 hours and fall markedly by 72 hours. (77) Consequently, a large portion of the iron would be mobolized from the injection site before the studies with radioactive Fe^{59} were begun.

The Radio-Ferrous (Fe^{59}) Citrate in sterile solution, pH of 6.0, with 33 micrograms per cc. of ascorbic acid added, was obtained from Abbott Laboratories, Oak Ridge, Tennessee. The assays of the various shipments received varied from 27 to 84 microcuries per cc. and the concentrations varied from 0.001 to 0.004 mgm. of iron per cubic centimeter.

The rats were prepared for the injections of Fe^{59} by giving them 38.5 mgm. of pentobarbitol per Kg. body weight by intraperitoneal injection one hour prior to the onset of the tests. The rats were placed on their backs and strapped down to the operating board with adhesive tape. After a 70 per cent alcohol wash of the left supraclavicular region, 0.5 to 1.0 cc. of one per cent procaine was injected subcutaneously in the area. After waiting 5 minutes a 1 to 2 cm. incision was made in the left supraclavicular area parallel with the strap muscles of the neck. The large, yellow fat pad overlying the jugular venous plexus was removed with forceps and scissors. Immediately below the fat pad was a very thin layer of fascia overlying the venous plexus. The fascia was carefully

removed so as not to inadvertently enter the vein. The vein is then easily exposed. The left clavicle was gently depressed causing partial obstruction and dilation of the left jugular veinous plexus. Using a No. 27 gauge, 1/2 inch needle on a disposable one cubic centimeter tuberculin syringe, approximately one microcurie of Fe^{59} in 0.5 cc. sterile, isotonic saline was injected slowly. After complete injection of the material the needle was held in the vein to allow circulation of the iron away from the injection site thus preventing loss into the tissues. The needle must be swiftly withdrawn and pressure hemostasis applied if necessary. The skin is closed loosely with surgical skin clips and the rats are returned to their pens.

The mortality with this procedure was 2.5 per cent and the percentage of faulty injections was 5.0 per cent in a total of 93 injections.

The rats were sacrificed by a sharp blow to the occipital region of the head. The fetal rats were delivered by a midline incision which exposed the two horns of the uterus. The placentas were removed and washed in tap water to remove the excess blood and then placed in glass tubes for counting in the Nuclear-Chicago scintilation counter for 2 minutes each. The fetal rats were killed by a blow to the head and also placed in glass test tubes for whole body counting.

The hemoglobin values were obtained by colorimetric determinations in a Coleman Colorimeter. The prenatal hematocrits were

obtained by using microtechniques and heparinized tubes. Prenatal hematologic values were on blood obtained from rat tail veins but postnatal determinations were on blood from the heart. The postnatal hematocrits were obtained by using the Wintrobe tube centrifugation method. The studies for plasma radioactivity were done on a 0.025 ml. aliquoit of plasma diluted in 2.0 cc. of distilled water.

C. Data, Results, and Discussion

A comparison of the per cent of injected radioactivity in the maternal blood of animals with and without Imferon injections is recorded in Figure VII. The level of radioactivity falls rapidly during the first hour and then levels to a plateau until 8 to 10 hours after injection. The blood levels of Fe^{59} then begin to slowly rise again.

This fall in blood level is probably due to the incorporation of Fe^{59} by the blood marrow and other hemopoietic tissues. A small amount of the iron stays in the blood stream for several hours. The blood level of Fe^{59} begins to rise again after several hours as the labeled red blood cells are returned to the blood stream from the hemopoietic system. Ulberg, Sorbo, and Clemedson (90) have published data in close correlation with these findings. They state that two minutes after injection all of the iron appears to be retained in the blood. After five minutes some of the iron is in the liver, bone marrow, and red pulp of the spleen but the major amount of the iron is still in the blood. Twenty minutes after the injection

the concentration in the hemopoietic tissues is increasing and the activity in the blood has decreased. At four hours the blood level is at its lowest point and the highest level is found in the bone marrow. Ten hours after injection the blood levels are arising again due to the release of radioactive red blood cells into the blood stream. Six days after the injection of Fe^{59} the blood level again is higher than the hemopoietic tissues. (90)

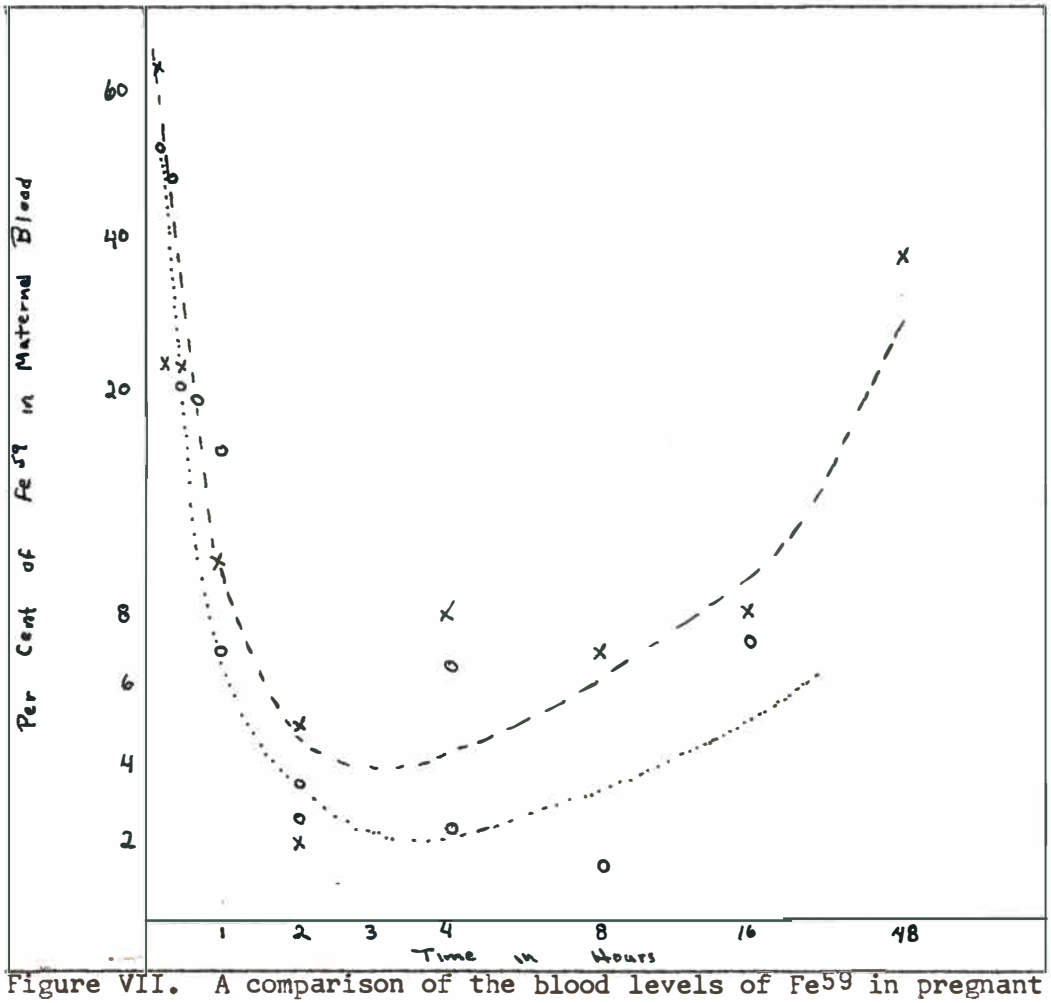

Figure VII. A comparison of the blood levels of Fe^{59} in pregnant rats with and without the injection of Imferon four days prior to delivery. (Without Imferon o---o; With Imferon x---x)

The experiments presented here differ from those of Ulberg, Sorbo, and Clemedson (90) only in that it was found that the blood level of iron decreased more rapidly. The lowest blood levels were found at 2 to 3 hours. The explanation for this probably lies in the fact that iron was injected intramuscularly in the experiments of Ulberg et. al. (90) and intravenously in the experimental work done here. In this manner the Fe^{59} could be presented to the hemopoietic system more rapidly for red blood cell synthesis. Consequently, the level of blood iron would fall more rapidly, which was demonstrated by these experiments.

Figure VII also illustrates that there is little difference between the graphs of rats given Imferon prior to delivery and those not given Imferon. No similar work could be found in the literature for comparison. However, the results could be partially explained by the work of Nylander. (91) The normal hemoglobin for rats is 12 to 13 Gm. per 100 cc. Since the hemoglobin levels during pregnancy are approximately the same the iron stores of the rat must be adequate to maintain the animal during pregnancy. The injection of additional iron would not be expected to alter the hematologic values; therefore, the results here are entirely plausible.

The clearance rate of Fe^{59} from plasma was also studied in the pregnant rat. The results are presented in Figure VIII. The fall in plasma Fe^{59} is rapid the first hour then progresses more slowly. The plasma is free of radioactivity 4 to 8 hours after injection. Thus any radioactivity in the blood must be due to the Fe^{59} in red

blood cells or bound to red blood cells in some manner. These experiments show that the iron is not only delivered to the hemopoietic system more rapidly but is metabolized and returned to the blood stream more rapidly then formerly stated. (90) The reason for this has been previously discussed.

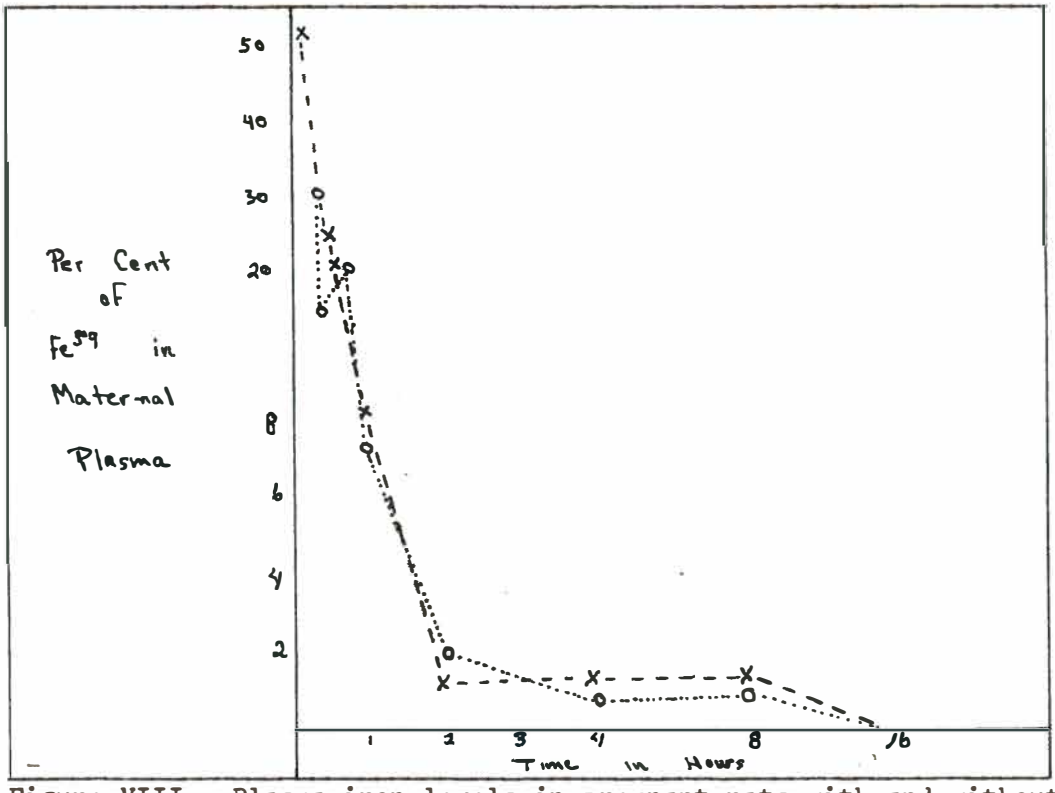

Figure VIII. Plasma iron levels in pregnant rats with and without previous injection of Imferon prior to delivery. (With Imferon x---x; Without Imferon o---o)

The hemoglobin values of pregnant rats were determined and the results appear in Figure IX. Most of the rats have a hemoglobin value above 12 Gm. per 100 cc. at term. This correlates well with the work of Nylander (91) and Van Donk, Feldman, and Steenbock (92). Nylander (91) states that pregnant rats are not

anemic on a diet of normal rat chow and these experiments correlate with his.

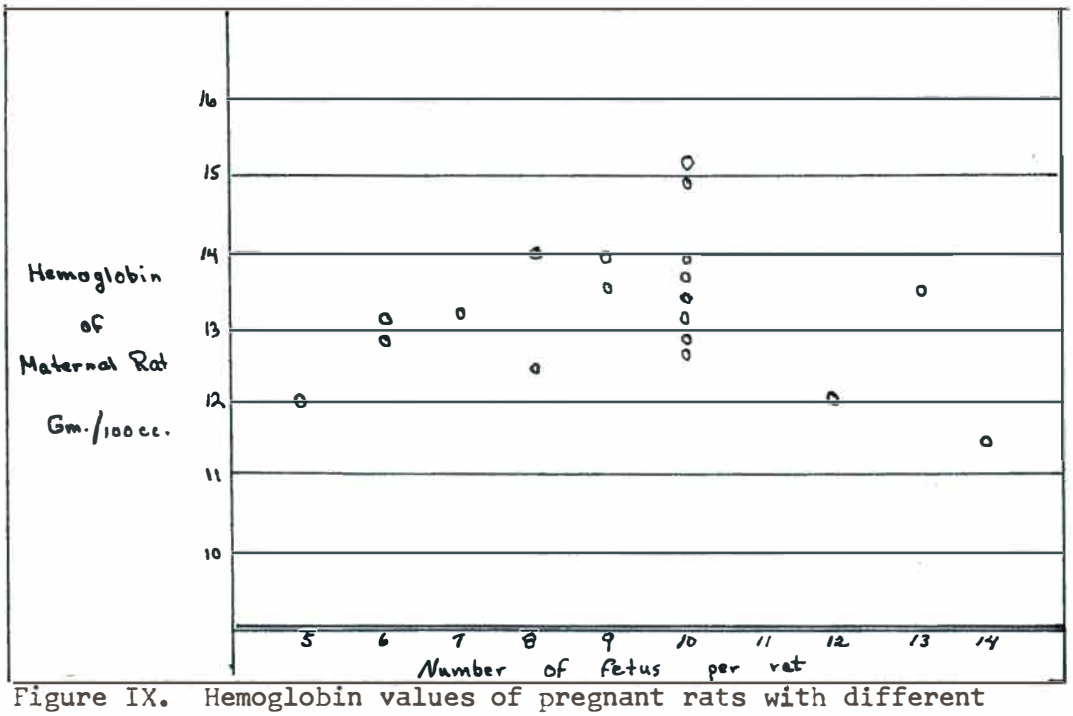

Figure IX. Hemoglobin values of pregnant rats with different litter sizes at the time of delivery.

The placentas from the maternal animals not given Imferon contained an average of 6.8 per cent of the injected radioactive iron. The placentas from the rats given Imferon contained 6.5 per cent of the injected dose. The difference is not statistically significant. The per cent of radioactive iron in the placentas did not vary with length of time after injection, litter size, or amount of iron injected.

The rat placenta probably does not store any appreciable amount of iron nor does it hinder the transfer of iron to the fetal rat late in gestation. These conclusions are drawn from the above data but investigation in this area is continuing in our laboratory.

D. Summary and Conclusions

1. A suitable method for injections into rats has been found which gives consistent results.

2. Pregnant albino rats, Sprague-Dawley strain, have approximately the same hematologic values whether they have or have not received iron-dextran prior to delivery.

3. Maternal plasma of rats is free of radioactivity of Fe^{59} four to eight hours after intravenous injection.

4. There is a rapid fall in blood iron one hour after intravenous injection of Fe^{59} as the iron goes to the hemopoietic tissues.

5. There is an increase in radioactivity in the blood eight to ten hours after intravenous injection of iron suggesting the return of Fe^{59} to the blood stream incorporated into red blood cells.

6. Maternal rats on standard laboratory diet are not anemic at delivery.

7. The rat placenta probably does not store any appreciable quantity of iron.

8. The rat placenta does not seem to hinder the transfer of iron to the fetal rat.

VIII. SUMMARY AND CONCLUSIONS

The preceeding work is in reality a brief summary of the writings in the literature concerning iron and its role in the metabolism of the pregnant woman. Literally volumes of material have been written discussing this topic. However, to be fair to all the authors concerned one must say that not all the material is unnecessary repetition. Iron in various forms is one of the most common physician prescribed and patient self-prescribed drugs in medicine. The famous "liver shots", tonics, and multiple vitamins plus minderals, which are a part of our medicinal armamentarium, are ample proof of this fact. It would be safe to say that every general physician and most physicians in special fields of medicine prescribe iron to their patients. Yet this form of therapy is one of the most inaccurately prescribed and dispensed items in the physicians hands! Not because the physicians prescribe erroneous dosages, but because they do not understand the basis of iron replacement therapy. Every physician and student of medicine should endeavor to completely understand the reason for prescribing iron and when to prescribe it. What is the absorption rate of iron? How much iron is lost with each normal pregnancy and delivery? Why are so many women iron deficient? When should therapy with iron begin? What route should be used for iron administration? What is a satisfactory response to iron therapy? When should therapy be discontinued? These are but a few of the questions to which every physician should know the answer. Only in this manner will

this "routinely" prescribed drug be intelligently dispensed by physicians.

This paper presents the basic facts of iron metabolism in pregnancy and a discussion of the current methods of therapy of iron deficiency anemia in pregnancy. Simple methods for determining the need for therapy and the amount of iron necessary are illustrated. This will enable anyone to grasp the basic concepts of iron therapy and metabolism. The author believes that physicians using any form of iron therapy should fully understand its use and how to apply this knowledge to the best advantage for the patient and himself. The preceeding paper endeavors to accomplish this goal.

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