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THE ANAEMIA OF PREGNANCY*

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Although Channing, an American obstetrician, as long ago as 1842 described a condition of severe anaemia which occurred in the course of and apparently as the result of pregnancy, relatively little attention has been paid to the subject. In 1919 Sir William Osler, in a paper entitled "The Severe Anaemia of Pregnancy," again drew attention to the occasional development during pregnancy and the puerperium of severe and dangerous degrees of anaemia, and suggested that the anaemia of pregnancy had not received the study which it deserved. Actually it is only during the last six or seven years that any serious attempt has been made to classify the various anaemias associated with the gravid state and to discover the factors—some of them peculiar to pregnancy—which are responsible for the changes in the mechanism of blood manufacture and maintenance during this period. In comparison with other haematological disorders the anaemia of pregnancy has in this country received little consideration even from obstetricians, and many aspects of the problem still await a solution. Indeed, the performance of routine blood counts or haemoglobin estimations during pregnancy is rare both at ante-natal clinics and in general practice, despite the fact that a woman with anaemia is inadequately fitted for the trials of labour.

Pregnancy may be incidental in the course of any number of diseases which in themselves cause anaemia, such as leukaemia, malignant disease, and nephritis. Severe anaemia may result from ante- or post-partum haemorrhage or puerperal sepsis. There is no evidence that pregnancy affects the course of the disease in conditions such as leukaemia or Banti's syndrome, though Larrabee and Swan have each described a case of familial haemolytic icterus with a haemolytic crisis during the course of what was otherwise a normal pregnancy.

Nomenclature

Disregarding patients with anaemia due to these well-recognized causes, I propose to deal with those blood disturbances in which there is no obvious aetiology and which are apparently due to or aggravated by the pregnancy itself. The literature on this subject is very confusing. It contains many references to a "physiological anaemia of pregnancy"—a condition in which red cells and haemoglobin values show a gradually progressive reduction during the second and third trimesters, with an improvement after delivery. Recent work, however, has shown that not infrequently this anaemia is due to maternal iron deficiency—a condition which can hardly be called physiological. Even greater confusion exists regarding an anaemia which has been described under various titles: pernicious anaemia of pregnancy; pseudo-pernicious anaemia of pregnancy; severe anaemia of pregnancy; haemolytic anaemia of pregnancy; macrocytic anaemia of pregnancy. From a review of the

literature it is evident that under these so-called synonyms two distinct entities have been described. First, a condition which I shall call the pseudo-pernicious anaemia of pregnancy; this is closely related to true Addisonian pernicious anaemia and other macrocytic anaemias both in its blood picture and in its response to liver treatment. Secondly, a true acquired haemolytic anaemia similar in its clinical and haematological manifestations to the haemolytic anaemias described by Lederer, Parsons, and others in non-gravid states; in this form not only does the haemolytic agent, whatever that agent may be, have a destructive effect on the red cells in the circulation, but the bone marrow may also be involved and the resultant temporary or permanent marrow paralysis is reflected in the blood picture. This damage to the red cell factory is the probable explanation of many of the "hypoplastic" and "aplastic" anaemias of pregnancy described by Whitby and others. I propose to describe this group under the title "erythronoclastic," suggested by Parsons.

Classification

The classification I have adopted is based on other recent classifications of haematological disorders and emphasizes the importance of the deficiency states, many of which are preventable and all readily curable with modern therapy.

A. PHYSIOLOGICAL ANAEMIA OF PREGNANCY—HYDRAEMIA.

B. DEFICIENCY OR ANHAEMATOPOIETIC ANAEMIA.

1. Deficiency of iron (microcytic hypochromic anaemia).

(a) Hypochromic anaemia induced by pregnancy.

(b) Idiopathic hypochromic (Witt's) anaemia, complicated or precipitated by pregnancy.

2. Deficiency of liver factor (macrocytic anaemia).

(a) Deficiency of extrinsic factor. Tropical macrocytic anaemia, complicated or induced by pregnancy.

(b) Deficiency of intrinsic factor. (i) True Addisonian pernicious anaemia complicated or precipitated by pregnancy. (ii) Pseudo-pernicious anaemia of pregnancy.

C. ERYTHRONOCLASTIC (HAEMOLYTIC) ANAEMIA.

1. Plastic.

2. Hypoplastic.

3. Aplastic.

D. POST-HAEMORRHAGIC ANAEMIA.

1. Ante-partum haemorrhage.

2. Post-partum haemorrhage.

E. THE ANAEMIA OF PUERPERAL SEPSIS.

F. OTHER ANAEMIAS COMPLICATED BY PREGNANCY.

Streptococcal and staphylococcal septicaemia, malignant disease, leukaemia, nephritis, familial haemolytic icterus, malaria, etc.

I propose to deal with the first three groups of this classification.

* Read in opening a discussion in the Section of Obstetrics and Gynaecology at the Annual Meeting of the British Medical Association, Oxford, 1936.

Physiological Anaemia

The gravid state is associated commonly with important and well-marked changes in the circulatory mechanism of the mother. The total blood volume is increased; the total volume of red cells and haemoglobin by about 20 per cent., and the plasma volume by an even greater amount, 25 per cent. or more. Hence, although the actual amount of circulating red cells and haemoglobin is increased, the blood is more dilute and a count shows an apparent anaemia. The red cells and haemoglobin are proportionately reduced so that the colour index remains at about unity—a feature which differentiates the condition quite clearly from the iron-deficiency anaemias. It is doubtful whether this hydraemia of pregnancy is ever responsible for a fall in the haemoglobin to a level lower than 70 per cent., and haemoglobin values of less than 80 per cent. are unusual. A diminution of the serum protein accompanies these changes in the red cells so that the blood viscosity is also reduced. This hydraemia is the mechanism by which the increased bulk of maternal tissue is supplied with blood; further, the decrease in the viscosity of the blood is accompanied by a greater cardiac output per beat, which provides adequate gaseous exchange between the mother and the foetus with a minimum of work. The hydraemic state also allows of a relatively big blood loss at the time of the confinement without a proportionate loss of haemoglobin. During the puerperium, rapid readjustments of the blood volume occur with apparent "cure" of this "anaemia."

Iron-deficiency Anaemia

The iron-deficiency anaemia of pregnancy, to which the synonyms hypochromic anaemia and chlorotic anaemia are applied, is by far the most common and important of the anhaematopoietic anaemias of pregnancy. Its incidence is world-wide and its frequency in mild forms is such as to have led to its being wrongly labelled physiological. Indeed, it may be said that from 10 to 20 per cent. of the poorer-class mothers of our large cities are in some degree affected. It is interesting that, so long ago as 1872, in his lectures at the Hôtel-Dieu, Trousseau mentioned the chlorotic anaemia of pregnancy previously described by Cazeau and clearly differentiated it from the hydraemia of pregnancy.

The blood picture is similar to that of other iron-deficiency anaemias. The red count may be normal or diminished but the reduction in haemoglobin is relatively greater, so that the colour index is below unity and may even reach 0.4. The reds are small as determined by estimation of cell volume and cell diameter; in stained films they have a pale appearance, while in many the pigment is seen to be distributed around the periphery of the cell—the so-called pessary forms or ring staining.

The clinical picture may not be striking. The chief complaints are excessive fatigability and loss of sense of well-being, which, however, are usually attributed to the pregnancy itself. In the more severe cases dyspnoea, prostration, and oedema of the dependent parts may be the presenting symptoms, but more often the anaemia is well tolerated and may be overlooked until, when labour is over, the patient collapses. Rarely dyspepsia, dysphagia, soreness of the tongue, and splenomegaly are present. Miscarriage or premature delivery appears to be rather common; further, it is stated that labour is prolonged, the foetal mortality rate higher, and maternal toxæmia and puerperal morbidity more common than in patients treated with iron.

AETIOLOGY

The cause of this widespread iron deficiency is to be found in certain changes in the metabolism of iron which occur during pregnancy—namely:

1. The increased iron requirements

- (a) of the mother

- (b) of the rapidly growing foetus.

2. The paucity of iron in the mother's diet.

3. The diminished alimentary absorption of the iron as a result of gastro-intestinal abnormalities.

During pregnancy the mother requires more iron to build up uterine muscle and to provide extra haemoglobin for the ever-widening vascular bed of the uterus. The demands of the foetus are even greater, since iron is required both for the synthesis of its tissues and for the accumulation of the large iron stores for utilization during the prolonged iron starvation of the milk-feeding period. The liver of young animals contains five times as much iron, weight for weight, as that of the adult, and it is this mineral drain by a ruthless intrauterine parasite that may bring about an acute anaemic breakdown in the mother whose own reserves are thereby exhausted.

The maternal iron reserves are dependent upon two factors: intake and absorption. There is little doubt that the diets of many women of the poorer classes are inadequate in iron-containing foods such as meat and green vegetables. De states that the average haemoglobin of the native women in Bengal is about 50 per cent., that the anaemia is usually hypochromic—that is, with a low colour index—and that it is worse in those who have borne many children and recurs more severely in successive pregnancies. Davidson, in his study of the poorer classes in Aberdeen, was able to demonstrate iron-deficiency anaemia at two age periods: first, in infancy during the latter half of the milk-feeding period; secondly, in women during the middle and later years of their reproductive life, especially in those who had borne children. Anaemia was not present during the years of childhood nor in males. He concludes, therefore, that the iron intake of the poor in Aberdeen, though sufficient for the requirements of the school child and the adult male, is often insufficient in the female to withstand the loss of iron in the menstrual fluid or the even greater demands of pregnancy. Moreover, the iron starvation of the mothers is also reflected in the development of "simple" nutritional anaemia in their infants who, though usually full-blooded at birth, have soon exhausted what little iron they were able to accumulate during foetal life. The work of Mackay on mothers and infants in the East End of London has shown similar results and has demonstrated that, far from being a "simple" and harmless anaemia, it is responsible for a greatly increased susceptibility to infections, particularly of the bowel and respiratory tract. The production of nutritional anaemia in the offspring as the result of deficiency in the maternal diet is strikingly shown by experiments carried out by Miss Hickmans at the Children's Hospital, Birmingham. Rats fed on an iron-deficient diet, though not themselves anaemic, produce young whose red cells at birth are smaller than normal and who rapidly develop hypochromic anaemia (Graph 1).

IMPAIRED ABSORPTION

The third factor is the impaired absorption, during pregnancy, of iron from the diet; this appears to be associated with a temporary hypochlorhydria. For some years it has been recognized that the pH of the upper intestinal tract is of great importance in the absorption

or utilization of materials necessary for blood formation, foremost among them iron.

In a series of twenty-four normal pregnancies Strauss and Castle demonstrated that 75 per cent. did not secrete

1. Pregnant women (106 cases) attending the ante-natal departments of two hospitals.

2. A similar group (59 cases) who were given iron and ammonium citrate (45 grains daily) for a period varying from one to three months before delivery.

GRAPH 1.—Showing the presence at birth of microcytosis and the development of severe hypochromic anaemia in the young of rats fed on a diet deficient in iron compared with results for the young of stock rats.

normal amounts of free hydrochloric acid or pepsin during more than half the period of pregnancy, that 80 per cent. secreted higher concentrations after delivery, and that secretion during the puerperium was approximately three times

as great as during the last three months. Their cases were investigated haematologically, and for purposes of comparison were divided into four groups according to the quality of the diet and the amounts of hydrochloric acid secreted. The results showed that of the three groups of patients who took an adequate diet the average haemoglobin loss during pregnancy was 5 per cent. for those with a high gastric acidity, 9 per cent. for those with low acid, and 18 per cent. for those with a total achlorhydria. In those with a low acid and an inadequate diet the average fall in haemoglobin was 14 per cent.

Graph 2 shows the hitherto unpublished results of a haematological investigation carried out in Birmingham by my colleague the late Dr. R. J. Gittins, on:

3. The infants born to women in Groups 1 and 2.

4. Non-pregnant women of similar social status.

The results are compared with those of other workers and with accepted normal values (Price-Jones), and demonstrate the presence of iron-deficiency states in these women and the development of an anaemia of pregnancy which may be relieved somewhat with iron medication.

SOCIOLOGICAL ASPECTS

Iron-deficiency anaemia is therefore to some extent a social problem. It is seldom seen in private practice. Its frequency and severity in the hospital patient is to some extent governed by the family income, especially by the proportion of that

income spent on food, and it may be prevented by the administration of iron. These facts have been well demonstrated by Pillman-Williams and Moore, and it is not surprising, therefore, that the reports of various workers have shown a greatly varying incidence of hypochromic anaemia of pregnancy in different countries,

GRAPH 2.—Showing: A, Average haemoglobin values for 106 pregnant women of the hospital patient class in Birmingham before and after delivery (shown thus —) and for a similar group of 59 cases who were given iron during the pregnancy (shown thus). B, Average haemoglobin values for the infants born to these two groups of women. C, Average haemoglobin values for non-pregnant women of similar social status in Birmingham (shown thus —).

cities, and even in different districts in the same city. The family income is not the only controlling factor, however. The capricious appetite of the pregnant woman, especially for meat dishes, is well known, and perhaps the obstetrician is not altogether blameless in restricting the intake of ferruginous foodstuffs, such as red meat, in his efforts to prevent toxæmia.

There is no doubt that the maternal diet should be one rich in iron, and that in this the diets of many mothers of the hospital class are extremely deficient. It may indeed be advisable in practice to supplement the diet with iron as is commonly done with calcium, particularly in the case of hospital patients. A daily dose of ferrous sulphate 6 to 9 grains, or iron and ammonium citrate 30 to 50 grains, may be regarded as a certain preventive. When anaemia is once established ferrous sulphate 15 grains, or iron and ammonium citrate 90 grains daily, will ensure a satisfactory recovery, whether given ante or post partum.

Macrocytic Anaemias

These deficiency anaemias of pregnancy constitute a much more dangerous complication than do the iron-deficiency group, but are uncommon in this country. Beckman reported six cases in sixty thousand labours, but it is probable that the condition is rather more frequent than these figures suggest.

The blood picture is similar in all members of this group. The red cell count is usually more markedly reduced than the haemoglobin, so that the colour index is greater than unity. An essential feature of the red cell picture is the increase in the average size of the cells as determined by measurement of their diameters or estimation of cell volume. Anisocytosis and poikilocytosis are almost constant. The white cells may be normal but often the number of polymorphonuclear cells in the circulation is reduced, so that the total white count is low and the differential count shows a relative lymphocytosis.

The work of the last decade has demonstrated that, in the production of macrocytic anaemias, one or more of three deficiencies may play a part—namely:

1. Deficiency of an extrinsic or food factor, probably allied to vitamin B₁₂ and present in large amounts in yeast, meat, and green vegetables.
2. Deficiency of an intrinsic factor normally secreted in the gastric juice.
3. Deficiency in the absorption and utilization of the "liver factor" produced by the interaction of 1 and 2.

Taking the macrocytic anaemias in order, there occur:

1. *Tropical Macrocytic Anaemia*.—This is rarely, if ever, seen in this country but is common in India, where the diet of the native women is often grossly deficient. This condition appears to be largely the result of a deficiency in extrinsic factor, and responds rapidly to treatment with liver or with preparations rich in extrinsic factor such as marmite. Pregnancy, when it occurs, appears to aggravate the anaemia.

2. *True Addisonian Pernicious Anaemia Complicated by Pregnancy*.—This again must be a rarity for two reasons. First, that the onset of true pernicious anaemia is usually post-menopausal, and, secondly, that pernicious anaemia, when it occurs during the reproductive life, appears to bring about a state of relative sterility. The clinical picture is that of "textbook" pernicious anaemia with superficial glossitis, achylia gastrica, occasionally splenomegaly, and not infrequently signs of spinal cord involvement. The condition persists after delivery, unless treated with liver, and relapses if liver treatment is discontinued. The pregnancy is only incidental, but tends to increase the degree of anaemia and in cases already under treatment may necessitate the administration of larger doses of liver. The strain of pregnancy may also be the last straw in causing the breakdown of a red cell mechanism already on the verge of true pernicious anaemia. In a series of twelve hundred cases of progressive

pernicious anaemia in America, Cabot states that in one case in every twenty-five the onset was during pregnancy or immediately post partum.

Pseudo-Pernicious Anaemia

There exists, however, as a complication of pregnancy, an entirely distinct clinical entity, which I have already referred to as the pernicious-like or pseudo-pernicious anaemia of pregnancy in order to differentiate it from true pernicious anaemia already described. This anaemia, first described by Channing, has all the haematological features of a macrocytic anaemia and usually develops during the last three months of gestation, though often the condition is not recognized until shortly after delivery. It occurs in younger patients than does true pernicious anaemia (20 to 40 years) and is common in multiparae. The patient fairly rapidly becomes pale and develops a slight icterus. As in true pernicious anaemia, the anaemia is usually comparatively well borne, though lassitude and dyspnoea are common symptoms. In severe cases oedema and albuminuria develop and give a clinical picture suggestive of nephritis, while the onset of coma may suggest toxæmia. Syncopal attacks and retinal haemorrhages are not uncommon, but spinal cord changes and glossitis do not arise. The catastrophes occur usually after delivery, when, as a result of the stress and shock of labour, the enfeebled patient suddenly collapses and becomes moribund. Premature labour is common and the outlook for the infant is correspondingly bad. Fortunately the amount of post-partum haemorrhage is usually surprisingly small. Fever without demonstrable infection, which abates when anti-anaemic therapy is employed, is not unusual, and when it occurs post partum may suggest puerperal sepsis. This anaemia tends to undergo a spontaneous recovery after delivery and, when once cured, to remain so without liver treatment, though in some of the recorded cases the anaemia has recurred with subsequent pregnancies. In this respect the pseudo-pernicious anaemia of pregnancy differs from true Addisonian pernicious anaemia. The causation of this macrocytic anaemia has been shown to lie in a temporary cessation of the manufacture of intrinsic factor by the gastric mucosa. This failure of one gastric secretion is sometimes, but not always, associated with a failure of acid secretion, but with the cessation of the pregnancy the intrinsic factor disappears, so that usually those patients who have survived the ordeal of labour make a spontaneous recovery.

In untreated cases the mortality rate is high: for the mother it is from 30 to 75 per cent., for the foetus even higher, so that the pseudo-pernicious anaemia of pregnancy must be regarded as a serious though fortunately a rare disease.

Treatment consists in the administration of large doses of liver parenterally, and the response is as dramatic as in true pernicious anaemia. If labour is not imminent, there will be usually sufficient recovery to allow of a normal labour without excessive danger or distress to the mother. In the presence of infection or if the patient is *in extremis*, or if labour is imminent or has already commenced, liver therapy must be supplemented by intravenous blood transfusion, repeated if necessary. Indeed, this emergency should be eminently suitable for the continuous drip transfusion recently introduced.

The question of delivery by Caesarean section may have to be considered in the severely ill patients in whom labour has already begun, and here the decision must depend upon the obstetrical difficulties of the individual case.

Erythronoclastic (Haemolytic) Anaemias

The essential feature of a haemolytic or erythronoclastic anaemia is blood destruction, and the clinical picture varies with the severity and rapidity of the haemolysis.

The onset is usually during the last three months of pregnancy, but in some cases symptoms do not develop until after delivery. In the more acute cases the patient rapidly becomes pale and ill, with dyspnoea and prostration. The skin and mucous membranes are pale and the conjunctivae may become icteric. Usually the spleen is palpable and the liver may also be enlarged. During the stage of red cell destruction the urine contains urobilin and urobilinogen in excess, and in the more severe cases haemoglobinuria may appear. The van den Bergh test shows a positive indirect reaction. The nature of the blood picture depends to some extent upon the state of the bone marrow and its reaction to the blood loss. The anaemia is usually severe. The red cells and haemoglobin are proportionately reduced, so that a colour index of approximately unity is usual. The cells are of average size or contain at most only a few macrocytes in contradistinction to the pernicious-like anaemia of pregnancy, in which well-marked macrocytosis is necessarily an essential feature of the disorder. Anisocytosis and poikilocytosis are present. In those cases in which the bone marrow has remained uninjured polychromasia is well marked and nucleated red cell forms may appear even in untreated cases. This type may be referred to as "plastic." In spite of all this bone marrow activity, however, the degree of anaemia may remain unaltered. A leucocytosis up to 40,000 per c.mm. is usual and immature white cells of the granular series may be seen.

The blood picture is therefore essentially different from that of the pseudo-pernicious anaemia of pregnancy, in which macrocytosis is invariably present, signs of blood regeneration occur only after delivery or as the result of liver treatment, and the white cell count is normal or reduced. In those cases in which bone marrow injury has accompanied the haemolysis of the circulating red cells, signs of regeneration are few or altogether absent, and these may be described as hypoplastic or aplastic forms. The disease is rare, but obstetrical shock following delivery is common and the mortality rate high. Cases that survive the trial of labour may recover spontaneously, especially the plastic forms. The nature of the poison responsible for the haemolysis is unknown. In many cases sepsis seems to have played a part. Pregnancy appears to behave as a predisposing factor, and there is some evidence that the disease may recur in subsequent pregnancies. In the treatment of erythronoclastic anaemia iron and liver are seldom of value, but intravenous blood transfusion, repeated, if necessary, may truly be regarded as a life-saving measure. By providing red cells for immediate use in the circulation, transfusion will tide the patient over a crisis: in most cases it appears to stir up the bone marrow to greater activity, and in a manner that is little understood it stops the haemolytic process.

Conclusion

To sum up the problem, there exist in this country, more especially in hospital patient class practice, mild degrees of hypochromic anaemia of pregnancy which, though seldom dangerous to life, are nevertheless responsible for minor ailments and ill-health in both mother and child, and may be prevented or cured by a generous diet and the exhibition of iron. Occasionally severe and dangerous degrees of anaemia develop during and as a result of pregnancy, especially in the later months of gestation. These conditions demand detailed haematological investigation, accurate diagnosis, and prompt treatment appropriate to the type of anaemia present. A routine haemoglobin estimation at about the seventh month of pregnancy and detailed haematological investigation of all cases showing severe degrees of anaemia should form an essential part of ante-natal supervision.

HYPOCHROMIC ANAEMIAS OF PREGNANCY AND THE PUERPERIUM

BY

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The effects of repeated pregnancies in producing iron-deficiency anaemia have already been discussed (*Journal*, September 12th, page 525). In this communication particular attention will be paid to the problem of hypochromic anaemia occurring during gestation, and the importance of the blood loss at parturition will be dealt with in some detail. During the last century Nasse and Fouassier¹ pointed out the reduction in red cells which takes place in gestation. Since then workers in many countries have contributed studies of the anaemias of pregnancy, and the increased interest in haematology during the past ten years has embraced this field. The work of many authors in America,^{1 2 3 4 5 6 7} Britain,^{8 9 10 11} Germany,^{12 13} Norway,¹⁴ India,¹⁵ and New Zealand,¹⁶ has shown that anaemia often appears in pregnancy and has a widespread geographical distribution. The aetiology of the anaemia has been discussed by Strauss,¹⁷ Strauss and Castle,¹⁸ Witts,¹⁹ Bethell,²⁰ Irving,²¹ Boycott,¹¹ and others; and Richter, Meyer, and Bennett,⁵ Corrigan and Strauss,²² Wills,²³ Toland,²⁴ Irving,²¹ and Bethell²⁰ have studied the effects of treatment. The views held by most authorities are that hypochromic anaemia, often of severe degree, occurs frequently during pregnancy; that its production depends on an iron deficiency due mainly to the supply of iron to the foetus; and that iron therapy is followed by good results.

There has been a tendency to confine investigations into the incidence of anaemia among women to the period of pregnancy, because it is during this time that large numbers of women present themselves for routine supervision at ante-natal clinics, and so render such investigations easy. It is a more difficult matter to obtain blood examinations in a large series of non-pregnant women who complain of no symptoms of ill-health. The high incidence of anaemia found in practically all series of gravid women has led naturally to the assumption that pregnancy is the cause of the anaemia. Our figures have shown clearly that, while anaemia is frequent among pregnant women, it is only slightly less frequent among non-pregnant women, and the incidence of severe anaemia is actually less in the former group. In addition, there is a greater tendency to perform blood examinations at this rather than at other times, because such symptoms as breathlessness and oedema of the ankles, which are so common in pregnancy, often raise the suspicion of anaemia. The frequency with which anaemia will be found has already been pointed out; it is therefore natural that its relation to pregnancy should have been repeatedly stressed, since the symptomatology of pregnancy tends to make more evident the chronic anaemia so common in women. For these reasons, then, the anaemias of pregnant women have been widely studied, and comparatively little attention has been paid to those of non-pregnant women, apart from the severe cases which form the "idiopathic hypochromic" group.

Fall in Haemoglobin

Practically all authors are agreed that there is a fall in the haemoglobin level in pregnancy, but the degree of this fall and the period of gestation at which it is maximal show considerable variation in different series of cases. Richter, Meyer, and Bennett,⁵ Feldman *et al.*,²⁵ Bland,