# MEGALOBLASTIC ANAEMIA IN PREGNANCY

by

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There is now a growing volume of opinion that megaloblastic anaemia is common in pregnancy (Dasgupta, 1953; Upadhyay, 1956). The differences in absolute values (MCV, MCHC etc.) as noted by us and other workers in India (Kothari and Bhende, 1950; Scott and Govan, 1952 and Menon, 1956 and 1965) are attributable to dimorphism due to coexisting iron deficiency.

The treatment of megaloblastic anaemia had been a problem till the discovery of folic acid by Spies *et al* in 1945, though folic acid alone has not been found that effective in our cases due to other commonly associated deficiencies like iron, protein and $B_{12}$. These deficiencies have been revealed particularly with the introduction of better diagnostic procedures following failure of folic acid alone in the treatment of megaloblastic anaemia. It has, therefore, become necessary to evaluate our therapeutic regime and the diagnostic procedure now introduced.

## *Material and Methods*

One hundred cases of megaloblastic anaemia were seletced consisting of 80 pregnant anaemic women in their 3rd trimester of pregnancy and 20 anaemic cases in the puerperium. The cases were diagnosed with the aid of haemogram, bone marrow biopsy and leucocytic lobe average count. The haematological techniques employed were those described by Dacie (1956). The interpretation and grading of bone marrow were done as follows (Dawson, 1962):

| | | |
|---|---|---|
| A. Grade I | — | Normoblastic. |
| B. Grade II | — | Normoblastic with giant metamyelocytes and/or Howell/Jolly bodies. |
| C. Grade III | — | Transitional megaloblastic. |
| D. Grade IV | — | Megaloblastic. |

The leucocytic lobe average was calculated by the number of lobes of polymorphonuclear leucocytes in 100 cells/100. The normal value was taken as $3.75 \pm .25$ as suggested by Herbert (1964).

To evaluate the therapeutic efficacy after the diagnosis, the cases were divided into the following groups:

(1) Group A—24 patients treated with vitamin B12 in the dose of 100 mcg. in 2 divided doses.

(2) Group B—26 patients treated with folic acid 30 mgm, in 3 divided doses.

(3) Group C—24 patients treated with folic acid in the dose of 30 mgm, and iron 100 mgm on alternate days.

(4) Group D—26 patients treated with folic acid 30 mgm, iron 100 mgm and high protein diet.

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The high protein diet consisted of eggs, liver, fish and milk giving an equivalent of 250 gms. of protein.

Eggs — 1 egg.
Liver — 50 gms.
Fish — 250 gms.
Milk-Proteins—1000 gms.)

The response to the treatment was judged by:

1. Improvement in clinical condition.
2. Increase in reticulocyte count.
3. Improvement in the peripheral blood picture with particular stress on leucocytic lobe average count, and
4. Increase in plasma protein level.

In the present series we have not included those cases of severe anaemia where diuretics and blood transfusions were used.

TABLE I

*Showing the type of anaemia in pregnancy and puerperium as observed by bone marrow biopsy*

| Type of anaemia | No. of cases during pregnancy. | No. of cases during puerperium. | Total |
|---|---|---|---|
| Normoblastic | 8 | 2 | 10 |
| Megaloblastic dimorphic | 57 | 6 | 63 |
| Pure megaloblastic | 15 | 12 | 27 |

N.B.—Megaloblastic dimorphic cases belong to bone-marrow Grades II and III.

TABLE II

*Showing the morphology of bone marrow in 100 cases of megaloblastic anaemia*

| Grades. | No. of cases. |
|---|---|
| I | 10 |
| II | 23 |
| III | 40 |
| IV | 27 |

*Discussion*

In the present series, 63 dimorphic and 27 pure megaloblastic cases were studied. Patients with pure megaloblastic anaemia responded well to folic acid, while the response of the dimorphic group was better with folic acid and iron and high protein diet. In all these cases the presence of oedema was a striking feature and this lead us to a study of plasma proteins, much before the deficiency of folic acid and Vit. $B_{12}$ as a cause of anaemia was known. Since anaemia and hypoproteinaemia are quite common in our state where the nutritional standards of the people are quite low, this deficiency of protein is further aggravated during pregnancy.

We have observed that the development of the syndrome of megaloblastosis, protein deficiency and oedema is first heralded by an almost imperceptible increase in the lobe average of the polymorphs in the peripheral blood, much before the appearance of the precursors of red blood cells, like the megaloblasts and normoblasts. It is known that it takes 20 weeks for overt megaloblastic anaemia to be established but the changes start appearing in the leucocytic series much earlier than those in the erythropoietic series.

Though the patients with pure megaloblastic anaemia responded well to folic acid and the response of the dimorphic group was better with folic acid and iron, addition of a high protein diet in both the groups was useful, as hypoproteinaemia with resultant oedema was invariably present in both the groups. This is natural in view of the poor nutritional stand-

TABLE III

*Group A Showing the haematological response to therapy with vitamin $B_{12}$ in megaloblastic anaemia of pregnancy*

| Response. | Hb. in gm | | RBC in mill/cum. | | MCV in cuu. | | MCHC in % | | Serum protein. | | Lobe average. | | Ret. count. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | 3rd day | 7th day |
| Grade IV | 5.95 | 6.1 | 1.58 | 1.75 | 120.95 | 118.6 | 34.8 | 32.6 | 4.3 | 4.4 | 5.0 | 4.9 | 2.0 | 2.05 | 2.1 |
| ,, III | 6.63 | 7.63 | 2.45 | 2.56 | 101.2 | 99.2 | 30.4 | 30.7 | 5.6 | 5.7 | 4.9 | 4.4 | 1.3 | 1.8 | 2.0 |
| ,, II | 5.8 | 7.2 | 1.81 | 2.41 | 102.0 | 96.0 | 31.3 | 30.4 | 4.0 | 4.4 | 3.8 | 4.0 | 4.5 | 4.8 | 4.1 |

BT—Before treatment, , AT—After treatement. Ret—Retuculocyte. Improvement shown is not significant.

TABLE IV

*Group B showing the haematological response to therapy with folic acid in megaloblastic anaemia of pregnancy*

| Response | Hb. in gm% | | RBC in mill/cum. | | MCV in cuu. | | MCHC in %. | | Serum protein. | | Lobe average | | Ret. count. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | 3rd day | 7th day. |
| Grade IV | 5.38 | 11.2 | 1.21 | 3.49 | 133.3 | 94.7 | 34.9 | 32.7 | 3.9 | 6.00 | 5.0 | 3.9 | 4.0 | 5.9 | 7.0 |
| ,, III | 6.6 | 8.7 | 1.68 | 2.63 | 116.2 | 104.7 | 34.3 | 30.8 | 5.2 | 7.2 | 4.7 | 3.75 | 3.2 | 4.5 | 5.1 |
| ,, II | 7.5 | 7.9 | 2.52 | 3.07 | 93.0 | 88.0 | 31.0 | 29.2 | 4.5 | 5.1 | 3.8 | 5.5 | 2.0 | 2.5 | 3.6 |

BT—Before treatment, AT—After treatment. Ret—reticulocyte. Improvement shown is significant.

TABLE V

*Group C showing the haematological response to therapy with folic acid and iron in megaloblastic anaemia of pregnancy*

| Response. | Hb. in gm. % | | RBC in mill/cum. | | MCV in cuu. | | MCHC in % | | Serum protein. | | Lobe average. | | Ret. count. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT. | AT. | BT. | AT. | BT. | AT. | BT. | BT. | BT. | AT. | BT. | AT. | BT. | 3rd day. | 7th day. |
| Grade IV | 5.1 | 11.07 | 1.22 | 3.34 | 135.1 | 99.5 | 33.3 | 33.0 | 3.0 | 6.3 | 5.6 | 3.8 | 4.8 | 6.0 | 6.5 |
| „ III | 5.1 | 11.3 | 1.20 | 3.96 | 123.3 | 89.6 | 33.2 | 31.7 | 4.9 | 6.6 | 4.8 | 3.7 | 6.0 | 7.1 | 7.0 |
| „ II | 8.3 | 11.9 | 2.95 | 3.88 | 115.9 | 96.3 | 27.2 | 30.5 | 3.8 | 5.0 | 3.9 | 3.7 | 5.4 | 6.8 | 6.8 |

BT—Before treatment, AT—After treatment, Ret—reticulocyte. Improvement shown is highly significant.

TABLE VI

*Group D showing the haematological response to therapy with folic acid, iron and high protein diet in megaloblastic anaemia of pregnancy.*

| Response. | Hb. in gm.% | | RBC in mill/cum. | | MCV in cuu. | | MCHC in % | | Serum protein. | | Lobe average. | | Ret. count. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | AT. | BT. | 3rd day. | 7th day. |
| Grade IV | 4.85 | 12.5 | 0.95 | 4.09 | 141.3 | 99.1 | 35.95 | 33.3 | 3.9 | 7.1 | 5.0 | 3.5 | 4.0 | 7.2 | 10.0 |
| „ III | 4.60 | 11.58 | 1.53 | 3.66 | 106.25 | 88.25 | 28.06 | 31.88 | 4.1 | 7.8 | 4.90 | 3.65 | 3.8 | 5.0 | 6.8 |
| „ II | 5.0 | 12.0 | 1.52 | 4.11 | 90.0 | 92.0 | 36.4 | 32.1 | 4.8 | 6.7 | 3.85 | 3.5 | 2.3 | 2.5 | 2.8 |

BT—Before treatment, AT—After treatment, Ret—reticulocyte. Improvement shown is strikingly significant.

ards of our people who subsist on a deficient protein diet which becomes still more deficient with the increasing requirements of pregnancy (Upadhyay, 1944). The dietary habits are such that there is no dearth of green leafy vegetables which contain an abundance of folic acid and iron, in comparison to the diet in the West where the incidence of megaloblastic anaemia is commoner during the winter season when the green vegetables are not available. In these cases it is probably the folic acid alone which is responsible for megaloblastosis, whereas in our cases it is the protein deficiency which is the primary factor. It is known that at the cellular level folic acid, vitamin $B_{12}$ and ascorbic acid are intimately associated and play an important role in the synthesis of nucleic acid. But a deficiency of first class proteins even in the presence of normal levels of folic acid or vitamin $B_{12}$ will result in defective nucleic acid and nucleoprotein synthesis and result in megaloblastic erythropoiesis. Since the foetus requires a large amount of nucleo-protein for its tissue synthesis it is understandable that the foetus represents a serious drain on the maternal protein stores.

While studying the problem of anaemia with hypoproteinaemia it has been noted that there is a decrease in the albumin fraction and increase in the globulin fraction in the pregnant women as compared to normal values, and oedema resulted whenever there was a significant lowering of the albumin fraction which is mainly responsible for maintaining the colloid osmotic pressure. We have found it essential to take note of oedema because it has been observed that cases of severe anaemia with oedema, when not promptly treated, have a tendency to develop hypertension and behave like pre-eclamptic toxaemia. This is a further complication of pregnancy endangering foetal and maternal life, hence the necessity of eliminating oedema as soon as possible. Here, we have tried oral diuretics and have found good results, in as much as they have rendered patients suitable for packed cell and whole blood transfusion. We seldom had to resort to exchange transfusions with this regime. Further study of such patients shall form another series.

It is interesting to observe that the response to treatment was shown more often with rise in the plasma protein than in the reticulocyte count. With our newer methods of diagnosis by determination of lobe average, the clue to erythropoietic and plasma protein regeneration is further emphasized by a decreasing lobe average. It would thus seem that a co-relation regarding haemopoietic activity and liver function is better indicated, and at a much earlier stage, by a fall in the lobe average and a rise in plasma protein than by any other method like reticulocyte count rise, rise in Hb.% and red blood cells. Thus, it will be noted that there is a picture about the megaloblastic anaemia that we see, comprising of oedema, hypoproteinaemia, increased lobe average, besides anaemia. Considering all the methods that we have tried, the first indication of impending megaloblastosis is proved by the rise in the lobe average. This has also been shown by Herbert, (1964). It

has been reported that it takes 20 weeks for the megaloblastic picture to be fully established in folic acid deficiency. During the course of treatment we noted again that the lobe average was the first to show the response. Next in order was the rise in plasma proteins, then reticulocyte count and lastly the changes in the peripheral blood picture. The serum folic acid estimation, before and after therapy, reflected a consistent change which ran parallel to the changes in the lobe average of the polymorphs. Thus, it would appear that the change in the lobe average provided us with the most rapid and easy method of detecting the development of megaloblastosis and the return back to normalcy with therapy. Again the changes in plasma proteins run parallel to the changes in the lobe average as noted earlier. Our recent observations conclusively prove that megaloblastosis occurs primarily due to protein deficiency. The changes in lobe average are the best pointers to concentration of plasma proteins and in the diagnosis and prognosis of megaloblastic anaemia. The value of lobe average count in the diagnosis and prognosis of megaloblastic anaemia is now fully established.

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