# PROPHYLAXIS OF ANAEMIA IN PREGNANCY

by

M. K. KRISHNA MENON*, B.A., M D.,

and

LAKSHMI RAJAN**, M.B., B.S., D.G.O.

Anaemia is the commonest complication met with during pregnancy in many countries of Asia. Its severity varies with geographical location and socio-economic standards. The aetiological factors are many and varied. So also the types of anaemia met with. There is considerable variation in the definition of "Anaemia". Varying standards of Hb. levels are adopted as normal in pregnancy. Because of the lack of standardisation, the incidence of anaemia also differs. From our studies we have found that the average Hb. level of the hospital class of patients in the so-called normal pregnant women is about 10.5 gms. (14.5 gms. = 100%) (Menon and Chandrasekharan, 1954) in the last trimester. In only about 10% is the Hb. in the region of 11 gm.% or more. Hence for classifying a patient as anaemic we consider only Hb. levels below 60% (8.7 gm.%), which according to Western standards is severe anaemia.

Many factors influence the incidence of anaemia in pregnancy. Firstly, there is the question of haemodilution in pregnancy which gives rise to falling Hb. levels while the total haemoglobin mass is not reduced. In the past it has been customary to attribute the well known fall in haemoglobin levels of pregnant women to hydraemia and to accept haemoglobin as low as 67% (10g/100 ml.) as physiological (Greenhil, 1951; Whitby and Britton, 1957). This view is based on the blood volume studies by Dieckman and Wegner (1934) and others which revealed that with advancing pregnancy the increase in plasma volume outstrips a similar increase in the red cell mass. Fisher and Biggs (1955) Kerr and Davidson (1958) have shown that a majority of such "Physiological anaemias" respond to iron therapy and hence it has become necessary to revise the definition of pregnancy anaemia. According to Giles and Burton (1960), the haemoglobin of a normal woman in late pregnancy should be at least 80%.

In India, conditions are different and though it would be highly desirable, it is only in a small percentage that haemoglobin levels are at 80% or more in late pregnancy. The large majority fall between 10.5 gms. and 11 gms.% and hence in pregnancy we would aim at keeping the haemoglobin level at least at 10.5 gms.%.

* *Director, Institute of Obstetrics and Gynaecology, Govt. Hospital for Women and Children, Madras-8 and Professor of Obstetrics and Gynaecology, Madras Medical College, Madras.*

** *Assistant Research Officer, Indian Council of Medical Research.*

There are various factors contributing to this anaemia. The malignant influence of malnutrition and unbalanced diet is too well known to require any more mention. Helminthic infections, fevers like malaria and Kala azar, the dysenteries and various other diseases of a like nature if rampant in a community are sure to show their baneful influences in the increased incidence of the severe type of anaemia when women so affected become pregnant.

Apart from these factors, there is the very important one—the growing foetus. The foetus requires for its proper haemopoeisis all the factors which are necessary for the same process in the mother, namely iron, folic acid, $B_{12}$ and various other factors. During its extrauterine existence for the first few months it usually exists on breast milk which contain little or no iron. Hence it has to lay down in its haemopoietic system a store of these haemopoietic factors. These it can obtain only from the mother, and in pregnancy, irrespective of the nutrition of the mother and her needs, the foetus absorbs for itself whatever is necessary. Hence in pregnancy, anaemia in the mother may be precipitated, if no extra haemopoietic factors are supplied to the mother to meet the increasing foetal demands. An anaemia may also become severe if the mother at the start of pregnancy is already anaemic or is on the border line with no reserves.

In our experience two types of anaemia are commonly met with in pregnancy: (1) Pure iron deficiency anaemia (microcytic hypochromic). (2) Dimorphic anaemia—Macrocytic hypochromic anaemia with either a normoblastic or megaloblastic bone marrow. The iron deficiency anaemia responds to iron therapy, oral or parenteral, and the dimorphic anaemia to iron with folic acid or $B_{12}$. Better results have been obtained when folic acid and iron have been used (Menon and Chandrasekharan, 1954).

This anaemia clinically manifests itself in the early second trimester and, if not treated, gets worse with the advancing pregnancy. It is not uncommon to observe a patient develop iron deficiency anaemia in early pregnancy and develop later a dimorphic anaemia. From our experience of treatment of these anaemias a scheme of prophylaxis suggested itself. As the anaemia is common in the low income group of patients and as it is obviously not possible for them to alter their diet and provide themselves with a suitable balanced diet in pregnancy it was considered rational to supply these pregnant mothers with iron and folic acid supplements during pregnancy and watch its result on the incidence of anaemia without altering their dietetic habits.

*Method*

As stated previously, a routine study of antenatal cases showed that in over 80% of the so-called normal pregnant women the haemoglobin level was only between 10.5 gms. and 11 gms.%. Hence, it was decided to accept for these trials only pregnant women between 16 weeks and 24 weeks whose haemoglobin level was at or above 10.5 gms.% (14.5 gms.=100%). All these patients were thoroughly examined and if

any complicating diseases were found they were discarded. The patients were divided into three groups: Group I was given 5 gr. of ferrous sulphate by mouth daily; Group II 5 mgms. of folic acid by mouth; and Group III 5 gr. of ferrous sulphate and 5 mgms. of folic acid. In addition all patients were given multivitamin tablets—three tablets daily. Each tablet contained Vitamin A 2500 I.U., Vitamin B 0.5 mg., Vitamin C 12.5 mg. and Vitamin $D_2$ 250 I.U.

There was no selection of cases—cases were allotted to each group in the order in which they registered but it was so done that there was a fairly equal distribution of primigravidae and multigravidae in each group. All patients were advised to take the tablets regularly and were asked to report to the clinic every fortnight till the 36th week and every week after that. At each visit along with routine antenatal examination the haemoglobin level was checked. The same medical officer did the investigation using the same technique and scale. The haemoglobin was estimated by the acid haematin method. A health visitor visited the patients in the homes as frequently as possible to check up on the regularity of their taking the drugs. Patients were followed up till delivery. The aim of the study was to find out in which group haemoglobin fell below 10.5 gms. and in which severe anaemia developed. Only cases who were taking the drugs regularly (as far as can be ascertained) were taken for final analysis. No extra diet was prescribed nor supplemented. Almost all were in the lower income group.

*Results*

450 women who satisfied the criteria for the trials were admitted for the study. Of these 10 aborted and 159 were so irregular in their attendance that they had to be dropped from the study. 273 patients who attended regularly and were followed up to term and delivery were available for the final analysis. The relevant data of these patients are given in the following tables.

The 273 were distributed into the three groups as follows:—

Group I (Iron alone), 88

Group II (Folic acid alone), 90

Group III (Iron and Folic acid), 95.

TABLE I

*Socio-economic Status of Patients —Income Group*

| Income in Rupees | Group I | Group II | Group III |
|---|---|---|---|
| Nil | 2 | 3 | 8 |
| 0 - 50 | 48 | 48 | 42 |
| 50 - 100 | 37 | 37 | 41 |
| Above 100 | 1 | 2 | 4 |
| Total | 88 | 90 | 95 |

TABLE II

*Distribution of Parity*

| Order of pregnancy | Group I | Group II | Group III |
|---|---|---|---|
| First | 16 | 16 | 16 |
| Second | 22 | 23 | 21 |
| Third | 13 | 14 | 14 |
| Fourth and above | 37 | 37 | 44 |
| Total | 88 | 90 | 95 |

TABLE III

*Distribution of Haemoglobin Level at Commencement of Trials*

| Hb in gm.% | No. of cases in Group I | No. of cases in Group II | No. of cases in Group III |
|---|---|---|---|
| 10.5 | 43 | 47 | 48 |
| 11 | 26 | 23 | 27 |
| 11.5 | 11 | 13 | 11 |
| 12 | 7 | 6 | 7 |
| 12.5 | 1 | 0 | 2 |
| 13 | 0 | 1 | 0 |
| Total | 88 | 90 | 95 |

TABLE IV

*Duration of Drug Period in Weeks*

| Duration in weeks | No. of cases in Group I | No. of cases in Group II | No. of cases in Group III |
|---|---|---|---|
| 15 - 17 | 10 | 11 | 15 |
| 17 - 19 | 20 | 25 | 22 |
| 19 - 21 | 27 | 21 | 26 |
| 21 - 23 | 20 | 23 | 18 |
| 23 - 25 | 10 | 10 | 13 |
| 25 - 27 | 1 | 0 | 1 |
| Total | 88 | 90 | 95 |

TABLE V

*Difference in Haemoglobin Levels before and after Treatment*

| Difference in gm.% | No. of cases in Group I | No. of cases in Group II | No. of cases in Group III |
|---|---|---|---|
| —4.0 | 0 | 1 | 0 |
| —3.5 | 0 | 2 | 0 |
| —3.0 | 2 | 2 | 0 |
| —2.5 | 2 | 2 | 0 |
| —2.0 | 2 | 12 | 2 |
| —1.5 | 8 | 13 | 9 |
| —1.0 | 14 | 17 | 5 |
| —0.5 | 16 | 19 | 17 |
| 0 | 21 | 16 | 32 |
| +0.5 | 16 | 6 | 15 |
| +1.0 | 4 | 0 | 11 |
| +1.5 | 1 | 0 | 4 |
| +2.0 | 2 | 0 | 0 |
| +2.5 | 0 | 0 | 0 |
| +3.0 | 0 | 0 | 0 |
| +3.5 | 0 | 0 | 0 |
| +4.0 | 0 | 0 | 0 |

TABLE VI

*No. of Cases Where Haemoglobin Level Fell to below 10.5 Gm.% Which Was Taken as the Base Line for the Trials*

| Group | No. of cases | No. showing drop below 10.5 gm. % | % of cases showing drop |
|---|---|---|---|
| I | 88 | 33 | 37.5 |
| II | 90 | 54 | 60 |
| III | 95 | 17 | 17.9 |

These statements clearly indicate that (1) the distribution of cases into the different groups have been very uniform in relation to income, parity, and haemoglobin levels at the start of treatment. (2) In the regularity of attendance and duration ot treatment it is also uniform. (3) That the number of cases whose haemoglobin level fell to below 10.5 gms. has been the least in Group III who were given iron and folic acid—17.9% as against 37.5% in the iron group and 60% in the folic acid group. It was further observed that the haemoglobin fell to 9.5 gm% and less at term in 16 women in Group I, in 37 in Group II while in Group III only in 3 patients did the haemoglobin level drop below 10.5 gm% and in none to less than 9.5 gm%. In one case in Group I the haemoglobin fell to 6 gm% and a dimorphic anaemia was diagnosed on investigation. In Group II, 4 patients developed severe anaemia haemoglobin falling to less than 7.5 gm%. All these cases were admitted into hospital. In Group III none developed severe anaemia.

The results were statistically analysed by Mr. G. Ranganathan, B.A. (Hons.), Statistician, Institute of Venereology, Madras Medical Col-

lege. A resume of his report is given below:—

Comparative study of the effects of three different treatments in the prevention of anaemia during pregnancy:—

The treatments are:—

(a) Iron,
(b) Folic acid and
(c) Iron with folic acid (combined).

*Aim of Study*

The experiment was conducted with a view to determine and compare the effects of the three different treatments in preventing the development of anaemia during pregnancy.

*Material and Method*

Taking 10.5 gms% as the minimum haemoglobin level for the absence of anaemia, 273 nonanaemic patients were selected for investigation.

The patients were numbered serially as they came in, and were divided into three groups without assigning any special preference to any one particular individual. Randomness was effected throughout the selection so as to avoid any bias that might have influenced the results. The division resulted in three groups of sizes 88, 90 and 95.

The 88 patients of the first group were given iron, whilst the second and third groups were given folic acid, and iron with folic acid respectively.

The two main factors that influence the causation of anaemia are: (1) the socio-economic status of the patients as judged by income, and (2) the number of the pregnancy. In this study the groups were at par in both the respects. The mean incomes of the three groups were almost equal, and the slight differences noticed were found to be insignificant for comparative purposes. The number of the pregnancy also did not affect the results in any way, and the groups were comparable in this respect too.

Having commenced the treatment, the patients were followed up at regular intervals and were advised to undergo the full course, and this was carried on upto the 40th week of pregnancy.

Though the duration of treatment varied among the patients, parity was maintained between the mean durations of each group. The moderate difference in duration of treatment between the groups were not significant.

*Analysis of Findings*:

| Income status: | Iron | Folic acid | Iron with Folic acid |
|---|---|---|---|
| Mean income $\bar{x}$ (in Rs.) | 46.6 | 46.9 | 48.6 |
| Variance $s^2$ | 711.96 | 993.44 | 999.88 |
| Standard deviation $s$ | 26.68 | 28.17 | 31.62 |

The differences in the mean incomes were not significant under preceding Table p. 306

| | | | |
|---|---|---|---|
| **Duration of treatment:** | | | |
| Mean duration x (in weeks) | 20.07 | 19.91 | 19.89 |
| Variance $s^2$ | 5.8 | 6.02 | 6.96 |
| Standard deviation s | 2.41 | 2.45 | 2.638 |

Differences in the mean durations were not significant. The groups were thus found to be comparable.

| | | | |
|---|---|---|---|
| **Changes in the haemoglobin levels:** | | | |
| Mean $\bar{x}$ | —0.36 | —0.69 | —0.0684 |
| Variance $s^2$ | 0.9130 | 1.5876 | 0.6402 |
| Standard deviation s | 0.95 | 1.25 | 0.8001 |

Test for comparison of differences of means ('t' test):

(a) *Iron group x Folic acid group*

Pooled standard deviation=$\sigma$ =1.12

Standard error of the difference of means =e=0.15 x 1.12

't'=1.964—significant at the 5% level,

i.e. the patients belonging to the iron group were found to have improved better than those of the folic acid group, at the end of the treatment.

(b) *Iron group x Iron with Folic acid group*

Pooled standard deviation=$\sigma$ =0.882

Standard error of the difference of means=e=0.882 x 0.148

't'=2.234—significant at the 5% level.

i.e. a comparatively better improvement was noticed in the patients belonging to the third group, viz. iron with folic acid treated group.

*Summary and Conclusions*

Three different treatments were tried for the prevention of anaemia during pregnancy on 273 non- anaemic patients.

88 patients were treated with iron,

90 patients were treated with folic acid; and

95 patients were treated with iron and folic acid combined.

The groups were found to be comparable in all respects.

Treatment was prolonged up to the 40th week of pregnancy in all the cases.

Haemoglobin per cent levels were evaluated before the commencement of the treatment and also after the completion of treatment.

The changes in haemoglobin per cent levels were calculated and noted down for comparison.

Findings when evaluated revealed that in the folic acid group, in 68 of the 90 patients (i.e. approximately 75.6%,) there was a drop in the haemoglobin level, while in 16 cases

(about 17.8%) there was no change at the end of the treatment. These percentages were 50 and 23.8 for the iron group, and 34.7 and 33.7 for the iron with folic acid group respectively.

The results indicated that these changes were quite significant in the iron with folic acid group and in the iron group, the former being more significant than the latter. That is, the treatment with iron was found to produce better results than with folic acid, while combined iron with folic acid treatment was the most effective".

*Discussion*

Giles and Shuttleworth (1958) in their investigations into the incidence and treatment of megaloblastic anaemia in pregnancy reported an incidence of 2.8%. They also showed that the anaemia responded satisfactorily to folic acid therapy. It is tempting to regard megaloblastic anaemia as a mere deficiency disease which is precipitated by the increased demands of the growing foetus. This is reflected in the high serum folic acid levels of new-born infants (Baker et al 1958). Alternatively, the disease may be due to defective folic acid absorption in pregnancy Scott 1954). According to Girdwood (1953), however, folic acid absorption is normal.

Chanarin et al (1958, 1959) by means of tests of folic acid clearance and absorption have shown that folic acid deficiency exists in pregnancy. Francis and Scott (1959) gave folic acid in addition to iron to all pregnant women with any tendency to develop pathological anaemia—the indication being a haemoglobin of less than 80%. None of these patients developed serious anaemia. They gave as one of the reasons for adopting the policy the iron and folic acid deficiency which tend to occur in the same poorly nourished pregnant patients. 75% of Forshaw's (1958) patients were deficient in iron and folic acid. Francis and Scott also stated that folic acid deficiency may be responsible for anaemia without the marrow being frankly megaloblastic.

In view of the fact that most of our pregnant mothers in the low income group subsist on a very inadequate diet, it is reasonable to assume that the diet will be deficient not only in iron (the daily iron content of the diet of the patients under study was only 9 mgm.) but also in folic acid. This deficiency will certainly be exaggerated when the foetal demands have also to be met. Nor can defect in absorption be ruled out. Hence the necessity for supplying both iron and folic acid to the mother.

All are agreed that iron should be given to the mother during pregnancy. Whether folic acid should be given is more debatable. Lowenstein et al (1955) gave it to all pregnant women during the last three months, a routine which they found effective. It is said that under such therapy there is admittedly a rare risk of treating a case of Addisonian pernicious anaemia this way. In our investigations of a large series of patients in normal pregnancy we have not come across a single megaloblastic bone marrow nor have we, during the last 25 years, seen a single case of Addisonian anaemia complicating pregnancy. To us here therefore the risk is indeed remote.

Our trials had a very limited but definite objective. It was to decide whether by giving iron and folic acid orally to all pregnant women with a haemoglobin level of 10.5 gms% or over from early pregnancy, the incidence of the severer degrees of anaemia could be prevented or reduced. It was suggested at the start of trials that the diet should be supplemented by skimmed milk. The suggestion was not accepted as our aim was to find out how far iron and folic acid supplements will be effective under the conditions in which the mothers normally lived. It has to be realised that once the trials were over no skimmed milk will be available to them in another pregnancy and hence the necessity for assessing the results under their normal dietetic conditions.

Even though our series is small, the results show that even under the existing socio-economic conditions the incidence of the severer type of anaemia in pregnancy could, to a very significant extent, be reduced by giving to all pregnant women 5 grs. of ferrous sulphate and 5 mgm. of folic acid daily till the end of pregnancy.

It was observed during the trials that in all groups, in a certain number, there has been a fall in haemoglobin level and, in a significant number, no increase in haemoglobin level. Considering the fact that the daily diet of those patients contained only 9 mgm. of iron, it is possible that the 5 grs. of ferrous sulphate was not an adequate dosage to meet the increasing demands of pregnancy. If a larger dosage of iron was employed perhaps better results in Groups I and III might have been achieved.

A question to be considered is that if folic acid is used as a prophylactic is it necessary to give 5 mgm. daily? Will not a smaller dose, say, 3 mgm., suffice? This question is difficult to answer. It has not been possible to determine the folic acid requirements in pregnancy. Five mgm. daily was an arbitrary choice and not based on any definite scientific data. Because of the malnutrition in the low income group, which constitute the bulk of mothers in the trials, a higher dosage was chosen. There is no scientific basis to believe that it is the right one either. All that the trial has shown is that if the woman starts her pregnancy with a haemoglobin level of 10.5 gm. or more, on this prophylaxis the incidence of all types and degrees of anaemia (haemoglobin less than 7.5 gm.) can be considerably reduced. It needs no mention that if aetiological factors like hookworm infection, malaria, etc., are found they should be actively treated.

*Summary and Conclusions*

1. 273 pregnant women between 16 and 24 weeks' pregnant and haemoglobin level of 10.5 gm.% or more are included in this study.

2. They were divided into three groups I, II and III. The allotment to the groups was done at random but taking care to see that there was uniformity in parity, socioeconomic standard and haemoglobin levels.

3. Group I was given 5 gr. of ferrous sulphate, Group II 5 mgm. of folic acid and Group III a combination of both.

4. All patients were followed fortnightly with routine antenatal examination and haemoglobin studies. The

number of cases in each group where haemoglobin fell to less than 10.5 gm.% at term was noted.

5. It was found in Group I in 37.5% the haemoglobin fell below 10.5 gm.% at term, while in Groups II and III the figures were 60% and 17.4% respectively.

6. The results were statistically analysed. The statistician's report is included in the paper and he confirms that the differences in the result are very significant.

7. Even though the series is small it is concluded that administration of 5 grains of ferrous sulphate and 5 mgm. of folic acid daily from early pregnancy till term will help considerably in reducing the incidence of severe varieties of anaemia.

This work was undertaken under the auspices of the Indian Council of Medical Research with financial assistance from the World Health Organisation. We are very grateful to the Indian Council of Medical Research and World Health Organisation for their assistance. We express our thanks to Mr. G. Ranganathan, B.A. (Hons.), for his help in statistical analysis of the data.

*References*

1. Baker H., Zitter H., Paster I., Soboka H.: Brit. Med. Jour.; 1478, 1958.
2. Chanarin I., Anderson B. B. and Mollin D. L.: Brit. Jour. of Haematology; 4, 156, 1958.
3. Deickman W. J. and Wegner C. R.: Arch. Intern. Med.; 53, 71, 188, 345, 353, 1934.
4. Forshaw J.: Lancet; 1, 102, 1959.
5. Francis B. H., Scott J. S.: Lancet; 1033, Dec. 5, 1959.
6. Giles C., Shuttleworth E. M.: Lancet; 1341, Dec. 27, 1958.
7. Giles C., Burton H.: Brit. Med. Jour.; 636, Aug. 27, 1960.
8. Kerr D. N. S., Davidson S.: Lancet; 483, Sept. 6, 1958.
9. Lowenstein I., Pick C., Philport N.: Amer. Jour. of Obst. & Gyn.; 70, 1955.
10. Menon M. K. K. and Chandrasekharan K.: J. of Obst. & Gynec. of India; V, 1, 1954.

---

"Please read Ferrous Gluconate in the text instead of Ferrous Suphate. We are grateful to Messrs. Unichem Ltd. for their generous supply of Ferrous Gluconate."