OBSERVATIONS ON ANEMIA IN PREGNANCY WITH PARTICULAR REFERENCE TO EFFECT OF PARENTERAL IRON AND IRON WITH FOLIC ACID

by

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The literature has been mounting about the use of folic acid in pregnancy. In fact, the reliance on folic acid is overshadowing the importance of the use of iron in pregnancy. B.M.J. (1967) writes, "The increased interest in and publicity given to the need of folic acid in pregnancy must not be allowed to detract from the fact that in clinical practice, iron is generally of far greater importance than folic acid in maintaining blood levels in pregnancy". It was therefore, decided to take up anaemia in pregnancy as a project study and undertake a comparative study of the effect of iron and iron with folic acid.

Material and Method

Haemoglobin level of 900 consecutive antenatal cases at Nair Hospital, Bombay, were studied and the mean average haemoglobin level at different trimesters were established. A haemoglobin level of 11 gm% was considered as a critical level for the following reasons: (a) with due allowance given to the haemodilution of pregnancy the reduction of haemoglobin down to the level of 11 gm% would not occur unless the patient was definitely anaemic. (b) That a total of 800 mgm of iron is required during pregnancy has been established. It will be difficult therefore for an expectant mother with haemoglobin less than 11 gm% to comply with such demands unless her intake or reserves are rich in iron. But failing this she would manifest anaemia.

Iron* and iron with folic acid*** was administered parenterally for the following reasons:

(1) this was the surest and most reliable mode of drug administration. (2) Parenteral route will eliminate the factor of intestinal intolerance and malabsorption. Since one third of our patients suffered from colitis or helminthiasis this was very essential. (3) The degree of anaemia in many cases warranted a quicker replenishment of iron supply. (4) 70% of our patients attended antenatal clinic for the first time after 34th week of pregnancy and therefore time available

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* Given as Injection Uniferon 2, an ampoule containing polyhydroxy carbohydrate complex of iron.

*** Given as Injection Uniferon-F 2, an ampoule containing polyhydroxy carbohydrate complex of iron plus 10 mgm. folic acid.

for treatment was limited. (5) Absorption of intramuscular iron starts within half an hour of injection and reaches a maximum in about 16 hours. Parenteral iron raises the blood iron level quickly and helps replenish the iron reserves at a faster rate.

Out of 113 anaemic patients, 49 were treated with 10 injections of iron with folic acid given deep intramuscularly on alternate days and 35 were treated with 10 injections of iron alone given in the same way. The remaining 29 cases had to be withdrawn from the trial as their haemoglobin level was less than 7 gm% and were treated with blood transfusions and intravenous total dose of iron. Every case had a full haematological check up before treatment and 3 weeks after treatment. A third haematological check up was done, just before delivery to know the delayed response of the treatment but as the majority failed to keep this appointment a third reading was taken within 24 hours of delivery.

Observations

The haemoglobin levels of 900 antenatal cases during different trimesters with mean average for each group is shown in Table 1. It is also evident from table 1 that the best time to detect anaemia is during 2nd trimester of pregnancy. The chief haematological findings of 113 anaemia cases is shown in the diagram from which it is also evident that our cases fell into the following groups.

This means 85 of 113 cases were cases of dimorphic anaemia and 26 were iron deficiency anaemia. There was no case with orthochromia. Among 85 cases of dimorphic anaemia, there were 13 cases whose lobe index was more than 3.3 (normal is 3); whilst among 26 cases of iron deficiency anaemia only 2 had lobe average over 3.3 What is most striking is that out of 113 anaemia cases, 100 showed evidence of hypochromia—which bespeaks of iron deficiency.

The average rise in haemoglobin in the two groups is as shown in Table II. The mean rise of haemoglobin in the two groups is almost identical (i.e. 1.39 gm.% and 1.37 gm.%). Expecting that addition of folic acid might have remarkable effect on cases of dimorphic anaemia, the results of these two groups were analysed in further details.

Table III shows comparison of cases of microcytic hypochromic anaemia treated with injection of iron and iron plus folic acid. There is no significant difference in the rise of average haemoglobin in the two groups. The same holds true for PCV, MCV and MCHC. The figures for

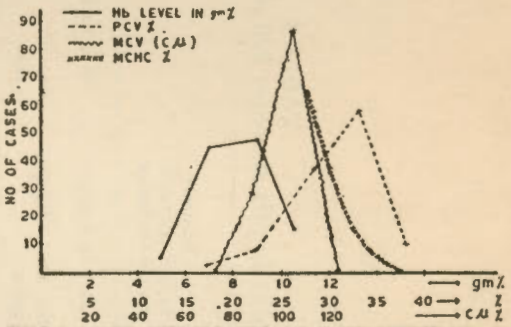

TABLE 2 SHOWING CHIEF HAEMATOLOGICAL FINDING AMONGST 113 CASES OF ANEMIA.

Fig. 1.
Showing chief haemotological finding amongst 113 cases of Anaemia.

both the series were identical, but is most striking that in spite of 10 injections, the PCV and MCHC were still very much below normal indicating the necessity of some more treatment.

Table IV showed the results of treatment in cases of dimorphic anaemia. The initial haemoglobin in cases of diamorphic anaemia is lower than the initial haemoglobin in iron deficiency (group 8.3-8.6

TABLE I

Haemoglobin Levels Amongst 900 Antenatal Cases Studied

Total No. of cases recorded	900	
Total No. of cases recorded in 1st trimester	45	5%
Total No. of cases recorded in 2nd trimester	459	51%
Total No. of cases recorded in 3rd trimester	669	74.3%

No. of Trimesters	Below 6 gms.		6.1 to 8 gms.		8.1 to 10 gms.		10.1 to 11 gms.		Above 12 gms.		Mean average in all cases.
	No. of cases.	Percent	No. of cases.	Percent	No. of cases.	Percent	No. of cases.	Percent	No. of cases.	Percent	
1st	—	—	6	13.3	18	40.0	18	40.0	3	6.6	9.8gm %
2nd	7	1.4	110	24.4	219	48.2	113	24.6	10	2.0	9.4 gm%
3rd	7	1.0	94	14.0	286	42.6	274	40.8	8	1.0	9.5 gm%

(1) Macrocytic	Orthochromic	0
	Normochromic	1 case
	Hypochromic	85 cases
	Orthochromic	0 case
(2) Normocytic	Normochromic	2 cases
	Hyopcaromic	23 cases
	Ortohochromic	0
(3) Microcytic	Normochromic	0
	Hypochromic	2 cases

TABLE II

Average Rise Haemoglobin in the Two Groups

Treatment received	No. of cases.	Mean Hb. in Gm.% before treatment	Mean Hb. in Gm.% after treatment	Mean Hb. in Gm.% after delivery.	Rise.
Iron	30	9.06	10	10.45	1.39
Iron plus folie Acid	49	9.23	9.8	10.6	1.37

TABLE III

The Result of Treatment in Case of Microcytic Hypochromic Aneamia

Treatment given	No. of cases.	Mean Average Readings before treatment					Mean Average Readings after treatment					Mean Average Readings after delivery				
		Hb.	PCV	MCV	MCH	MCHC	Hb.	PCV	MCV	MCH	MCHC	Hb.	PCV	MCV	MCH	MCHC
Inj. Uniferon	12	9.8	32.83	91.17	26.17	28.83	10.78	36	92.83	27.5	29.33	10.91	37	98.54	28.73	28.63
Inj. Uniferon F	8	9.8	32.17	85.83	28	28.8	10.08	35	96	28	29	10.75	38.28	93.86	26.57	28.14

TABLE IV

The Results of Treatment in Cases of Dimorphic Anaemia

Treatment given.	No. of cases.	Mean Average Readings before treatment					Mean Averaege Readings after treamtent					Mean Average Readings after delivery.				
		Hb.	PCV	MCV	MCH	MCHC	Hb.	PCV	MCV	MCH	MCHC	Hb.	PCV	MCV	MCH	MCHC
Inj. Uniferon.	23	8.23	31.57	104.32	26.83	25.91	9.23	35.08	101.5	28.07	29	10	36.12	93.94	27.28	27.63
Inj. Uniferon F.	41	8.67	31.39	107.1	28.58	27.27	9.53	34.64	103.43	28.18	28.14	10.46	36.23	98.34	27.92	28.52

and 9.8 respectively). Here again addition of folic acid has made no significant change in improving the average haemoglobin level, PCV, MCV or MCHC as compared to the group who received iron alone.

Discussion and Conclusions

The trial reveals that:

(1) Ten injections of intramuscular polyhydroxy carbohydrate complex of iron raised the haemoglobin level immediately following the administration and that it continued to rise for 3-5 weeks, irrespective of the onset of labour.

(2) Ten injections of intramuscular iron or iron plus folic acid are not sufficient for our cases. Administration of ten injections of Uniferon or Uniferon F. raised the haemoglobin by 1.39 and 1.37 gm% respectively. Obviously then, there is a need for further administration of iron to increase the haemoglobin to a level of 12 gm.% or more.

(3) Although ten parenteral doses of iron also improved other parameters of blood, the rise in MCHC with ten injections was hardly 0.2 (from 28.8 to 29). This indicates that there still exists a wide margin of iron deficiency that needs correction.

Supplementation of iron rectified the mean corpuscular volume, values lower than 95 showed a rise while pretrial values of 102 and over fell with treatment. The PCV improved soon after the injections and continued to improve till postpartum.

(4) There is no appreciable difference in the effect of plain Uniferon on iron deficiency and on diamorphic anaemias, in the present series.

(5) Addition of 10 mg. (5 mg./ml.) of folic acid to every injection of intramuscular iron had no significant effect on the mean haemoglobin values in the cases studied, irrespective of the type of anaemia encountered, dimorphic or microcytic, nor do other parameters reveal any beneficial difference.

It is a known clinical fact that folic acid deficiency can exist in pregnancy even in the absence of a megaloblastic anemia (Chanarin *et al* 1959). Supplementary folic acid in doses of 500 μg. to 5 mg./day is known to improve the folate nutrition in pregnant women (Chisholm, 1966). But the mean haemoglobin and haematocrit values failed to rise. Eldestein *et al* (1968) investigated a series of anaemic Bantu women from South Africa who subsist on suboptimal diet low in folate by supplementing them with folic acid during pregnancy and yet could not demonstrate even the small increments in the mean haemoglobin levels reported by Giles and Burton (1960).

The lack of any demonstrable effect of 10 mg. of folic acid given intramuscularly, on the haemoglobin and other parameters of blood in the present series also indicates that a subclinical folic acid deficiency does not materially contribute to anaemia in pregnancy at least in the absence of a frank megaloblastosis.

(6) The incidence of megaloblastic anaemia in this series is low as reported earlier. Although the diet of the patients studied was extremely poor in protein and minerals the custom of chewing "pan" (bettle leaf, nuts, etc.), and the consumption of at least some green vegetables might have some relation to this low incidence.

(7) Controversy still exists over routine supplementation of folic acid in pregnancy. While this can prevent the occurrence of megaloblastic anaemia in pregnancy (Giles and Burton 1960; Dowson, 1962 and Lowenstein *et al*, 1955), we are doubtful about the desirability for such a routine supplementation of folic

acid, since there has been no additional rise whatsoever, in haemoglobin values as compared to the rise after therapy with iron alone in the present series. Again there has been no general confirmation about any relation between obstetric and neonatal complications and folate deficiency in pregnancy. (Menon, 1966; Thambu & Lewellyn-Jones, 1966). This would augment our belief against the necessity for routine supplementation of folic acid during pregnancy.

(8) The present study has brought out an emphasis on iron. Iron is the most important single element required during pregnancy and supplying this by a parentral route will quickly bring about a significant improvement in haemoglobin level and other parameters of blood. Channarin *et al*, 1965 have observed that maintaining the haemoglobin at a higher level with adequate iron therapy alone will reduce the risk of development of megaloblastic anaemia.

(9) Both, injections Uniferon & Injection Uniferon F were well tolerated. Side effects and their incidence were almost similar in both these injections. They constitute pain at the site of injection in 15 to 20% of cases and skin discolouration in 9.5% of cases. Joint pains and body aches were complained of in 12% of cases and responded well to usual treatment; giddiness and itching was complained of in only 2 cases, which subsided within few hours without treatment.

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References

1. British Medical Journal **1**: 415, 1947.
2. Chanarin, I., Macgibbon, B. M., O'Sullivan, W. J. and Mollin, D. L.: Lancet. **2**: 634, 1959.
3. Chanarin, I., Rothman, D. and Berry, V.: Brit. Med. J. **1**: 480, 1965.
4. Chisholm, D. M. and Sharp, A. A.: Brit. Med. J. **2**: 1366, 1964.
5. Chisholm Morag: J. Obst. & Gynec. Brit. Emp. **73**: 2, 1966.
6. Edelstein, T., Stevens, K., Banmslag, N. and Metz, J.: J. Obst. & Gynec. Brit. Emp. **75**: 133, 1968.
7. Gatenby, P. B. B. and Lillie, E. W.: Brit. Med. J. **2**: 1111, 1960.
8. Giles, C. and Burton, H.: Brit. Med. J. **2**: 636, 1960.
9. Menon, M. K.: J. Obst. & Gynec., **15**: No. 2, 1, 1965.
10. Menon, M. K., Sengupta, M. and Ramaswamy, N.: Jour. of Obst. & Gynec. of Brit. Empire **73**: 49, 1966.
11. Paintin, D. B., Thompson, A. M. and Hytten, F. E.: Jour. of Obst. & Gynec. of Brit. Empire. **73**: No. 2, 1, 1966.