TRIAL OF UNIFERRON F. IN PREGNANCY ANAEMIA

by

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The commonest complication met with in pregnancy in India is anaemia. It is so severe and so common that in Rajasthan it accounts for nearly 12.2% of maternal deaths and in 4.5% it is an associated factor. Anaemia as it exists in tropical country like India is mostly nutritional resulting from poverty, ignorance or religious tenet, the deficient factor being either iron, folic acid or both. These are further aggravated during pregnancy. Hence the dimorphic type of pregnancy anaemia which is very common needs a dual form of treatment. This concurrent administration of iron and folic acid is fashionable and reliable in the wake of recent advances in folate metabolism. Chanarin *et al,* (1965) have reported increased Figlu (Folic Acid Metabolite) excretion in patients with iron deficiency. There is a defect in the enzyme formimino transferase and thus marked iron deficiency produces secondary folic acid deficiency. Stores of folic acid in the body falls throughout pregnancy. The fall is larger when there is a twin pregnancy and when folic acid deficiency becomes severe, megaloblastic anaemia develops. This occurs in the last trimester of pregnancy and in puerperium. The mechanism, whereby parentral iron retards improvement in folate nutrition, is unknown. It is probably related to increased utilization of haemopoietic factors following on the intense stimulation of erythropoeisis due to rapid replenishment of iron stores in iron deficient patients.

Some correlation has been established between folate deficiency in spontaneous abortions, abruptio placentae and even foetal abnormalities. Giles (1966) found an increased rate of still births but no teratogenic effect on the foetus. He advocated prophylactic folic acid in the last trimester to eliminate nutritional megaloblastic anaemia. It is apparent that folate deficiency is a more frequent cause of megaloblastic anaemia than Vit. B.12 deficiency anaemia, probably due to some inhibition of the bacterial enzymes in the pregnant women's blood or to some other undetermined technical factor. As Adisonian pernicious anaemia is rare in reproductive period, the danger of folic acid administration is virtually nil and hence its use is widely advocated. Scott *et al,* (1963) have reported that reactions to intramuscular or intravenous iron occurs if folic acid is not given simultaneously to patients who are deficient in folic acid. Bonar (1965) noted that in antenatal patients who received intravenous Imferon, 20% developed signs of unsuspected folate deficiency which resulted in an impaired response to iron therapy. Similar findings have been reported by Scott (1963).

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The lack of folic acid is due more to dietary inadequacy, increased foetal demands and to intestinal malabsorption; hence coupled with the urgency and severity of pregnancy, parentral therapy is the treatment of choice.

Therefore, a parentral preparation containing iron and folic acid has been tried for its efficacy in combating pregnancy anaemias.

Chemistry of Uniferron—F.

Uniferron—F. is a neutral isotonic sterile solution of polyhydroxy carbohydrate complex of iron stabilized with gelatine. Each ml. of this solution contains 50 mgm. of elemental iron and 5 mgm. of folic acid stabilized at neutral pH. Its haemolytic effect is nil and anticoagulent activity negligible. It has been proved that there is a rapid absorption at the site of injection and only 7% of iron is excreted in first four hours and 3% in the next two hours and that more than 90% iron injected is available for haemopoeisis.

Selection of Cases

Pregnant women with haemoglobin level below 60% estimated by Sahli's method were admitted for these investigations after excluding all respiratory, skin and alimentary infections on the first day of admission, total red blood cells, haemoglobin in gm.%, reticulocyte count packed cell volume and total proteins and albumin globulin ratio being done. Uniferron—F. 100 mgm. intramuscularly was given daily till completion of 10 injections. A rigid control was kept of the haematological value every week. No other anti-anaemic treatment was instituted except proteins and Vit. C. by mouth and in some cases liver extract injections intramuscularly. After discharge of the patient or after delivery, whichever was earlier, the patients were reassessed haematologically weekly for a fortnight.

Observations and Results

Fifty-one pregnant and delivered women were subjected to a detailed study. Forty-three women were pregnant, while 8 were in puerperium. Out of 43 women who were pregnant, the duration of pregnancy was more than 28 weeks in 24 patients, the remaining 19 were of less than 28 weeks. In 20 cases pregnancy varied from 29 to 36 weeks and in 4 it was above 37 weeks. Only 5 cases were pregnant for the first time. Thirty-one cases were between second to fifth pregnancy and 15 were grande multiparae. The range of haemoglobin in these 51 cases varied from 4 to 8.5 gm.%. Out of 51 cases, 27 were of severe anaemia and 24 were of mild type. By calculating the absolute values the typing of anaemias were done. Peripheral blood smear, marrow smear and serum iron estimation were not done as all these have got little value. All the 51 cases were hypothromic, 30 were microcytic and 21 were macrocytic i.e. dimorphic anaemia. Only 3 cases had pre-eclamptic toxaemia, 13 cases were of abortions and one-of vesicular mole. All the patients presented a classic picture of anaemia and in 21 cases there were haemic murmurs.

Response to Treatment

Clinically, response was satisfactory. In assessing the nature of response, haemoglobin P.C.V., R.B.C. and reticulocyte count values were observed every week for two weeks till the full dose was completed.

The doses of iron administered varied from 400 mgm. to 1600 mgm. Out of 51 cases, 8 cases delivered during the middle of therapy, but the course was continued in all. It was observed that the

rise of haemoglobin percentage was quicker in severe type of anaemias.

Severe anaemia (6 gm. and below 6 gm.%) was present in 27 out of 51 of the cases. Out of 27, 17 were of the hypochromic microcytic anaemia and 10 were of dimorphic anaemia. Average Hb. in microcytic hypochromic anaemia was 5.388 gm.% before treatment and average dose given was 0.988 gm. The rise in haemoglobin with 1 gm. of Uniferron—F was 1.54 gm.% while in 10 cases of dimorphic anaemia average haemoglobin was 5.13 gm.% before treatment and Uniferron—F. given was average dose of 0.76 gm. The rise in haemoglobin with 1 gm. of Uniferron—F. was observed to be 4.5 gm.%.

In moderate anaemias (above 6 gm.%) average initial haemoglobin in hypochromic microcytic was 7.108 gm.%. Total average dose of Uniferron—F. given was 0.91 gm. The rise of Hb. with 1 gm. of iron was 2.03 gm.%. In dimorphic anaemia with average initial haemoglobin 7.975 gm.% average dose of Uniferron F. given was 0.85 gm. and increase with 1 gm. of Uniferron—F. was 2.54 gm.% showing that rise is more in dimorphic type as compared to microcytic and more so in severe type of anaemia as shown in Table 1.

Table II shows average initial value of red blood cells, haemoglobin and P.C.V. in severe and moderate anaemias and its response to Uniferron—F. after 10 days of therapy. It shows that the response is better when the anaemia is more severe.

The daily average rise in haemoglobin percentage was 0 to 0.3 gm.% in the first week and 0 to 0.28 gm.% in the second week. The average rise of haemoglobin was 2.35%., the rise being more in the first week than in the second week. 100 mgms. of Uniferron—F. raise haemo-

TABLE I

Response of Uniferron—F. as Seen by Rise in Hb. gm.% in (A) Severe (A Hb. 6 gm. and below 6 gm.) and (B) Moderate Anaemias

	Average dose of Uniferon-F given.	Average initial Hb. in gm. %	Average rise of Hb. in gm. %	Average increase of Hb. with 1gm. of Uniferron-F.
A. Hypochromic Microcytic	0.988 gm	5.388	6.911	1.54
Dimorphic	0.76	5.13	8.6	4.5
B. Hypochromic microcytic	0.91	7.108	8.958	2.03
Dimorphic	0.85	7.975	8.191	2.54

TABLE II

Comparison of the Response of Uniferron—F. Therapy in Severe and Moderate Anaemias

	Average values before treatment			Average values after treatment.		
	Hb. gm. %	R.B.C. million per cm.	P.C.V. %	Hb. gm. %	R.B.C. million per cm.	P.C.V. %
A.	5.25	1.7	19.295	8.996	2.692	26.51
B.	7.187	2.526	23	8.858	2.925	29.7

globin to 0.29 gm.% or 2% daily. During the therapy no severe reactions were noticed in any of the cases.

Discussion

Confining the evaluation of our results only to relevant facts it has been deemed proper to discuss under three broad lines:

1. Route of administration
2. Haematological response
3. Reactions.

1. *Route of Administration*

Benjamin (1966) expressed that the rate of haemoglobin rise is the same irrespective of the route of administration. The popularity of intramuscular iron dextran which replaced intravenous iron saccharated oxide was nullified by the carcinogenic effect (Richmoug, 1959) and Dunlop (1966) latest reports of inguinal lymphadenopathy due to local iron pigment deposition wiped off iron Dextran for intramuscular use (Parick, 1968). Hence the other compound iron sorbitol seems to be the ideal with low molecular weight and rapid absorption except that 30% is excreted in urine. In Uniferron—F. there is rapid absorption and only 10% is excreted in the urine. Although iron dextran fell out of intramuscular use it is found to be reliable as total dose. Intravenous infusion, Basu (1963) and Varda (1964) claimed superiority of total dose infusion over intramuscular iron due to absence of staining, pain and abscess formation at the site of injection. In spite of the hospital stay being minimised, Clay *et al.* (1965) reported a high incidence of severe reactions to intravenous infusion especially in antenatal cases and abandoned the technique in treating pregnancy anaemias. Hence although total dose infusion is rapid and reduces hospital stay, yet due to severe toxicity and limited use in selected cases coupled with difficulty in management due to want of proper facilities and equipment intramuscular iron has a place in parentral therapy.

2. *Hematological Response*

The nature of response has been compared only with Indian authors using iron sorbital compound, iron dextran complex with or without oral folic acid and Uniferon—F. in pregnancy anaemias, from Madras—Menon (1965), Mary Willmott (1965), Rajasekharan (1970); Bombay—Chaubal *et al* (1966); Banglore —Padma Rao (1969); Baroda—V. Bhatt (1969). The average increase in Hb. % per day varied from 0.21 to 0.33. In the present series the average increase in severe anaemia was 0.29 while that in moderate type of anaemia it was 0.16 only as shown in Table III.

Follow up of a few cases has revealed that the rise of haemoglobin was maintained even after delivery.

3. *Reactions:*

Analysing the four series for a comparison of reactions, Chaubal did not observe any complications, but Willmott mentioned mild reactions like pain, nausea and vomiting in 9 cases and staining in one case, in iron sorbitol. Padma Rao noted slight pain at the site of injection in 7 cases and no staining in any with Uniferon—F. In the present series no complications occurred, and no metallic taste was complained of by any patient.

Summarising it can be said that Uniferron—F. intramuscular must be the drug of choice as it contains folic acid which is essential for the management of anaemias, particularly in pregnancy This addition of folic acid minimises the adverse reaction of iron intramuscular (Dunlop, 1966).

TABLE III

Comparative Figures of Parentral Iron Therapy in Pregnancy Anaemia by Various Indian Authors

Serial No.	Name of Authors	Drug used	Befoer treatment Hb. in gm. %	P.V.C.	after treatment Hb. in gm. %	P.V.C.	Average daily rise of Hb. %
1.	Menon (1965) Madras.	(a) Parentral iron + oral folic acid.	3.5	17.1	8.5	30	0.33 gm. %
		(b) Jectofer	3.85	17.71	8.4	31 1	0.33 gm.%
		(c) Imferon	4.3	19.9	8.2	30.4	0.27 gm.%
2	Marry Willmott (1965) Madras.	Jectofer	3.85	17.5	7.15	29.2	0.22 gm.%
3	Chaubal et al (1966) Bombay.	Jectofer	4.5 7.2	—	6.3 8.6	—	0.27 gm. %
4	Padma Rao (1969) Bangalore	Uniferon-F	2.99	—	5.97	—	0.27 gm.%
5	Rohit V. Bhatt (1969) Baroda.	Uniferon-F	2.5	—	5.1 8	—	0.21 gm. %
6	N. Rajasekharan (1970) Madras	Uniferon-F	2.9— 8.4	11.27	4.35— 10.3	14.32	0.22 gm. %
7	Present Series (1970) Jaipur.	Uniferon-F	5.25	19.2	8.196	26.5	0.229 gm.%

Conclusion

The results of treatment with Uniferron—F. intramuscular on 51 cases of antenatal anaemia at Zenana Hospital, Jaipur, has been reviewed.

1. The duration of pregnancy was more than 28 weeks in 24 cases, the rest 19 were of less than 28 weeks. In 20 cases pregnancy varies from 29 to 36 weeks and four cases were above 37 weeks.

2. Only five cases were pregnant for the frst time and the rest were multiparae grande-multipare.

3. The range of haemoglobin varied from 4 to 9 gm.% Twenty-seven were severely anaemic while 24 were of mild type.

4. The doses of iron administered varied from 400 to 1600 mgm.

5. Out of 51 cases, 8 delivered during therapy but continued the treatment.

6. Only one out of 51 cases did not complete the full dose.

7. There was no staining noted at the site of injection.

8. No local or general reactions were observed in any of the cases.

9. The average rise of haemoglobin was 2.35 gm.%, daily rise being 0.235 gm.%.

10. 100mg. of Uniferron—F. intramuscular was effective in raising the haemoglobin level to 0.235 gm.% or 1.62 gm.% per day.

11. The rise in haemoglobin level was greater in the first week and pronounced in severe anaemia.

12. The satisfactory haematological response and clinical improvement and the absence of untoward reaction speak for the efficacy of Uniferron—F. intramuscular.

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