Anaemia in Obstetrics: an Evaluation of Treatment by Iron-dextran Infusion

JOHN BONNAR,* M.B., CH.B., M.R.C.O.G.

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Anaemia remains one of the commonest problems facing the obstetrician. In clinical practice the problem is most acute in two groups of patients. The first group consists of patients with anaemia in the last few weeks of pregnancy; the second group is made up of patients with anaemia following obstetric haemorrhage, particularly that associated with abortion and delivery. Elective blood transfusion is commonly employed as a quick solution to this problem.

This report concerns the use of an infusion of iron-dextran (Imferon) as a method for the rapid correction of the anaemia of patients within these two groups. The study was carried out at Robroyston Maternity Hospital, Glasgow, from August 1963 to November 1964.

Patients and Methods

Two hundred and fifty women with anaemia were treated by an infusion of iron-dextran and reviewed. No patient was considered for treatment by this method unless the haemoglobin concentration was less than 68.5% (10 g. on the scale 100% = 14.6 g./100 ml.).

The first group consists of 50 patients with iron-deficiency anaemia in late pregnancy. The mean duration of pregnancy at the time of treatment was 36.4 weeks (S.D.=2.4) and the average haemoglobin level was 62.7% (S.D.=3.8).

The second group was composed of 200 patients with anaemia following obstetric haemorrhage as a result of abortion, ruptured tubal pregnancy, or ante-partum or post-partum haemorrhage. When blood transfusion was given to patients in this group the volume administered was restricted to that required to correct shock. After resuscitation and arrest of the bleeding no further blood was given and the remaining anaemia was treated by iron-dextran infusion. The rise of the haemoglobin concentration after the iron-dextran infusion was observed over the next four to six weeks. Of this group, 120 patients had anaemia following abortion and the mean haemoglobin level was 58.4% (S.D.=6.9). Most of these patients had a pre-existing iron-deficiency anaemia which was aggravated by the uterine haemorrhage. The remaining 80 patients were treated in the puerperium and the most of them had a post-haemorrhagic anaemia. The mean haemoglobin level of the post-natal patients recorded on the third and fourth days of the puerperium was 60.6% (S.D.=4.6).

Venous blood was used for all haematological investigations and the haemoglobin level was estimated as oxyhaemoglobin on a single photoelectric absorptiometer. The diagnosis of iron-deficiency anaemia was made from the history, from the estimation of the haemoglobin, the packed cell volume (P.C.V.), and the mean corpuscular haemoglobin concentration (M.C.H.C.), and from examination of a blood film. Bone-marrow was examined and the serum iron and total iron-binding capacity were ascertained in a few cases.

All patients were weighed and the amount of iron required by each patient was calculated from the formula given by the

makers of Imferon ($0.3 \times \text{weight in lb.} \times \text{haemoglobin deficit in \%}$). In antenatal patients an additional 500 mg. of iron was given to meet foetal demands. The calculated volume of iron-dextran was added aseptically to sterile normal saline or 5% dextrose to make a concentration not exceeding 5% iron-dextran. The solution was made up immediately prior to setting up the infusion. Thirty minutes before the infusion was begun each patient was given an oral antihistamine (Actidil (triprolidine hydrochloride) 5 mg. or Phenergan (promethazine hydrochloride) 25 mg.). The infusion was given via a small needle in the largest available arm vein. The skin was cleansed with ether soap and dried before insertion of the needle. Contamination of the solution with alcohol or detergents renders the iron-dextran complex unstable (Powell, 1963). As a test dose the iron-dextran solution was infused over the first 15 to 30 minutes at 10 drops a minute. If no side-effects were observed with the test dose the drip rate was increased to 45 drops a minute and the infusion completed in four to eight hours. After the iron-dextran infusion the patient was instructed not to take any form of iron therapy.

Results

The results of treatment by iron-dextran infusion have been calculated for each of the three groups of patients—antenatal, post-abortion, and post-natal. The mean haemoglobin levels prior to treatment and the average weekly haemoglobin increase during the first four weeks after the infusion are shown in Table I.

TABLE I.—Haemoglobin Response to Iron-dextran Infusion in 250 Obstetric Patients with Anaemia

Group	No. of Patients	Mean Hb Level		Standard Deviation		Mean Weekly Hb Increase		Standard Deviation	
		%	g./100 ml.	%	g./100 ml.	%	g./100 ml.	%	g./100 ml.
Antenatal . . .	50	62.7	9.16	3.8	0.55	7.8	1.14	2.7	0.39
Post-abortion . .	120	58.4	8.53	6.9	1.01	7.4	1.09	2.1	0.30
Post-natal . . .	80	60.6	8.85	4.6	0.67	6.7	0.97	1.9	0.28

Antenatal Anaemia

In the group of 50 patients with antenatal anaemia the range of haemoglobin levels before treatment was 50–68.5% (7.3–10 g./100 ml.) and the mean weekly haemoglobin increase after the iron-dextran infusion was 7.8% (1.14 g./100 ml.). The initial haemoglobin level in 18 patients was in the range 52–60% (7.6–8.8 g./100 ml.) and the average weekly haemoglobin rise for these patients was 9.5% (1.39 g./100 ml.). In the other 32 patients the haemoglobin level was in the range 61–68.5% (8.9–10 g./100 ml.) and the average weekly haemoglobin increase after treatment was 7.1% (1.04 g./100 ml.). This suggests that, as with other forms of iron therapy, the rate of the response to iron-dextran infusion is related to the severity of the anaemia (Table II).

Within three weeks of the iron-dextran infusion 10 patients showed signs of folic-acid deficiency, though such deficiency

* Senior Registrar in Obstetrics and Gynaecology, Victoria Infirmary and Robroyston Hospital, Glasgow.

TABLE II.—Response to Iron-dextran Infusion in Relation to Severity of the Anaemia in 50 Antenatal Patients Treated Between 34th Week of Pregnancy and Term

Initial Hb Range		No. of Patients	Average Weekly Hb Increase	
%	g./100 ml.		%	g./100 ml.
52-60	7.6-8.8	18	9.5	1.39
61-68.5	8.9-10.0	32	7.1	1.04

was not evident in the initial blood investigation. Treatment with folic acid was restricted to these patients. This complication is discussed below.

Anaemia Following Abortion

The initial range of haemoglobin levels of the 120 patients in this group was 41-68.5% (6-10 g./100 ml.). The distribution of the haemoglobin levels before and four weeks after the iron-dextran infusion is shown in Fig. 1. Four weeks after the iron-dextran infusion 94% of the patients had a haemoglobin concentration above 80% (11.7 g./100 ml.).

The mean weekly haemoglobin increase for the whole group during the first four weeks after treatment was 7.4% (1.09 g./100 ml.). Approximately half the patients had an initial haemoglobin level less than 60% (8.8 g./100 ml.) and the others

FIG. 1.—Haemoglobin levels in 120 patients with post-abortion anaemia before and four weeks after treatment with iron-dextran infusion.

FIG. 2.—Increase of haemoglobin despite severe wound sepsis in a patient with anaemia following a ruptured tubal pregnancy.

were in the range 60-68.5% (8.8-10 g./100 ml.). The mean weekly rise in the former was 8.6% (1.25 g./100 ml.) and in the latter 6.3% (0.9 g./100 ml.).

A typical rise of the haemoglobin concentration after an iron-dextran infusion is shown in Fig. 2. This patient had anaemia following a ruptured tubal pregnancy and she developed severe wound sepsis during the first week after operation. Oral iron therapy was administered during the first week after operation with no response, and an iron-dextran infusion was given on the eighth post-operative day. The response is interesting, as despite the wound sepsis the subsequent rise of the haemoglobin level was dramatic. The patient had to stay in hospital almost four weeks because of the infected wound. Infection is generally regarded as depressing marrow response in anaemic patients, though such depression does not affect the leucocytes. The response noted above suggests further investigation to find out if infection depresses erythropoietic activity by interfering with absorption of iron from the gut or intramuscular deposits rather than with bone-marrow activity.

Post-natal Anaemia

The range of haemoglobin levels in the 80 post-natal patients prior to treatment was 45-68.5% (6.6-10 g./100 ml.). The distribution of haemoglobin levels before and four weeks after treatment is shown in Fig. 3. The mean weekly rise for the whole group during the first four weeks after treatment was 6.7% (0.97 g./100 ml.). In 44 patients the haemoglobin was 60% (8.8 g./100 ml.) or less and the average weekly increase was 7.7% (1.13 g./100 ml.). The other 36 patients had a haemoglobin level in the range 61-68.5% (8.9-10 g./100 ml.) and the mean weekly haemoglobin increase was 5.8% (0.85 g./100 ml.).

FIG. 3.—Haemoglobin levels in 80 patients with post-natal anaemia before and four weeks after treatment with iron-dextran infusion.

Folic acid was not given to this group, but it is probable that a degree of folic-acid deficiency was present in some of these patients. This may explain the difference between the response in the post-natal patients and that of the post-abortion group, where the presence of folic-acid deficiency would be unlikely.

Complications

Folic-Acid Deficiency and Iron Therapy

In late pregnancy the treatment of iron-deficiency anaemia by parenteral iron therapy may reveal an unsuspected folic-acid deficiency (Scott, 1954, 1963; MacKenzie and Abbott, 1960). This complication occurred in 10 out of 50 antenatal patients and manifested itself initially by a poor response (eight patients)

or an actual drop of the haemoglobin level (two patients). An example of the complication is shown in Fig. 4. The patient, a gravida-16, reported for the first antenatal visit at 34 weeks' gestation with a haemoglobin level of 62% (9.1 g./100 ml.). The blood picture suggested a simple iron-deficiency anaemia. After the iron-dextran infusion the haemoglobin level remained at 62% (9.1 g./100 ml.) for one week and then fell over the next week to 47% (6.9 g./100 ml.). During the second week the peripheral blood picture changed to that of a frank megaloblastic anaemia of pregnancy. At this time the patient was complaining of lower-abdominal pains suggestive of premature labour and she was transfused with 2 pints (1,140 ml.) of blood. The pregnancy, however, continued to term and folic-acid therapy produced a marked reticulocyte response and rise of the haemoglobin level. The deficiency of folic acid in this patient would probably have been evident if bone-marrow examination or formimino-glutamic-acid excretion tests had been performed prior to iron-dextran infusion.

FIG. 4.—An impaired response to iron-dextran infusion due to unsuspected folic-acid deficiency.

Routine administration of folic acid with the iron-dextran infusion (Varde, 1964; Goldthorp *et al.*, 1965) will prevent this complication. The argument against this is the same as that against the routine administration of folic acid to all pregnant women—namely, the risk of producing serious neurological changes in a masked Addisonian pernicious anaemia. Additional vitamin B₁₂ would prevent such a complication, and Ainley (1961) thought this advisable in older women. Addisonian pernicious anaemia is certainly rare in women of child-bearing years (Adams, 1958), but it is doubtful whether one should run the risk of giving folic acid in such a case. A histamine-fast achlorhydria is unusual in megaloblastic anaemia of pregnancy (Scott, 1962) but is present in Addisonian pernicious anaemia. A simple screening measure for achlorhydria is the Diagnex test, and if this test suggests the absence of free hydrochloric acid a gastric analysis can decide if a histamine-fast achlorhydria is present. If the latter is demonstrated, both vitamin B₁₂ and folic acid are advisable in a patient with megaloblastic anaemia of pregnancy except in large centres where facilities are available for more elaborate investigation.

Local Reactions

During the first part of the study the iron-dextran complex was diluted in 5% dextrose. This solution produced some

degree of local phlebitis of the infused vein in 25% of the patients. The phlebitis of the infused vein usually developed within 24 to 48 hours, and in patients where the soreness and inflammation caused discomfort for more than three days it was classified as moderate or severe phlebitis. The local reaction was classified as moderate or severe phlebitis in 5% of the patients.

In an attempt to reduce the incidence of local phlebitis 50 patients were given an infusion of iron-dextran in 5% dextrose to which a small dose of hydrocortisone was added (25 mg./500 ml. of solution), and this slightly lowered the incidence of phlebitis. The addition of heparin (1,000 units/500 ml. of solution) did not seem to lower the incidence of local phlebitis, and was discontinued after 30 patients had been so treated. Eighty patients who were treated with an infusion of iron-dextran diluted in normal saline at a similar concentration (5% iron-dextran V/V) showed the lowest incidence of local phlebitis (Table III). Lowering the concentration of the iron-dextran to less than 5% (V/V) in normal saline may further reduce the incidence of local phlebitis (Lane, 1964).

TABLE III.—Incidence of Local Phlebitis of the Infused Vein in Relation to the Solution Used as Diluent for Iron-dextran

Solution Used as Diluent for Iron-Dextran	No. of Patients	Incidence of Mild Phlebitis	Incidence of Moderate and Severe Phlebitis
Dextrose 5%	90	20%	5%
Dextrose 5% + 25 mg. hydrocortisone/500 ml.	50	15%	2%
Dextrose 5% + 1,000 units heparin/500 ml.	30	25%	3%
Normal saline	80	15%	2%

General Reactions

Of the 250 patients treated, three had serious reactions to the iron-dextran infusion, and all three were antenatal patients.

The first was in an antenatal patient, gravida-2, aged 26, with a haemoglobin of 55% (8 g./100 ml.) at the 37th week of pregnancy. The reaction occurred within a few minutes of the beginning of the infusion, which was immediately discontinued. The patient complained of chest pain, dyspnoea, and nausea. This was followed by lower abdominal pain and vomiting. The uterus appeared to be in a state of tonic contraction for approximately 10 minutes and the foetal heart slowed to 80 beats a minute. Oxygen was given and an intramuscular injection of Phenergan 25 mg. Within 10 minutes the foetal heart had returned to normal and the patient had fully recovered, apart from a slight facial flush. During the reaction the pulse rate rose to 120 a minute, but the blood-pressure remained at 140/80 mm. Hg. Labour began within the next hour, and 10 hours later the patient delivered spontaneously a healthy male infant weighing 7 lb. 2 oz. (3,230 g.). On the fourth day of the puerperium she had two further episodes of chest pain and dyspnoea and no satisfactory explanation for the attacks was found.

The second patient, a gravida-4 aged 32, had a haemoglobin level of 60% (8.8 g./100 ml.) at 34 weeks' gestation. After 350 ml. of the iron-dextran solution had been infused she complained of severe chest pain and feeling hot. The symptoms subsided when the infusion was discontinued, and no further treatment was required.

The third patient had an asthmatic history which had been overlooked, and during a test dose of the iron-dextran infusion she developed an asthmatic attack. After an injection of aminophylline the bronchospasm was relieved.

The last reaction should have been avoided, as at the outset of the study it was decided that no patient with an asthmatic or allergic history would be given an iron-dextran infusion. The other two reactions are difficult to explain, especially that in the first patient, when the amount of iron-dextran

administered was only a few millilitres. Using Imferon intramuscularly, Scott (1956), in a series of 300 patients, reported one patient who complained of chest symptoms as an immediate reaction.

Discussion

The iron-dextran complex (Imferon) given by the intramuscular route was widely used for hypochromic anaemia until Richmond (1959, 1960) and Haddow and Horning (1960) reported the induction of sarcoma in rats and mice at the site of injection of iron-dextran. Several well-known authorities, after careful reassessment of intramuscular iron-dextran, gave their conclusion "that its use in the clinical dosage recommended carries a negligible risk" (Duthrie *et al.*, 1960). The average weekly rise in the haemoglobin level with intramuscular iron-dextran is just under 1 g./100 ml. (Scott, 1962).

The advantages of the intravenous administration of iron-dextran over the intramuscular route are: the iron requirement is given as one treatment, a more rapid response is obtained, staining of the skin does not occur, and any possible carcinogenic effect of a local deposition of the iron-dextran is avoided.

In the later weeks of pregnancy urgent correction of anaemia is necessary to minimize the dangers of haemorrhage at confinement and infection in the puerperium. Scott (1961) reported among the complications of anaemia the incidence of post-partum haemorrhage as 11% and that of post-partum infection as 45%. The infusion of iron-dextran has proved to be a reliable means of rapid correction of anaemia in late pregnancy. Delayed or impaired response in late pregnancy will occur if an associated folic-acid deficiency is present. This deficiency of folic acid may be unsuspected when the initial blood investigations are performed, but in the antenatal patients in this study it was usually manifest within two weeks of the infusion of iron-dextran. This complication was present in 10 out of 50 antenatal patients, and is in accord with that found by Scott (1963) in a similar population after treatment with Jectofer. In view of this high incidence it is important that regular examination of the blood should follow the infusion of iron-dextran to detect impaired response due to a deficiency of some other factor.

In the management of anaemia following obstetric haemorrhage iron-dextran infusion has proved to be a safe and effective treatment. No reaction other than local phlebitis was encountered in 200 patients, and the more anaemic the patient the more rapid the response. It is likely that most of these patients would have shown a similar response over a longer period if oral iron had been taken regularly for several months. One of the reasons, however, for the prevalence of anaemia in obstetric patients, particularly in the lower social classes, is that many women cannot be relied upon to take the prescribed oral iron. A major advantage of treatment by iron-dextran infusion is that the iron requirements both for correcting the anaemia and for building up the iron stores are in the patient and not in a forgotten bottle of tablets.

Recently a high incidence of reactions to the infusion of iron-dextran in antenatal patients was reported (Clay *et al.*, 1965). It is interesting that the general reactions encountered in the present series were all in the 50 antenatal patients and no such reactions were encountered in the 200 patients with post-abortion and post-natal anaemia. As yet no satisfactory explanation of such reactions has been offered. To minimize the likelihood of reaction, an antihistamine prior to the infusion, as used in the present series, may be an advantage. Many of the patients in this study would previously have been treated by elective blood transfusion, and such treatment cannot be considered to be without risk (Graham-Stewart, 1960). A comparison of intravenous saccharated iron oxide and whole blood in the treatment of hypochromic anaemia of pregnancy was made by Bare and Sullivan (1960), and they concluded that intravenous iron was the method of choice, the percentage of

side-effects with whole blood and intravenous saccharated iron oxide being similar (6%). The iron-dextran complex is stable and virtually free of ionic iron. Toxic reactions to intravenously administered iron occur when ionized iron exceeds plasma iron-binding capacity (Marchasin and Wallerstein, 1964). Clinically the stability of the iron-dextran is demonstrated by the lack of symptoms when plasma iron levels are extremely high after large intravenous doses of undiluted iron-dextran complex (Wallerstein, 1960; Marchasin and Wallerstein, 1964).

In view of the low incidence of reactions encountered in this study iron-dextran infusion is considered to be a practical and effective treatment for anaemia in the obstetric patient. The use of iron-dextran infusion has produced a marked reduction in the use of blood transfusion and has practically eliminated blood transfusion for anaemia in the later weeks of pregnancy.

Summary

The results of treatment by iron-dextran infusion in 250 obstetric patients with anaemia have been reviewed. The series consisted of 50 antenatal patients and 200 patients with anaemia following obstetric haemorrhage as a result of abortion or ante-partum or post-partum haemorrhage. The haemoglobin levels of the patients prior to treatment were in the range 41–68.5% (6–10 g./100 ml.), and many of them would previously have been treated by blood transfusion.

Iron-dextran infusion is regarded as a practical method of rapid and reliable correction of iron-deficiency anaemia.

In 50 antenatal patients a low incidence of reactions was encountered, but in 10 of them an unsuspected folic-acid deficiency appeared. This is not thought to be an indication for prophylactic folic acid but rather of the need for regular blood examination after the infusion of iron-dextran in antenatal patients and the investigation of the patient with an impaired response.

Local phlebitis at the infusion site could not be eliminated, but the incidence of moderate or severe phlebitis was low (2%) when the iron-dextran was diluted in normal saline.

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