INTRAMUSCULAR IRON THERAPY IN ANAEMIA OF PREGNANCY

TWO-YEAR SURVEY

BY

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Since publishing a preliminary report on the treatment of the iron-deficiency anaemias of pregnancy with intramuscular injection of iron ("imferon") (Scott and Govan, 1954), we have continued to use this drug and can now review the results obtained in a series of 300 patients. In practice almost double that number have been treated in this hospital with imferon. Ultimately, however, many of these cases were discarded in the final analysis for various reasons, such as an inadequate period of observation, failure on the part of patients to co-operate, and the intervention of obstetrical complications.

Of these patients, 200 had antenatal anaemia. Their average age was 30.9 years and average parity 4.1. When they were first seen at the blood clinic the mean duration of their pregnancies was 33.8 weeks (S.D.=5.3) and their average haemoglobin and red-cell count were 8.5 g. per 100 ml. (S.D.=0.9) and 3,370,000 per c.mm. respectively. In 156 the anaemia was of moderate degree (haemoglobin between 8 and 9.9 g./100 ml.), but in the remainder the readings were below 8 g./100 ml.

The second group of 100 patients were all post-natal. The majority had post-haemorrhagic anaemia and low haemoglobins and red-cell counts, the average being 8.3 g./100 ml. and 2,760,000 per c.mm. respectively. These patients, unlike those with antenatal anaemias, did not belong solely to the older parous groups, their average age being 27.7 years and the parity 2.6.

Venous blood was used for all haematological investigations, and the haemoglobin estimations were made in a photoelectric colorimeter. The intramuscular iron was administered personally at the antenatal clinic, but post-natal patients received their injections from the nursing staff. A test dose of 100 mg. (2 ml.) was given in every case, and, unless contraindicated, this was increased to 250 mg. (5 ml.) at the next injection. Injections were given into opposite buttocks on alternate days, an average of 500-600 mg. being given in a week. All patients were weighed, and the amount of iron required by each patient was calculated from the formula given by the makers of imferon ($0.3 \times \text{weight in lb.} \times \text{haemoglobin deficiency in percentage Haldane}$). It was found that treatment according to this formula did not always satisfy the requirements of individual patients. Some naturally need more iron than others, and in order to recognize these various types it was decided to calculate the amount of iron necessary to raise the haemoglobin of the antenatal patients to a minimum level of 11 g./100 ml. (75% Haldane). No such restrictions in the amount administered was put on the post-natal patients.

Results in Antenatal Anaemia

On the basis of the above dosage scheme 80% of the patients showed a satisfactory response, although, as detailed later, the calculated haemoglobin level of 11 g. was not always attained. The weekly rise in haemoglobin is shown

in Fig. 1. During the first week the average increase was 0.77 g./100 ml. and it is interesting to note that this is exactly the same figure as that found in our previous report (Scott and Govan, 1954). During the later weeks the increments were if anything slightly less than those found in the earlier trial, but the curves are essentially similar.

If the figures for the 44 cases of severe anaemia (haemoglobin less than 8 g./100 ml.) are abstracted it will be seen from Fig. 2 that the weekly increments are much greater in these cases, and an average rise of 1.11 g./100 ml. can be expected in the first week.

Certain cases, 27 in number, showed no rise in haemoglobin in the first week. Four even showed no rise in the second week. Yet when their bloods were examined more fully it was obvious from the increase in anisocytosis and polychromasia and the appearance of reticulocytes in the peripheral blood that they were responding. The curve of their weekly haemoglobin increments is shown in Fig. 3, and in comparison with the other curves the difference is quite striking. Initially there was nothing to differentiate these patients as a special group. Their average haemoglobin reading was 8.9 g./100 ml., their parity 4, age 34 years, and weight 140.9 lb. (64 kg.). The mean duration of their pregnancies was 31.7 weeks.

FIG. 1.—Average weekly haemoglobin increments in 200 cases of antenatal anaemia.

FIG. 2.—Average weekly haemoglobin increments in 44 cases of severe antenatal anaemia with haemoglobin below 8 g./100 ml.

FIG. 3.—Average weekly haemoglobin increments in 27 cases showing "delayed response."

Utilization of the Injected Iron

Since the average weekly rise in haemoglobin varies considerably from case to case, it is obviously more accurate to assess the response to treatment over a longer period and calculate the degree of utilization of the iron injected. Thus for every 100 mg. of iron injected an average haemoglobin increase of 0.3 g. was found, and it is interesting to note that this average was also obtained in the initial trial. In the previous report it was pointed out, however, that the value for utilization might vary with the weight of the patient and her blood volume. This impression has been

confirmed. Analysis of results has shown that optimum utilization occurred in patients weighing 100–119 lb. (45.4–54 kg.). As the weight increased utilization slowly deteriorated, until at weights over 160 lb. (72.5 kg.) it was approximately half that found in more sparsely built patients. The results are shown in Table I. These figures were

TABLE I.—Utilization and Weight

Weight		Utilization	Standard Deviation	Coefficient of Variation
lb.	kg.			
100–119	45.4–	0.309	0.121	39.15
120–139	54.4–	0.261	0.080	30.66
140–159	63.5–	0.228	0.114	50.00
160+	72.5+	0.173	0.088	50.88

examined statistically. The low utilization in extremely heavy patients appeared to be significant, but the coefficient of variation was wide. One very stout patient failed to respond to intramuscular therapy. Treatment was discontinued after 350 mg. had been given. Intravenous iron therapy ("ferrivenin") was then administered, with satisfactory results. Her buttocks were badly stained after the injections, and it is probable that in these cases deposition of iron in the fat delays absorption.

In the treatment of the iron-deficiency anaemia of pregnancy striking results may be obtained, but it is important to ascertain whether this improvement is maintained, especially when treatment is begun early in pregnancy. Prior to the 28th week the patient achieves a satisfactory haemoglobin level more quickly than later in pregnancy and the utilization would thus appear to be greater. If, however, these patients are followed throughout their pregnancy it is found that the haemoglobin level is not maintained and without exception a further course of treatment becomes necessary. From the 28th week onward the demand

FIG. 4.—Curve of haemoglobin levels following intramuscular iron early in pregnancy. Utilization of the iron between the 12th and 20th weeks was 0.646, whereas utilization for the whole of pregnancy was 0.343.

for iron would appear to increase, and where the haemoglobin reaches the calculated level of 11 g./100 ml. prior to this date a further fall takes place. Thirteen such patients were given the calculated dose of imferon, and haemoglobin readings were made at weekly or two-weekly intervals thereafter. Initially all responded well and showed a high utilization coefficient of 0.363; but this improvement was not maintained, and when the haemoglobin had fallen again below 10 g./100 ml. a further calculated dose of imferon had to be given. The average utilization was thus reduced to 0.253. This point is probably better illustrated by taking one of the cases as an example. The results are shown in Fig. 4.

This patient was 12 weeks' pregnant and had a haemoglobin reading of 7.6 g./100 ml. She was given the calculated dose of 650 mg. and her haemoglobin rose to a maximum of 11.8 g./100 ml. at 20 weeks, giving a utilization of 0.646. On her next visit the haemoglobin had started to fall, and by the 32nd week was as low as 9.3 g./100 ml. A second calculated dose of 400 mg. was given, and by term her haemoglobin was again 11.2 g./100 ml. Since she required nearly double the amount of iron to maintain her haemoglobin the actual utilization in her case was almost halved, and became 0.343.

This patient is of course an extreme example of the condition, possibly because she was treated very early in pregnancy. Apart from the 13 cases in the series, several other early cases of pregnancy anaemia have been treated, but in these the pregnancy was complicated by some other condi-

tion such as hydramnios, hypertension, or infection. The impression was gained that these patients showed a response varying from that found in uncomplicated anaemia. Patients found to be anaemic early in pregnancy require, on an average, 300 mg. of elemental iron in addition to their apparent requirements calculated from the initial haemoglobin value. Even in the later months, with a dose calculated for 11 g., many patients did not reach this level, although their haemoglobin rose above anaemic levels. It is obvious from this that the need for additional iron is not strictly confined to the early months of pregnancy and that generous allowance must be made for foetal demands. Of the 200 cases of antenatal anaemia, 19.5% required a second course of treatment, and this figure includes all cases in early pregnancy.

Iron Utilization and Degree of Anaemia

Since the rate of haemoglobin regeneration appears to be greater in severe anaemias, this investigation was carried out to see whether the utilization was also higher in such cases. The results are shown in Table II, but again, though the

TABLE II.—Utilization and Degree of Anaemia

Hb in g. 100 ml.	Utilization	Standard Deviation
Below 8	0.309	0.068
8–8.9	0.280	0.094
9–9.9	0.232	0.078

findings suggest that there is a direct relationship between the degree of anaemia and the utilization of the injected iron, the figures are not statistically significant.

Cases Showing Delayed Response

When the haemoglobin increments of the 27 patients showing delayed response were being considered one or two interesting points were noted. The utilization on the injected iron was calculated as before and was found to be significantly lower than that of the whole series—namely, 0.220 (S.D. = 0.062) as compared with 0.3. Moreover, only two patients (7.4%) reached and maintained a haemoglobin level of 11 g./100 ml., though 28.6% of the whole series managed to do this. Of the remainder, 11 patients (40.7%) had actually deteriorated and required further treatment before term. On the average, treatment was begun in the 29th week (S.D. = 3.97). The stage of pregnancy could therefore not be an important factor.

Thus it is evident that though these patients do not appear to form any distinctive group initially, an analysis of their response to treatment shows certain definite features. Apart from the initial delayed rise in haemoglobin, they seem to require more iron to raise their haemoglobin to a satisfactory level, quite apart from maintaining it, and one can say with certainty that any such case seen before the 28th week and given the calculated dose of iron will require further treatment before term.

Yet, although the rise in haemoglobin values is slow, the delay in response is more apparent than real. Every indication points to a state of increased erythropoiesis, and, since there is no evidence of increased red-cell destruction, the haemoglobin and red-cell mass must be increasing. The apparent lack of change in the peripheral blood can only be due to concomitant changes in the blood volume. In the initial trial daily haemoglobin and haematocrit readings were made on patients receiving daily injections of iron, and it was suggested that the initial drop in haemoglobin after starting iron therapy might be due to an increase in blood volume.

To illustrate this point more fully the following experiments on blood volume were carried out. One of the simplest methods of estimation is that involving the use of azovan blue. Unfortunately for accurate purposes, analysis cannot be repeated at short intervals. For this reason it was

decided to utilize imferon itself as a measure of the plasma volume. Since the iron is in combination with a colloidal molecule, it will not be absorbed on to the plasma proteins, and it remains in the circulation for a considerable time without an appreciable fall in the concentration. It remained, however, to show that the readings obtained by azovan blue and the iron method were comparable. Two non-anaemic patients, one a cardiac case near term and the other in early pregnancy, had their plasma volumes estimated by the azovan blue method and the results were 5,120 and 3,716 ml. respectively. The following day their serum iron levels were estimated and 100 mg. of imferon was injected intravenously. Blood was withdrawn from the opposite arm for estimation of serum iron 10 minutes later, and from the two serum-iron readings the plasma volumes were again calculated. The readings were 5,330 and 3,563 ml. respectively, both of which show close correlation with the previous azovan blue reading.

In a third patient the reverse process was carried out. On the first day the plasma volume was estimated by the imferon method and was found to be 3,675 ml. Two days later by azovan blue it was 4,450 ml., and when checked the next day by the serum-iron method it was 4,202 ml.

Thus it seems evident that when the plasma volume is estimated first by azovan blue and then by the serum-iron method the results agree closely, but if the order of testing is reversed an increase in plasma volume is detected two days after the imferon injection. The next stage in the investigation was to determine whether the increase in plasma volume was actually occurring with treatment. Two anaemic women had their blood volume estimated by the serum-iron method at various stages in their treatment. The results are shown in Table III. The findings suggest that an

TABLE III.—Blood-volume Changes in Two Patients Receiving Imferon

	Case 1	Case 2
Beginning of treatment	4,620 ml.	3,864 ml.
2nd day	—	5,593 ..
5th	5,067 ml.	4,325 ..
End of treatment ..	4,180 ..	4,260 ..

increase in plasma volume occurs and is probably maximal about the second or third day, disappearing towards the end of treatment. Neither of these two cases showed a delayed rise in haemoglobin, and it is possible that changes in blood volume were less in their case. Unfortunately the next patient given imferon intravenously had a nasty reaction and administration by this route was discontinued.

Results in Post-natal Anaemia

As stated previously the majority of these cases were post-haemorrhagic anaemias in which haemopoiesis was normal prior to the haemorrhage. Compared with the antenatal iron-deficiency anaemias one would therefore expect a more active response in these cases, and reference to Fig. 5 shows that this is actually so. The results, however, were not as good as those obtained with intravenous iron (ferrivenin), where the weekly haemoglobin increments were 1.7, 1.8, and 1.5 g. respectively (Scott and Govan, 1951).

Reactions

Most people will now agree that the administration of imferon intravenously is not without risk (Callender and Smith, 1954; Baird and Podmore, 1954). In the seven cases we have treated in this manner we have had one severe reaction, of early onset and very similar to the immediate reactions found with ferrivenin. On the other hand, when imferon is given intramuscularly the toxicity is extremely low, and, provided the cases are properly selected and investigated, treatment can be given quite safely to out-patients. Only two patients weighing under 100 lb. (45.4 kg.) were treated with imferon. Both found the larger injections painful, but were able to tolerate 100 mg. (2 ml.) and re-

sponded satisfactorily. Since we reported the occurrence of a skin rash during therapy we have not treated patients with any previous history of dermatitis, and to date have had no further reactions of this type. Of the 300 patients in the present series only three have had reactions after intramuscular injection. In two the reactions occurred soon after injection.

One patient had backache and difficulty in walking, but she had frequently suffered from backache. The remaining injections were given at home by her own doctor, and, apart from some local spasm, they caused no undue upset. It is doubtful if this can be regarded primarily as a true reaction. In the second patient the immediate reaction was of a more distressing nature. She complained of tightness in the chest and backache about five minutes after the injection. Her pulse was rapid; she had no sweating, but appeared somewhat distressed and anxious. The symptoms passed off within five minutes and she was able to go home soon afterwards. No further injections were given and she was admitted to hospital for transfusion as she was very near term. The third patient

had a delayed reaction 12 hours after the injection. She had a chronic bronchitis as well as a severe iron-deficiency anaemia, and complained of a sudden attack of acute breathlessness during the night following the injection. From her description it seemed to be of an asthmatic nature. She was admitted to hospital the next day, when she was still a bit breathless, but with rest in bed her symptoms soon subsided. Sensitivity and precipitin tests with both the dextran and the dextran-iron complex were carried out by us and by Bengers Ltd. in these last two cases, but all the investigations proved negative. No patient with bronchitic changes has since received imferon and no further reactions have occurred. For the same reason intramuscular iron therapy has not been given to any patient with an asthmatic history.

Of the three reactions the first is doubtful and the last could have been avoided. We can find no obvious explanation for the second. It may well be that every injection, no matter how innocuous, will cause a reaction at some time or other. The figure for imferon is certainly low, probably less than 0.5%.

Discussion

When the initial tests with imferon were made (Cappell *et al.*, 1954; Baird and Podmore, 1954; Scott and Govan, 1954) the *British Medical Journal* (1954) and Ross (1955) suggested that more extensive investigations should be carried out before recommending this drug for out-patients. Our experience, now extending over more than two years, has not caused us to change our original opinion. Intramuscular iron is a valuable asset in the treatment of the

FIG. 5.—Average weekly haemoglobin increments in 100 cases of post-natal anaemia.

iron-deficiency anaemias of pregnancy, especially those near term, and has replaced intravenous saccharated iron oxide in this hospital.

In comparison with the latter preparation the advantages from the administrative point of view are obvious. The drug itself, given by the intramuscular route, is less toxic and, owing to its higher concentration of elemental iron, fewer injections are required. In the first week of therapy the average rise in haemoglobin is less than that obtained with intravenous saccharated iron oxide—approximately 80%—but the second and third weeks show greater increases. The utilization is as good—namely, 0.3 g. rise in haemoglobin for every 100 mg. of iron injected—and only in exceptionally stout women was it found to be significantly reduced. Thin patients with weights below 100 lb. (45.4 kg.) tolerate the 2-ml. (100-mg.) injections remarkably well.

The contraindications are few, provided complete blood investigations have been carried out before treatment is begun. It is advisable to avoid treating any patient giving an allergic history such as dermatitis or asthma, and any inflammatory process should be regarded as a contraindication. Callender and Smith (1954) first reported reactions following the administration of imferon intravenously, and we would agree with them that injections by this route should be discontinued.

In pregnancy it is more difficult to assess the amount of iron which the patient will require. Apart from her weight and the severity of the anaemia, other factors have to be taken into consideration. Of these the most important are the foetal demands for iron, which are greatest in the last three months, and the increase in the maternal haemoglobin mass, which is progressive from the 16th week. Possibly because of all these variables none alone was found to be statistically significant as a factor in determining the amount of iron necessary. However, it can be said with certainty that every patient who becomes anaemic before the 28th week of pregnancy will require on the average an extra 300 mg. of iron to cover her requirements in the later months.

Patients showing no response to iron after one week's treatment form a special group. The haemodilution caused by the intramuscular iron therapy is prolonged in their case. It is possible that they start off with a lower blood volume and haemoglobin mass. Roscoe and Donaldson (1946) observed a variation in the blood volume of anaemic pregnant women and showed that, in certain cases, as the anaemia developed the blood volume decreased. In one of their patients the haemoglobin fell by 12% but the actual fall in the haemoglobin mass was 24%. Treatment in such a patient might well correct this relative haemoconcentration and mask any increase in the haemoglobin mass initially. This theory offers a reasonable explanation for the "delayed response" and would explain why these patients require more iron. Cases of this type seen before the 28th week needed an extra 400 mg., and later cases required another 200 mg. to reach a satisfactory haemoglobin level.

Summary

The treatment of 200 antenatal cases and 100 post-natal cases of iron-deficiency anaemia with intramuscular iron (imferon) has been reviewed.

The results are very satisfactory and confirm our original opinion of this preparation. Except in very stout patients the utilization of the iron is as good as that obtained with saccharated iron oxide. The rate of haemoglobin regeneration, however, is slightly less. In the first week of treatment the rise was only 80% of that obtained with ferrivenin, but later the weekly increments improved.

In calculating the amount of iron necessary for these pregnancy anaemias allowance has to be made for the foetal demands and for the increase in maternal blood volume. Cases seen before the 28th week respond well

and quickly to treatment by formula, but a satisfactory haemoglobin level is not maintained and all become anaemic again unless these extra demands of pregnancy are taken into consideration. The average case requires an additional 300 mg.

It is suggested that patients showing no rise in haemoglobin after the first week of treatment have an initial low blood volume. It appears that intramuscular iron causes a temporary haemodilution and, to begin with, masks any rise in haemoglobin. These patients require more than the calculated amount of iron. Before the 28th week an extra 400 mg. should be given and after that an extra 200 mg. is usually sufficient.

Provided the drug is given by the intramuscular route, reactions are rare, probably less than 0.5%. Certain precautions, however, are necessary. It should first be established that the patient has a simple iron-deficiency anaemia and that there are no complicating factors, such as infection, affecting erythropoiesis. It is also inadvisable to treat any patient giving a history of asthma or of allergic skin rashes, and we would not now recommend administration by the intravenous route.

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TREATMENT OF IRON-DEFICIENCY ANAEMIA

COMPARISON OF METHODS

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This paper reports a therapeutic comparison of the value of ferrous succinate taken orally with the same amount of iron given either intramuscularly or intravenously in the treatment of hypochromic anaemia. We know of no similar work, and consider that individual doctors form their own opinions on the merits of the three methods of administration from their own clinical impressions rather than from a knowledge of a scientific investigation. The present investigation is an attempt to fill this gap.

Design of the Clinical Trial

"Ferromyn" (ferrous succinate) was chosen as the oral iron because one of us (Gillhespy, 1955), in a recent clinical trial, had obtained a satisfactory daily rise of haemoglobin percentage with a relatively small dose in 150 patients with hypochromic anaemia resulting from various causes. These findings have been confirmed by O'Sullivan *et al.* (1955).