Total dose infusion of Imferon in Obstetrics

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ANAEMIA IS A common problem in antenatal patients. Some very severely anaemic patients are seen in this country. Kwa and Ko (1968) found 33 per cent of patients in Singapore to have a haemoglobin level of less than 10.0 gm./100 ml. at booking. Many patients book late and some not at all. Hence there is a special problem in that many women do not give their obstetricians time to correct their anaemia. In this region, observations show that many of the anaemia in pregnancy are due to iron deficiency, some due to folate deficiency and some combined deficiency.

Iron therapy is a problem amongst Malaysian women; unfortunately, those who needed it most are the greatest defaulters. For the slightest constipation, loose stool or nausea, the women will flout the advice of the doctors. The alternatives to oral iron therapy, iron given intermittently by intramuscular or intravenous routes, are not very convenient. Some patients find it difficult to attend every other day for injections because of other children in the house or other domestic chores. Other women find that the bus-fare to and from the hospital drains off her day's marketing allowance.

Hence the anaemic obstetric patient in Malaysia presents one of the best indications for total dose infusion of imferon (iron-dextran) as advocated by Basu (1963). Many have low haemoglobin; many are late in pregnancy before this is detected; for socio-economic reasons, many are either unsuitable or un-co-operative for oral or other forms of parenteral iron therapy.

Since the opening of the Maternity Unit of the University Hospital, total dose infusion of imferon was carried out as a prospective study. In spite of this some data are inadequate because new doctors joined the unit and used this method of therapy before having been fully briefed.

Material and Methods

When this series was carried out, all patients with a haemoglobin level of 11.1 gms./100 ml. in the antenatal clinics were referred to the Anaemia Clinic. Here they were seen by the author in conjunction with a haemotologist. Full investigations were carried out and patients for TDI were selected.

The basis for selection of patients are as follows:

(1) The period of gestation is an important factor. Whenever there is time for an alternative means of giving iron, this is always preferred.

Unless otherwise indicated, no TDI is given to patients until they are 37 weeks pregnant.

(2) The haemoglobin level is another factor; unless indicated by lack of time or failed therapy by other methods, TDI is not given to patients with a haemoglobin level above 8.5 gms./100 ml..

(3) Iron deficiency state is established prior to TDI. At first, a serum iron is a prerequisite to TDI. Later, it was found that in many patients it was not justified to wait for serum iron results.

Hence, later in the trial many patients are given TDI on the evidence of iron deficiency from their peripheral blood picture alone.

(4) Failure of oral or other forms of parenteral iron therapy. This may be because the patient does not attend the antenatal clinic or does not take the tablets or there is no clinical response (perhaps due to malabsorption syndrome). In this group are included postnatal patients who are unlikely to return for their check-up and therapy as they failed to book antenatally. Many of those with higher levels of haemoglobin belong to this group.

Once selected, a patient was given an appointment to receive the TDI's as an outpatient procedure. However, many turned up late because of various reasons, like too much work to settle in the house or missing the bus. Those whose TDI were not completed by 1800 hours were kept overnight.

On admission, the following observations were recorded: maternal pulse rate, blood pressure and respiration rate. A check was carried out to make sure that none with an allergic history (e.g. asthma) had been inadvertently put on trial. The foetal heart rate was recorded.

The dose of imferon required is calculated according to the following formula: $\frac{W.D. \times 13}{1,000} + 10 =$ ml. of imferon required, where w= weight of patient in kgm. and D = haemoglobin deficiency in percentage. It will be found that this is, in fact, the formula supplied by manufacturer. Some mathematical juggling has been carried out for easy calculation.

The dose required is then diluted. Unless hypertension, pre-eclampsia or other conditions contraindicate, normal saline is the diluent of choice. Five per cent dextrose is used for the others. The maximum concentration used is 25 ml. diluent. It is noted that 36 (10 per cent) of the patients are given TDI in excess of recommended 5 per cent V/V concentration.

Half-way through the trial, because of a spate of unexplained reactions, it was decided to give the patient phenergan (promethazine hydrochloride 25 mg.). This was either given intramuscularly 30 minutes before the TDI was started, or was put into the drip. This also served as a study to find out if the giving of an antihistamine would reduce the reactions.

The drip was set after blood samples for a full count were taken. It was run at 10 drops per minutes for 30 minutes. During this half hour, close observation was carried out. The resuscitation tray was kept in readiness (this contains adrenaline, hydrocortisone and aramine injections). If no reaction was seen, the drip rate was increased until 50 drops per minute was attained. The rest of the drip was then run under observation.

Patients were also given folic acid. Usually 5 mg. thrice a day was the dose. In some, a loading dose of 15 mg. intramuscularly was given on the first two days.

All being well, the patient was allowed to go home. She was seen in a week's time at the clinic. Blood samples were sent for investigations to follow the progress of the therapy. Folic acid therapy was continued but these patients were given no more iron therapy of any form.

Table I shows the racial distribution of patients who total 359. The respective population of Selangor state is shown for comparison:—

TABLE I

Racial Distribution Of Patients & Population In Selangor State.

Race	No. of Patients	Percentage	Pop: of Sel	Percentage
MALAYS	83	23.1	88,960	32.2
CHINESE	124	34.5	135,280	49.4
INDIANS	150	41.8	51.540	18.4
OTHER	2	0.6	—	—

The patients are all between the ages of 16-45 years. There were 82 women having their first pregnancy. The majority (74.0 per cent) were patients who have had less than four children. The details are shown in Fig. I.

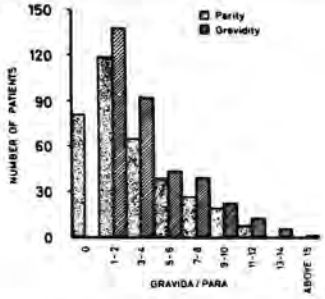
Fig. 2 shows the maturity of the pregnancies when the patients presented for booking and when TDI was given. Only 119 (33.7 per cent) of the 359 patients booked before the 30th week of gestation. It is also seen that 38 patients were given TDI before the 30th week of pregnancy.

The socio-economic status of patients is rather difficult to assess. As far as could be ascertained, the total family income of the patients is shown in table II.

TABLE II

Socio-Economic Status Of 359 Patients.

Monthly Income	Number of Patients
ABOVE M $600	8 (2.2%)
M $400 — M $600	30 (8.4%)
M $201 — M $400	90 (25.1%)
BELOW M $200	225 (62.7%)
UNKNOWN	6



GRAVIDITY & PARITY IN RELATION TO NUMBER OF PATIENTS GIVEN IMFERON DRIP

Fig. 1

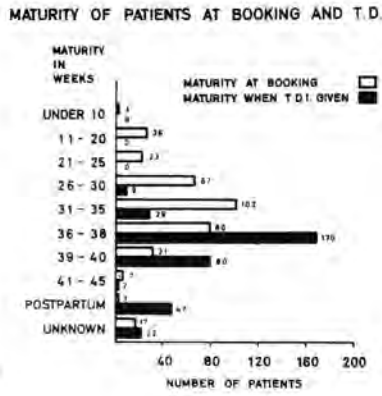


Fig. 2

Table III shows the concentration and the total amount of imferon given. The figures given are in millilitres of imferon. (Multiply by 50 to get the same in milligrams of imferon.)

TABLE III

Concentration & Total Imferon Given To Patients.

Imferon Volume (ml.)	Number of Patients: Maximum Imferon/500 ml.	Number of Patients: Total Imferon
Under 10	2	8
11 — 15	15	8
16 — 20	174	9
21 — 25	129	55
26 — 30	23	36
31 — 35	8	69
36 — 40	2	97
41 — 45	1	40
46 — 50	—	28
51 — 56	2	2
56 — 60	—	5
Unknown	3	2

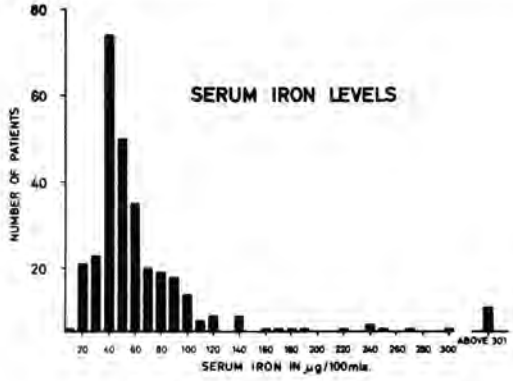


Fig. 3

As stated, 36 (10 per cent) patients were given imferon in greater concentration than the recommended 5 per cent V/V. These were all given by new members of the staff and unintentional. The majority (206 patients) received between 31-45 ml. (1550-2250 mg.) of imferon each. These were all given in the same day.

The diluents used for the infusion are shown :—

Normal Saline	224
5% dextrose	94
Unknown	41
Total	359

Of 359 patients, 43 (12 per cent) required blood transfusion either during labour or after the delivery.

Of these, six patients required three or more units of blood.

Stool Examinations

Specimens were sent from 260 patients. The results are shown in Table IV.

TABLE IV

Result Of Stool Examination.

Result	No. of Population
Not Done	99
Negative	85
Ascariasis	26
Mixed Infections	77
Ankylostomiasis	43
Others (e.g. Trichuriasis)	29
Total	359

It is seen from the table that 146 (56.2 per cent) patients required therapy for worm infestation.

Haematology

Serum Iron

The serum iron levels are shown in Fig. 3. It is seen that of 284 patients who had serum iron assayed, 243 (85.6 per cent) patients have serum iron level below 80 mg./100 ml. In this laboratory, any reading below this level is considered to be a deficiency state. Those patients who had abnormally high serum iron level probably had taken iron therapy from other sources without informing us.

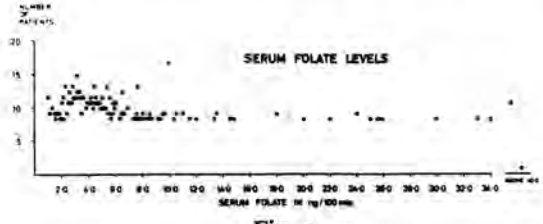


Fig. 4

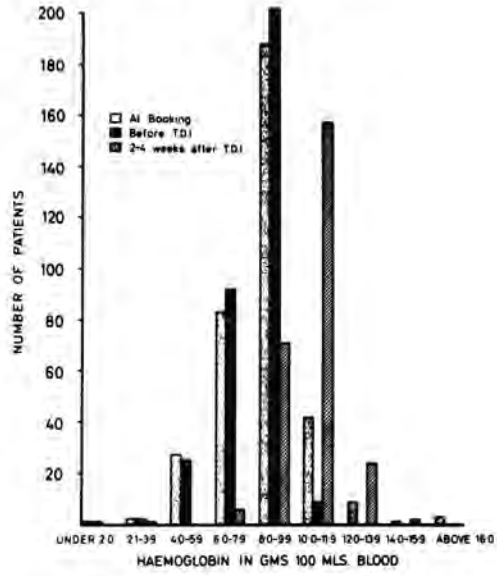
Serum Folate

The scattergram in Fig. 4 shows the serum folate levels. In this laboratory, any reading below 6.0 mg./100 ml. is taken to be deficient. It is seen that a total of 183 (68.3 per cent) patients, of the 268 who had serum assays done, showed a deficiency state. Again the extremely high level may be due to folate therapy unknown to us.

Result

Haemoglobin:

Fig. 5 shows the haemoglobin distribution of 359 patients at booking, before and after TDI was given. The haemoglobin after delivery has not been taken into consideration as this is influenced by postpartum blood, less blood transfusions.



HAEMOGLOBIN DISTRIBUTION AT BOOKING, BEFORE & AFTER IMFERON DRIP

Fig. 5

It is seen that the haemoglobin distribution at booking has an even scatter with a peak at the 8.0-9.9 gm./100 ml. group. The distribution before TDI is almost totally below 8.0-9.9 gm/100 ml. group. At 2-4 weeks after the imferon drip, the peak of the distribution has moved to the right to the 10.0-11.9 gm./100 ml. group. The average rise of haemoglobin in the first four weeks was 1.4 gm./100 ml. per week.

PCV & MCHC

The pack cell volume (PCV) and the mean corpuscular haemoglobin concentration (MCHC) before and after TDI are shown in Fig. 6. It is seen that there is a definite shift to the right after TDI in the result of the PCV. A similar but less pronounced trend is shown in the MCHC results.

Peripheral Blood Film

The peripheral blood pictures were studied in 317 of the 359 patients. The results are as shown in table V:

TABLE V

Peripheral Blood Film Of 317 Patients.

Result of PBF.	No. of Patients
Not Done	42
Microcytic	50
Hypochromic	49
Macrocytic	38
Mixed	17
Poikylocytic	3
Anisocytic	6
	359

Causes of Anaemia

After all the factors have been considered, the causes of anaemia in these patients are computed. The results are shown in table VI.

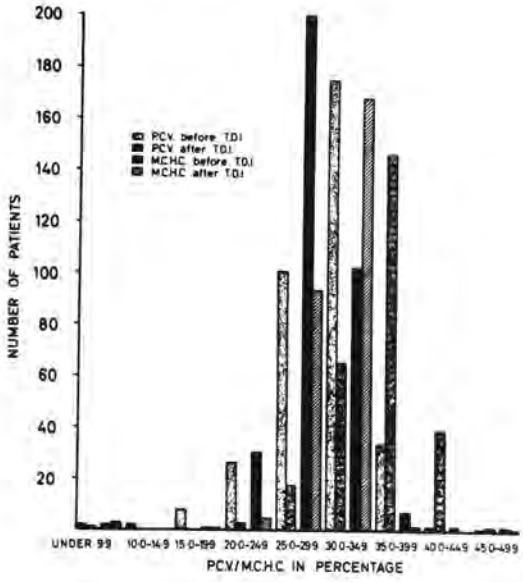
TABLE VI

Diagnoses Of Anaemia In 359 Patients.

Causes of Anaemia	No. of Patients
No Definite Diagnosis	27
Iron Deficiency	80
Folate Deficiency	12
Iron-Folate Deficiency	238
Others	2
Total	359

It is seen that the majority of patients show a combined deficiency. These diagnoses are mainly computed from the results of the serum assays, peripheral blood morphology and from the PCV and the MCHC. Unfortunately, the planned study on blood marrow had to be abandoned as the majority of the patients refused this procedure. If this had been done, perhaps a diagnosis will be made for the 27 patients under "no definite diagnosis". The two patients under "others" were cases of sickle cell traits and thalassaemia.

Some of the patients, of course, had concommitant infections (urinary tract, septic foci, etc.....). These were treated accordingly.



P.C.V. & M.C.H.C. BEFORE & AFTER IMFERON DRIP

Fig. 6

Outcome of Pregnancy

TABLE VII

Outcome Of Pregnancies.

	No. of Patients
Live Birth	346
Fresh S.B.	4
Macerated S.B. (+IUD)	4
Neonatal Deaths	5
Total	359

There were eight stillbirths (2.2 per cent) and five neonatal deaths (1.4 per cent). In none of these is there any relationship between the TDI and the fetal loss.

Reactions

The details of these are reported in another publication by the author. Only a summary will be given here.

The reactions recorded are all mild. No fatal anaphylactic reaction was observed. The most severe reaction was seen in a woman who had been on oral iron for a month and was receiving a TDI of 20 ml. imferon in 500 mls. of five per cent dextrose.

She had a fall in blood pressure, tachycardia and was sweating. Stopping the drip and an intramuscular injection of hydrocortisone stopped the reaction.

Other reactions are listed in table VIII. One patient usually has one or two of the symptoms listed.

TABLE VIII

Reactions Of TDI.

Reactions	No. of Patients
Immediate	
Giddiness	6
Coldness	1
Chest pain	8
Constriction	
Sweating	1
Knee-joint pain	1
Hypotension	2
Delayed	
Thrombophlebitis	3
Skin rash	1

The rate of reactions is 2.5 per cent but it must be explained that only a total of nine patients had reactions. All of these were mild reactions. Of these, all responded immediately to routine management which consists of either or a combination of the following :—

(1) stopping the TDI, (2) giving promethazine hydrochloride and/or hydrocortisone intramuscularly.

In most patients, this therapy is started as a prophylaxis. No permanent effects have been observed.

Discussion

The results of this prospective study are in line with those of Varde (1964) and Basu (1965). A rapid rise in the haemoglobin level is noted following TDI. This rise was optimal when the initial haemoglobin level was lowest. (See Fig. 7). Kwa (1966) and Pathak et al (1967) also found the response to TDI to be greater in the group of patients who had lower haemoglobin levels before therapy. A prolonged follow-up carried out in a small proportion of patients showed a gradual secondary rise in the haemoglobin level. (See Fig. 8). This has also been shown by Kwa (1966), who stated that there is a very rapid rise in the haemoglobin level which is most marked in the first two weeks, after which there is a more gradual rise until the haemoglobin reaches normal levels between the 4th to 8th weeks.

The average rise of haemoglobin in the first four weeks was 1.4 gm./100 ml. per week. At the end of the fourth week, only 78 patients had haemoglobin levels between 8.0-9.9 gm./100 ml. (See

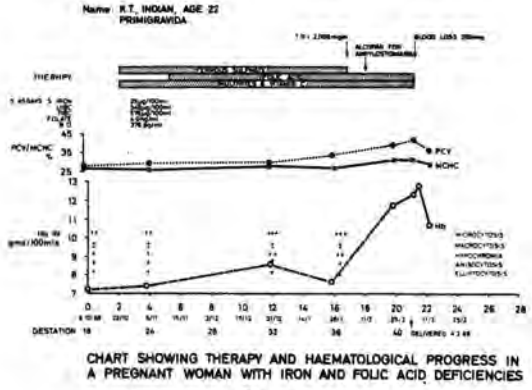


CHART SHOWING THERAPY AND HAEMATOLOGICAL PROGRESS IN A PREGNANT WOMAN WITH IRON AND FOLIC ACID DEFICIENCIES

Fig. 7

Fig. 5). It must be noted the 120 patients had haemoglobin levels below 7.9 gms./100 ml. before TDI was given. Not all the 78 patients can be classified as poor response. Hence, the patient with an original haemoglobin of below 2 gms./100 ml. had reading of 3.7 gms./100 ml. two weeks after the TDI. Therefore she was transfused as she went into labour. It is believed that the giving of massive doses of iron often unmasks or induces folate deficiency as has been shown by Scott (1963), Basu (1965) and Garland (1964).

Hence in the management of this series of patients, folic acid was given as a routine. Chanarin et al (1965) observed that iron deficiency may mask the morphological criteria of a megaloblastic anaemia and iron deficiency in itself produced an additional stress on folate metabolism. In this series, there was evidence of a combined iron-folate deficiency in 236 (66.3 per cent) patients.

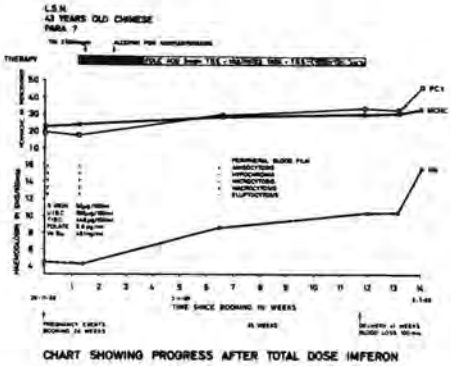


CHART SHOWING PROGRESS AFTER TOTAL DOSE IMFERON

Fig. 8

After the TDI, no further iron therapy was given. Perhaps in those with a poor response, the serum iron should have been repeated and further iron therapy given. Kwa (1966) found that after TDI, a number of patients continued to show low serum iron levels, even amongst those showing good response.

Examination of the stools for ova showed that 56.2 per cent of patients required therapy for worm infestation. The majority of these were ankylostomiasis which would certainly contribute towards the anaemia. In this country, it is very important to include investigations and therapy for helminthiasis in the management of anaemic patients.

In 359 TDI infusions, only one patient demonstrated a mild anaphylactic type of reaction. Anaphylactic reactions have been reported by other authors. Like most reactions to TDI, they occur immediately following commencement of the therapy. A reaction rate of 2.5 per cent is recorded. While this is high compared with Lane and Scott's (1965) reported reaction rate of 0.28 per cent in 1,807 fully documented cases, it has to be pointed out that all the reactions were mild. Clay et al (1965) observed 13 (8.7 per cent) reactions out of 150 patients, seven of them severe. No other worker has so far reported similar results. A review by Mills (quoted by Manton 1966) gives the overall incidence of severe reactions based on 2,898 reported cases, as less than 0.28 per cent if the results of Clay et al (1965) are excluded, or 0.50 per cent, if these are included. Perhaps close observation and prompt prophylactic treatment of mild reactions do avert more severe reactions.

The perinatal loss is 36 per thousand. Unfortunately, the autopsy rate here is negligible. Clinically, there does not appear to be any reason to believe that any of these foetal loss was due to the TDI. The overall perinatal mortality rate for the same period in this hospital is 33.1 per thousand. Pathak et al (1967) submitted the three stillbirths in their series to thorough autopsies. A detailed search failed to reveal increased iron deposits in the various viscera. Further, there was no iron staining in the placentae of these patients.

The use of iron-dextran in a total dose infusion therapy has the following advantages:

(1) TDI raises the haemoglobin rapidly and is safe. Varde (1964) and Martin et al (1965) have commented on the low toxicity, high stability and freedom from ionic iron of this compound. For the anaemic patient in the last weeks of pregnancy, it offers a rapid way to raise the haemoglobin. This, besides making delivery safer, reduces the need for blood tranfusion.

(2) TDI reduces the need for blood transfusion. Blood tranfusion is costly, difficult to come by and carries inherent danger. The reduction in the use of blood tranfusion has been shown by Lane (1964), Varde (1965) and Kwa (1966).

(3) In TDI, the dose is individually calculated not only to raise the haemoglobin level but also to replenish the body stores of iron. It is important to remember that when peripheral blood shows evidence of hypochromic anaemia, the body iron stores are virtually exhausted (De Gruchy 1964) and that satisfactory treatment requires replacement of the total body deficit.

(4) TDI does away with problems posed by patients who are unable and/or unwilling to accept oral or repeated parenteral iron therapy. Furthermore, the rise in haemoglobin is more brisk in the group treated with imferon — 2.2 gm./100 ml. per week during the first two weeks compared with 1.3 gm./100 ml. per week in the group given ferrous sulphate. (Patel and Tulloch 1967).

(5) Following TDI, there is not much excretion of iron as shown by Will and Groden (1968). Using a radioistope, ^{59}Fe labelled preparation of iron-dextran given intravenously to patients, they found no significant radioactivity in their urine and faecal collections

(6) From the patient's point of view, it saves a lot of time and repeated (sometimes long and tedious) journeys to crowded outpatient's clinics. This is important in this country, especially in the rural areas.

(7) From the point of view of the hospital, precious time of medical staff is saved. There is no need to run weekly clinics to give patients parenteral iron.

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