IRON AND THE "PHYSIOLOGICAL" ANAEMIA OF PREGNANCY*

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The volume of the vascular bed increases during pregnancy, necessitating a commensurate increase in the blood volume. Dieckmann and Wegner (1934) found that the total blood volume was increased by 23% during pregnancy, and that, although this increase was proportionately much greater in the plasma content, the cellular element was also increased. Since the haemoglobin level tends to return to normal values during the puerperium there would appear at first sight to be a *prima facie* case for the assumption that the anaemia of pregnancy is physiological and for the acceptance of the minimal normal figures of: haemoglobin 10 g.%, erythrocytes 3,360,000, and a packed cell volume of 33%, which were suggested by Adair, Dieckmann, and Grant (1936). On the other hand, many investigators deny that haemodilution can cause such low figures as those quoted above, and believe that the so-called physiological anaemia of pregnancy denotes a marked deficiency of iron.

Before animadverting upon the conflicting reports in the literature it is desirable to see the main factors of the problem in perspective. They are: the level of the maternal haemoglobin before pregnancy occurs, the cessation of menstruation during pregnancy, the increased blood volume, and the foetal demand for iron.

Davies *et al.* (1946), in a survey of 2,000 women in the London region, found that anaemia was encountered twice as often in married as in single women, and there is evidence, particularly that emanating from the blood transfusion services, that anaemia is more widespread in England in 1951 than it was in 1946. Strauss and Castle (1932), Strauss (1934), Corrigan and Strauss (1936), Linder and Massey (1939), Young *et al.* (1946), Laurell (1947), Cartwright and Wintrobe (1949), Lundström (1950), and Ventura and Klopfer (1951) are all of the opinion that there is manifested during pregnancy a tendency towards anaemia which is commonly caused by iron deficiency. Davidson and Fullerton (1938) showed that the saving of iron due to the cessation of menstruation failed to counterbalance the loss of iron to the growing foetus, and maintained that the normal pregnant woman is dangerously near to iron starvation. Whitby and Britton (1942) assert that an erythrocyte count below four millions is pathological, and Vaughan (1936) doubts whether an anaemia which responds to iron can be physiological.

On the other hand, Wolff and Limarzi (1945) regard a normocytic normochromic anaemia occurring during pregnancy as physiological and, together with Rath and Finch (1949), consider it unnecessary to give iron to pregnant women unless there is evidence of patho-

logical anaemia. Some observers, indeed, regard the lowered blood viscosity associated with the hydraemia of pregnancy as mechanically advantageous, and it is true that the loss of haemoglobin during delivery is thereby lessened.

Adair *et al.* (1936) and Evans (1943) go further and aver that iron administered during pregnancy fails to maintain the normal level of haemoglobin. Dieckmann *et al.* (1950) have more recently shown that the addition of molybdenum renders the iron more efficacious, and in an earlier paper Dieckmann *et al.* (1949) showed that even in cases of true anaemia of pregnancy the haemoglobin can be raised from 9.9 to 11.8 g.% by this modified form of iron therapy.

The Present Investigation

This clinic serves a large industrial area in the centre of the heavy woollen industry. The purpose of the investigation was to report: (1) the incidence of anaemia in patients attending the antenatal clinic; (2) the results obtained by administering iron from the 16th week of pregnancy until term; (3) the results obtained by administering iron for eight weeks only, beginning at the 24th week of pregnancy; and (4) whether the addition of a small amount of molybdenum increases either the absorption or the utilization of iron.

All the patients who participated in the following investigations were in the third decade of life, and each group was carefully matched according to age, parity, previous health, and home conditions. They were all reasonably healthy, and each case was carefully supervised by one of us (N. B.), who got to know each woman personally.

All these women took four tabellae calcii cum vitamino D (N.F.) daily. Each tablet contained calcium sodium lactate, 7½ gr. (488 mg.), calcium phosphate, 2½ gr. (163 mg.), and calciferol 1/4,800 gr. (0.014 mg.), which is equivalent to 500 international units of vitamin D. They also took the extra rations and vitamins supplied by the Ministry of Food.

Experiment 1.—Seventy-two patients at or before the 16th week of pregnancy whose initial haemoglobin levels were not below 11 g.% were divided into two matched groups—A and B, the latter being the control group. *Group A* took iron in the form of tabellae ferri sulphatis compositae (N.F.), two tablets thrice daily. Each tablet contained: exsiccated ferrous sulphate, 3 gr. (195 mg.), copper sulphate, 1/25 gr. (2.4 mg.), and manganese sulphate, 1/25 gr. (2.4 mg.). *Group B (Control)* took a mixture known as "mist. antenatal," which was made up to the following prescription:

Syrup	20 min. (1.2 ml.)
Glycerin	10 min. (0.6 ml.)
Blackcurrant flavouring q.s.	
Aqua	to 1 fl. dr. (3.5 ml.)

1 fl. dr. (3.5 ml.) to be taken twice daily.

Experiment 2.—Thirty patients at or before the 16th week of pregnancy whose initial haemoglobin levels were not below 11 g.% were divided into two matched groups C and D. *Group C* took tabellae ferri sulphatis compositae (N.F.), two tablets thrice daily for eight weeks, beginning at the 24th week of pregnancy. *Group D* took White's "mol-iron" tablets,* two thrice daily for eight weeks, beginning at the 24th week of pregnancy. Each tablet contained ferrous sulphate, 3 gr. (195 mg.), and molybdenum oxide, 1/20 gr. (3 mg.).

Methods of Blood Examination

Investigations were carried out at monthly intervals until term, and again on the sixth day of the puerperium. The estimations made were the haemoglobin and the packed cell volume, from which was calculated the mean corpuscular

*The expenses of this investigation were defrayed by a grant from the Endowment Fund generously afforded to one of us (G. W. T.) by the Bradford Hospital Management Committee (A), to whom we express our grateful thanks.

*These tablets, similar to those used by Dieckmann *et al.*, were most generously sent to one of us (G. W. T.) free of all cost through the kindness of Dr. H. A. Strade, of the Medical Department of Messrs. White Laboratories, Inc., Newark, New Jersey.

haemoglobin concentration. The haemoglobin was estimated by means of a Sahli colorimeter (standard 14.8 g. = 100%). This was calibrated at the beginning of the experiment and recalibrated six months later. The packed cell volume was estimated by Wintrobe's method.

The initial haemoglobin estimations used in Fig. 1 were made by the pathological laboratory of St. Luke's Hospital, and were estimated by means of a "unicam" photoelectric colorimeter. The remaining blood examinations were carried out by one of us (N. B.) not more than 30 minutes after collecting the blood.

FIG. 1.—Distribution of the initial haemoglobin values of the 2,000 consecutive antenatal patients mentioned in the text.

The initial haemoglobin estimations of 2,000 consecutive cases, all less than 16 weeks pregnant, attending the booking-in clinics from January to October, 1950, were as follows (see Fig. 1):

40.15%	had readings of 12 g. or more per 100 ml.
59.85%	" " " below 12 g. " " "
37.25%	" " " " 11.5 g. " " "
18.85%	" " " " 11 g. " " "
12.05%	" " " " 10.5 g. " " "
6.55%	" " " " 10 g. " " "

Notes on Statistical Analysis of Experiments.—The standard error of the difference between the means was calculated by using the second method described by Bradford Hill (1948), and, in order to facilitate these calculations, the haemoglobin estimations are all reported as percentages. Where the difference between the means (D.M.) is greater than twice the standard error of the difference between the means—that is, $D.M./S.E.D.M. > 2$ —it is regarded as significant.

Discussion of Results

It is a matter of no little concern that 6.5% of 2,000 consecutive patients attending this clinic were severely anaemic at the 16th week of pregnancy, before any significant haemodilution had occurred, and that about 60% of all cases showed readings below 12 g.%. The normal range for adult non-pregnant women is regarded by Whitby and Britton as lying between 12 and 15.5 g.%. The results reported in Figs. 2 and 3 and in Tables I to III vary significantly from those published by most other

FIG. 2.—Experiment 1. (a) Shows the arithmetic means of the haemoglobin values plotted at four-weekly intervals in group A and the control group B. (b) Shows the arithmetic means of the packed cell volume in the same two groups plotted at the same intervals of time. (c) The curves denote the arithmetic means of the mean corpuscular haemoglobin concentration of groups A and B at the same time intervals.

authors. It will be seen that the adequate administration of iron makes it possible for normal haemoglobin values to be maintained throughout pregnancy, whereas if the woman does not take iron she begins the puerperium with a significantly lessened amount of haemoglobin.

This latter observation is all the more important when it is realized that the average initial haemoglobin value for the control group (B) was 88.8%, which means that the subjects chosen for the investigation were almost exclusively recruited from 40% of those who booked at the clinic (see Fig. 1).

Similar advantages are observed in the mean corpuscular haemoglobin concentrations from taking iron throughout pregnancy, but although the differences between the two

FIG. 3.—Experiment 2. (a) Shows the arithmetic means of the haemoglobin values for groups B (control), C, and D plotted at four-weekly intervals. (b) The curves denote the arithmetic means of the packed cell volumes in the same three groups plotted at the same time intervals. (c) The curves show the arithmetic means of the mean corpuscular haemoglobin concentration of the same three groups at identical intervals of time.

groups on the sixth day of the puerperium are significant, it will be noted that the value for the 16th week of pregnancy in the control group is almost identical with that for the sixth day of the puerperium.

It is certainly a matter of interest that the administration of iron for eight weeks only, beginning at the 24th week of pregnancy, causes a rapid recovery from the commencing "physiological" anaemia, and that thereafter satisfactory normal blood values are maintained. It will be observed that all the figures for the sixth day of the puerperium are higher in groups C and D than in Group A.

This investigation provides no evidence to support the contention of Neary (1946), Chesley and Annitto (1948), and Dieckmann *et al.* (1949), that molybdenized iron is more

efficacious than ferrous sulphate in either the treatment or the prevention of anaemia during pregnancy. On the other hand, the important observation made by both Neary (1946) and Chesley and Annitto (1948) that molybdenized iron is more easily tolerated has been amply confirmed. It was found that 33% of the patients in group A and 40.2% in group C found it difficult or impossible to tolerate ferrous sulphate tablets, and it can be assumed that between 30 and 40% of all antenatal patients will not, in fact, take these tablets if they are routinely prescribed in the antenatal department. The mol-iron tablets were tolerated by 86% of the patients in group D and were equally well tolerated by other patients not included in the experiment (Table IV). It must, however, be borne in mind that the old scale preparation

TABLE I.—Experiment 1 (Groups A and B) (See Fig. 2)

	Weeks Pregnant							Puerperium
	16	20	24	28	32	36	40	
Average Hb estimations (%):								
Group A	90.8	90.6	91.5	90.7	91.2	92.9	93.3	88
Control (group B) .. .	88.8	87.4	83.2	78.7	76.6	77.1	80.8	79.5
S.E.D.M. .. .	2.67	2.38	2.16	2.23	1.75	2.18	3.63	2.83
Significance (D.M./S.E.D.M. >2) ..	0.75	1.35	3.05	5.38	8.35	7.25	3.44	3.26
Average P.C.V. (%):								
Group A	39.7	38.3	38	38	38.3	39.2	39.2	37.4
Control (group B) .. .	39.8	38.3	37.1	35.5	34.6	35.5	36.8	35.9
S.E.D.M. .. .	0.88	0.85	0.64	0.597	0.54	0.614	0.965	1.01
Significance (D.M./S.E.D.M. >2) ..	0.114	0	1.4	4.9	6.81	6.03	2.7	1.49
Average M.C.H.C. (%):								
Group A	33.0	34.0	34.8	34.7	34.5	34.2	34.2	34.1
Control (group B) .. .	32.4	33.2	32.4	31.9	32.2	31.5	31.8	32.3
S.E.D.M. .. .	0.815	0.66	0.61	0.409	0.588	0.673	1.02	0.721
Significance (D.M./S.E.D.M. >2) ..	0.736	1.21	3.91	6.85	3.91	4.01	2.35	2.5

TABLE II.—Experiment 2 (Groups B and C) (See Fig. 3)

	Weeks Pregnant							Puerperium
	16	20	24	28	32	36	40	
Average Hb estimations (%):								
Group C	85.8	83.3	82.3	86.7	100.6	98.2	100.1	94.3
Control (group B) .. .	88.8	87.4	83.2	78.7	76.6	77.1	80.8	79.5
S.E.D.M. .. .	3.19	2.42	3.44	2.92	2.83	3.55	3.57	3.4
Significance (D.M./S.E.D.M. >2) ..	0.94	1.69	0.262	2.74	8.48	5.94	5.41	4.35
Average P.C.V. (%):								
Group C	38.7	36.4	35.8	37.6	39.4	39.4	39.5	38.8
Control (group B) .. .	39.8	38.3	37.1	35.5	34.6	35.5	36.8	35.9
S.E.D.M. .. .	0.945	1.3	1.06	0.834	0.725	0.729	1.11	1.18
Significance (D.M./S.E.D.M. >2) ..	1.16	1.46	1.23	2.52	6.62	5.35	2.43	2.46
Average M.C.H.C. (%):								
Group C	32.1	33.1	33.2	33.5	36.3	36.4	36.1	35.3
Control (group B) .. .	32.4	33.2	32.4	31.9	32.2	31.5	31.8	32.3
S.E.D.M. .. .	1.02	1.19	1.11	0.822	0.757	0.791	1.18	0.802
Significance (D.M./S.E.D.M. >2) ..	0.294	0.084	0.721	1.95	5.42	6.19	3.64	3.74

TABLE III.—Experiment 2 (Groups B and D) (See Fig. 3)

	Weeks Pregnant							Puerperium
	16	20	24	28	32	36	40	
Average Hb estimations (%):								
Group D	88.0	83.8	83.7	89.4	91.7	95.2	94.0	94.7
Control (group B) .. .	88.8	87.4	83.2	78.7	76.6	77.1	80.8	79.5
S.E.D.M. .. .	3.49	2.77	2.32	2.45	2.44	3.05	4.09	3.62
Significance (D.M./S.E.D.M. >2) ..	0.229	1.3	0.216	4.37	6.19	5.93	3.23	4.2
Average P.C.V. (%):								
Group D	39.3	38.1	37.3	37.7	37.8	38.3	39	38.4
Control (group B) .. .	39.8	38.3	37.1	35.5	34.6	35.5	36.8	35.9
S.E.D.M. .. .	0.884	0.825	0.818	0.712	0.706	0.808	0.91	1.09
Significance (D.M./S.E.D.M. >2) ..	0.566	0.242	0.244	3.09	4.53	3.47	2.42	2.29
Average M.C.H.C. (%):								
Group D	32.4	32.3	32.6	34.2	35.2	35.8	35	35.6
Control (group B) .. .	32.4	33.2	32.4	31.9	32.2	31.5	31.8	32.3
S.E.D.M. .. .	0.865	0.67	0.624	0.734	0.868	0.799	1.14	0.64
Significance (D.M./S.E.D.M. >2) ..	0	1.34	0.32	3.13	3.46	5.38	2.81	5.16

TABLE IV.—*Tolerance to Iron*

Group	Intractable Diarrhoea and Vomiting (Removed from Experiment)	Gastro-intestinal Symptoms (Persevered with Treatment)
A	6	6
C	3	3
D (mol-iron)	1	1

ferri et ammonii citras was even better tolerated and proved equally efficient. The mol-iron tablets are easier to prescribe and to take than this latter preparation, but the increased expense involved and the world shortage of molybdenum may delay the routine use of these tablets (which are now made in England). The important point to realize is that many pregnant women cannot tolerate ferrous sulphate pills and therefore do not take them.

This investigation suggests that a high percentage of pregnant women in Bradford suffer from iron deficiency, and that the administration of iron together with calcium and vitamin D prevents both the microcytic and the "physiological" anaemia of pregnancy. An idea to be considered further is whether iron deficiency may in some way be associated with the occurrence of miscarriage and hypertension (see Table V). The only disadvantage of maintaining the haemoglobin level at its normal value throughout pregnancy would

TABLE V.—*Additional Observations*

Group	Miscarriage	Hypertension (Blood Pressure Exceeding 140/90 mm. Hg on at Least 2 Occasions)	Post-partum Haemorrhage—More than 20 fl. oz. (570 ml.)
A	—	—	3 (one required blood transfusion)
Control (B)	2 { 18 weeks	5 (1 eclampsia)	1
C	— " "	1	1 (required transfusion)
D	—	1	1

appear to be a slightly increased risk of post-partum haemorrhage. We therefore conclude that the so-called "physiological" anaemia of pregnancy is in reality the expression of iron deficiency, and that the diet in Bradford, and probably in many other centres, is and is likely to remain deficient in this mineral. It would clearly be important to see whether the controlled administration of iron to a much larger group of women would decrease the high incidence of hypertension in pregnant women in Bradford, and whether the maintenance of the normal haemoglobin level throughout pregnancy is associated with the accepted figure for the increase in blood volume.

Summary and Conclusions

A review of haemoglobin readings obtained from 2,000 consecutive cases at or below the 16th week of pregnancy showed that about 60% were subnormal, and that 6.5% of the women were severely anaemic.

The changes in haemoglobin and packed cell volume readings which occurred during pregnancy in matched groups of young healthy women lead us to conclude that: (a) the "physiological" anaemia of pregnancy is associated with a low or subnormal mean corpuscular haemoglobin concentration; (b) normal (non-pregnant) blood values are maintained if therapeutic doses of ferrous sulphate are administered throughout pregnancy; and (c) the administration of ferrous sulphate, or of molybdenized iron, from the 24th to the 32nd week of pregnancy, results in recovery from the commencing "physiological" anaemia, followed by maintenance of normal (non-pregnant) blood values.

The mol-iron tablets were not found to be more efficacious than ferrous sulphate tablets either in preventing or treating the "physiological" anaemia of pregnancy, but they were better tolerated. We would suggest

that ferrous sulphate is not a suitable preparation for the routine administration of iron in antenatal clinics.

We think that the controlled administration of iron to a large group of women should be undertaken in order to see whether the incidence of hypertension would thereby be lessened. It would also be of interest to determine whether the maintenance of the normal haemoglobin level throughout pregnancy is associated with the accepted value for the increase in blood volume.

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HAEMOGLOBIN LEVELS IN ADULTS AND CHILDREN

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This paper reports the results of haemoglobin studies on 245 males and 266 females of adult age employed in clerical and industrial work, on 214 housewives under 60 years, all living in and around London, and on 1,628 boys aged 6, 10, and 14 years living in two Lancashire towns (I and K), one Surrey town (J), and one Gloucestershire town (L) (see Table I). The method was the same as that employed in earlier studies (Magee and Milligan, 1951), except that oxyhaemoglobin was the pigment determined instead of alkaline haematin. As before, many precautions were taken to ensure accuracy—the two photometers were re-checked by the National Physical Laboratory, pipettes were re-calibrated, and blood was drawn by finger-prick after a period of rest, depending on the previous state of activity of the individuals. The findings are expressed as grammes of haemoglobin per 100 ml. of blood, and, for comparison with previous findings, especially those of the M.R.C. 1943 Survey (M.R.C., 1945), as Hb% on the Haldane scale.