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Investigation of Folic Acid Requirements in Pregnancy

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The minimum daily oral requirements of pteroylglutamic acid in the non-pregnant adult are probably of the order of 50 μ g./day (Herbert, 1962), and there is little doubt that requirements are increased in pregnancy (Chanarin *et al.*, 1959 ; Ball and Giles, 1964 ; Hibbard, 1964), but the magnitude of increase is not known (*Brit. med. J.*, 1964).

There is evidence that oral supplementation of 500 μ g. daily is adequate (Lowenstein *et al.*, 1964), and of 20 to 30 μ g. is inadequate (Chanarin *et al.*, 1965) to meet the folic acid requirements of pregnancy in urban communities. Since 1964 we have been investigating the effects of oral supplements at levels of 100, 300, and 450 μ g./day—namely, intermediate between the the level employed by Lowenstein and that by Chanarin—in an attempt to define the minimum level more closely.

As part of this investigation the fasting serum folate levels were measured between the second and fourth day postpartum in a consecutive series of 350 patients from five different randomly allocated supplementation groups as described below. These results are shown in the Chart and Table II, where they are compared with similar results from cases of megaloblastic anaemia of pregnancy and also with a group of patients not allocated to a supplementation group.

Clinical Material

All patients attending the antenatal clinic were randomly allocated, according to their hospital number, to one of five trial groups at their first visit, which was usually at about three months' gestation. Patients with initial haemoglobin levels below 10 g./100 ml. were excluded from the trial. Thereafter all patients had haemoglobin estimations performed at every visit to the clinic. If the haemoglobin level fell below 10 g. they were removed from the trial and treated appropriately

according to the haematological findings. This surveillance continued after delivery until the postnatal visit.

Group 1 patients received no haematinics. The remaining groups were given three bottles labelled "breakfast," "lunch," and "tea" containing chelated iron aminoates with or without various amounts of folic acid, so that the daily dosage of three tablets supplied the amounts shown in Table I. All patients were also given a multivitamin preparation (Vitavel) free of folic acid.

TABLE I.—Details of Antenatal Oral Supplements

Group:	1	2	3	4	5
Iron (mg./day)	0	105	105	105	105
Folic acid (μ g./day)	0	0	100	300	450
" " " actual*	0	0	124	355	530

* These figures are derived from microbiological assays on batches of tablets at different periods of storage arranged by Riker Laboratories.

Every endeavour was made to encourage the patients to take the tablets regularly by the nursing staff, dietitians, and obstetricians, and by enlisting the help of the patients' general practitioners. Where it was clearly established in the case notes that a patient had not been taking the tablets their results were excluded from analysis.

Between the second and fourth days postpartum a venous sample for serum folate estimation was collected at approximately 11 a.m., more than two hours after the last meal.

Methods

Screening haemoglobin estimations were performed from finger-prick blood samples with an oxyhaemoglobin method and an EEL haemoglobinometer. In patients with a haemoglobin level in the region of 10 g./100 ml. this was confirmed on a venous sample of blood by means of a cyanomethaemo-

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globin method and a Unicam S.P. 1300. The latter method was calibrated by means of lysed haemoglobin standards and a standard solution of cyanomethaemoglobin supplied by Diagnostic Reagents Ltd.

Dietary assessment was made on the basis of weekly intake of food items by using the tables of McCance and Widdowson (1960), and correcting for a loss of folic acid during cooking according to figures suggested by these authors.

The blood for fasting serum folate estimations was collected with disposable syringes into specially washed disposable tubes. After one hour at 37° C. and brief centrifugation 2 ml. of serum was aspirated with a sterile Pasteur pipette into a tube containing 10 mg. of ascorbic acid and stored at -20° C. until assayed, usually within 10 days. The *Lactobacillus casei* assay method of Waters and Mollin (1961, 1963) was employed, and the results were expressed as $\mu\text{g./ml.}$ of serum with reference to a crystalline sample of pteroylglutamic acid. In 21 healthy non-pregnant adults the normal range was 2.8 to 8, with a medium value of 5 and mean 5.14 $\mu\text{g./ml.}$

The criterion for the diagnosis of megaloblastic anaemia of pregnancy was a haemoglobin level of less than 10 g./100 ml., and the presence of at least two of the following morphological features in films made from the peripheral blood: (1) more than 4% of the neutrophil polymorphs with five or more lobes; (2) orthochromatic macrocytes of over 12 μ in their longest diameter measured by micrometer eyepiece; (3) Howell-Jolly bodies in the erythrocytes; (4) macropolycytes—namely, giant polymorphs with very numerous lobes; and (5) normoblasts showing premature haemoglobinization for their stage of nuclear development, described as “out of step” normoblasts by Rannie and McTaggart (1961). Features 2 to 5 were sought for in films from the buffy coat.

These criteria are similar to those suggested by Rannie and McTaggart (1961) and Chanarin (personal communication, 1963). Goodall (1957) showed that though narrow examination was a slightly more sensitive index of megaloblastic anaemia of pregnancy the same information could be obtained by examination of buffy-coat films in most cases. Similarly it has been shown by Lowenstein *et al.* (1966) that, though the very earliest white-cell changes attributed to folic acid deficiency of pregnancy can be detected only by marrow examination, in those cases with actual macrocytic anaemia there is also hypersegmentation of the neutrophils in the peripheral blood with a mean of 10% of cells having five lobes. There is little doubt, therefore, that cases fulfilling the criteria used here had true megaloblastic anaemia of pregnancy, but it is also probable that some of the milder grades of megaloblastic change will have been missed or diagnosed later than would have been the case if marrow examinations had been performed at every antenatal visit. This consideration does not, however, materially affect the findings or conclusions of the present investigation.

Serum *L. casei* or folate levels in different groups of postpartum patients. Fe=Iron supplementation, 105 mg./day. FA=Folic acid supplementation, given in $\mu\text{g./day.}$ =Mean value for the group. * =Patients with post-partum macrocytic anaemia (arrow indicates number of patients).

Results

The postpartum levels of serum folate in the 350 patients from the five different supplementation groups are shown in the Chart. Also shown are the results in 88 similar postpartum patients who were not on the trial for some reason and who had not received folic acid supplementation (group 0). For purposes of comparison a group of 52 patients with established megaloblastic anaemia of pregnancy either antenatally or postnatally are also shown.

The mean and median values, together with the proportion of the patients giving results below the limits of 2, 2.5, and 3 $\mu\text{g./ml.}$ are shown in Table II. There was no statistical difference between the mean values of group 0, 1, or 2. Between groups 2 and 3, however, the P value was less than 0.05, between groups 3 and 4 it was less than 0.001, and between groups 4 and 5 it was less than 0.02. The megaloblastic group also gave values significantly lower than those of group 1 (P less than 0.01).

TABLE II.—Results of Postpartum Serum Folate Estimations Expressed as $\mu\text{g./ml.}$

Group:	0	1	2	3	4	5	Megalo	Normal
No. of patients	88	38	77	88	77	70	52	21
Mean serum folate ..	3.15	3.05	3.13	4.1	7.43	10.4+	1.97	5.14
S.D. ..	2.14	1.94	1.76	3.17	5.82	8.4	0.63	1.45
Median serum folate ..	2.75	2.7	2.8	3.6	5.0	7.2	1.8	5.0
% < 3.0 ..	59	66	58	33	23	10	85	5
% < 2.5 ..	47	47	42	28	16	6	75	0
% < 2.0 ..	28	32	22	13	5	6	58	0

The results show that a significant increase in the level of postpartum serum folate is obtained by the prophylactic administration by mouth of 100, 300, and 450 $\mu\text{g.}$ of folic acid a day during pregnancy. The mean and median serum folate levels increase with increasing levels of supplementation, and the percentage of patients having serum folate levels below 2, 2.5, and 3 $\mu\text{g./ml.}$ correspondingly decreases.

The median value of group 4 patients was the same as the median value of 5 $\mu\text{g./ml.}$ found in healthy non-pregnant adults. The mean values of groups 4 and 5 were above the normal mean, and those of all other groups were below the normal mean (Table II).

Since patients developing an anaemia with a haemoglobin value less than 10 g./100 ml. were removed from the trial groups for treatment, the postpartum serum folate levels in groups 1 to 5 are derived from a population of women who, with very few exceptions, had haemoglobin values above this level. The number of such patients excluded from analysis because of the development of antenatal megaloblastic anaemia were two in group 1, two in group 2, one in group 3, and none in group 4 or 5. The total incidence of antepartum and immediate postpartum megaloblastic anaemia in the groups of patients is shown in Table III.

Random dietary surveys on 150 of the antenatal patients allotted to the different supplementation groups suggested that the folate intake was less than 50 $\mu\text{g./day.}$ in 60% of patients. Even allowing for the considerable errors of estimation in this

TABLE III.—Number of Patients Developing Anaemia

Group:	1	2	3	4	5
Total No. in group	44	80	90	77	70
Total No. with antepartum anaemia*	6	3	2	0	0
No. with antepartum megaloblastic anaemia	2	2	1	0	0
No. with postpartum megaloblastic anaemia	3	3	1	0	0
Total with megaloblastic anaemia { No. % ..	5 11	5 6.2	2 2.2	0 0	0 0

* Patients developing antepartum anaemia were removed from the trial for treatment and were therefore excluded from the postpartum serum folate levels shown in the chart and Table II.

method of assessment it was the opinion of the dietitians that most of these patients were taking diets deficient in folic-acid-containing foodstuffs.

Discussion

The immediate postpartum period was chosen for purposes of measuring the serum folate, since the lowest levels associated with pregnancy are reached at this time (Solomons *et al.*, 1962; Ball and Giles, 1964; Chanarin *et al.*, 1965; Edelstein *et al.*, 1966), when the body stores have presumably been put to the maximum strain as a result of both foetal demands and the variable blood loss of delivery. From a practical point of view it would be valueless to establish a suitable folic acid supplement which would sustain a normal folic acid status throughout pregnancy but perhaps fail to do so in the puerperium, which is when a high proportion of megaloblastic anaemias of pregnancy first become manifest.

Unfortunately the serum folate level is a less precise measurement of body stores than, for instance, the hepatic folate (Chanarin *et al.*, 1966), though superior to the F.I.G.L.U. test in pregnancy (Chanarin *et al.*, 1963; Chisholm and Sharp, 1964) and probably a more sensitive index than the presence of overt megaloblastic anaemia (Herbert, 1964). Representative figures from the literature are shown below for normal late pregnancy in Table IV and for megaloblastic anaemia of pregnancy in Table V, where they are compared with the corresponding groups of the present series. It is apparent that all workers have found some degree of overlap between the levels in normal pregnancy and those in megaloblastic anaemia of pregnancy. It is not certain, therefore, at what level the serum folate must be maintained before it can be said that the folic acid supplements have met the requirements of pregnancy. The lowest non-pregnant normal adult value was 2.8 m μ g./ml., and by contrast 75% of the patients with megaloblastic anaemia of pregnancy had less than 2.5 m μ g./ml. With the criterion of maintaining the postpartum serum folates above this level of 2.5 m μ g./ml., it can be seen that this was achieved in 72% of patients in group 3, 84% in group 4, and 94% in group 5, whereas only between 53% and 58% (mean 55%) of patients in groups 0, 1, and 2 were above this level (Table II).

The mean values of postpartum serum folate were significantly below the normal mean in groups 0, 1, 2, and 3 but above it in groups 4 and 5. Because of skew distribution of all groups of serum folate results (the Chart has a logarithmic

ordinate), Lowenstein *et al.* (1966) have suggested that the median values of a group are more meaningful than the means. These median results showed an exactly similar pattern among the different groups, but that of group 4 was identical, at 5 m μ g./ml., with that of the normal non-pregnant adults (Table II).

These findings, especially the median figures, indicate that the normal drop in serum folate that is found in late pregnancy, and in an exaggerated form in those developing overt megaloblastic anaemia, can largely be prevented by oral supplementation with 300 μ g. of folic acid a day during pregnancy. Supplementation with 450 μ g. a day results in supranormal median and mean values, while supplementation with 100 μ g. a day results in higher levels than in unsupplemented patients, but in median and mean values still below normal, and with a high proportion of patients in the deficient range of less than 2.5 m μ g./ml. postpartum. It appears highly likely, therefore, that in populations where low dietary folic acid intake is common a daily supplement of 300 μ g. is close to the minimal daily requirement in late pregnancy. This is supported by the absence of antepartum or postpartum megaloblastic anaemia by the criteria employed here in the group 4 or 5 patients, though this occurred in groups 0, 1, 2, and 3 (see Chart and Table III). In order to verify this point a larger series of 3,600 antenatal patients similarly allocated to the same supplementation groups 1 to 5 is being analysed for the incidence of megaloblastic anaemia and will be reported elsewhere (Willoughby, 1967).

This conclusion is also consistent with the report of Dawson (1966) that a daily supplement of 150 μ g. of folic acid by mouth was insufficient to maintain a normal serum folate in late pregnancy, since this was above 3 m μ g./ml. in only 12 out of 20 patients at term. From intensive investigations of two patients with megaloblastic anaemia at 32 and 36 weeks' gestation, Alperin *et al.* (1966) also concluded that the minimal requirement of these patients was in excess of 200 μ g. a day in spite of proved normal intestinal absorption. There is, however, a slight reservation in interpreting the minimal effective therapeutic dose in established megaloblastic anaemia, since this could be different from the minimal prophylactic dose in normal late pregnancy. This difference presumably explains the reports of Pritchard (1962) and Lowenstein *et al.* (1966) that some cases of established megaloblastic anaemia of pregnancy require more than 400 μ g. a day for haematological response to occur. We have made similar observations.

Regarding our conclusion that 300 μ g. a day is close to the minimal requirement in late pregnancy, Herbert (1966), while discussing such requirements in patients with conditions associated with increased metabolic demands, such as pregnancy, has stated: "Hopefully it will not be greater than 300 μ g., because daily doses of 400 μ g. may produce haematologic response in patients with vitamin-B₁₂ deficiency and no evidence of folate deficiency." In a similar context Hansen and Weinfeld (1962) have expressed reservations regarding the safety of prolonged administration of 400 μ g. a day.

By establishing that a prophylactic dose at this level of approximately 300 μ g. a day is effective in maintaining the postpartum serum folate levels in the majority of pregnant patients, we feel that we have defined a dosage free from the criticism that it is either wasteful or apt to mask vitamin-B₁₂ deficiency, especially if it is given only during the limited period of the second and third trimesters.

At the present time prophylactic folic acid tablets are available commercially in dosage ranges suggested by the makers of 100, 150, 300, 500 μ g., and 1, 3, and 15 mg. a day. No doubt it is equally important to general practitioners, obstetricians, and the drug firms themselves that attempts are made to establish the optimum prophylactic dose in populations where dietary insufficiency is common.

It was also of interest that there was no difference in the serum folate levels between groups 1 and 2, only the latter

TABLE IV.—Serum Folate Levels in Unsupplemented Late Pregnancy—Puerperium. Results in m μ g./ml.

	Stage of Pregnancy	No.	Mean	S.D.	Range
Present series (1), Glasgow	Postpartum	38	3.05	1.94	0.8–9.0
Ball and Giles (1964), Stoke-on-Trent	Last trimester	99	3.19	0.97	1.6–5.3
Dawson (1966), Manchester	At term	20	2.6	0.87	1.5–4.4
Chanarin <i>et al.</i> (1962), London	Puerperium	42	4.3	—	1.5–11.0
Solomons <i>et al.</i> (1962), Brooklyn	Postpartum	40	4.6	—	—

25% less than 3 m μ g. (Mollin and Hoffbrand, 1965; Lowenstein *et al.*, 1962) and about 50% less than 4 m μ g. (Lowenstein *et al.*, 1962, 1964).

TABLE V.—Serum Folate Levels in Macrocytic Anaemia of Pregnancy. Results in m μ g./ml.

	No.	Mean	S.D.	Range
Present series—all cases	52	1.97	0.63	0.8–3.6
Ball and Giles (1964) { All cases	47	1.89	0.96	0.3–4.0
(1964) { Grade 2	9	1.88	1.00	0.6–3.5
Kershaw and Girdwood (1964)—all cases	11	2.45	0.89	1.1–3.7
Chanarin <i>et al.</i> (1965)—postpartum	15	3.5	—	—
Giles 1966) { All cases	100	1.0	0.5	0.3–2.4
{ Grade 1	26	1.3	0.6	0.5–2.4

Over 50% had less than 3 m μ g. (Mollin and Hoffbrand, 1965; Lowenstein *et al.*, 1962).

receiving iron, and neither receiving folic acid. This finding is superficially at variance with that of Chanarin *et al.* (1965), who found a greater fall of serum folate in late pregnancy among unsupplemented compared with iron-supplemented patients. However, this difference was not continued into the postpartum period in their cases, and this was the time at which the serum folate level was measured in the present series. Like Chanarin *et al.* (1965), we have found a higher incidence of megaloblastic anaemia, though different criteria were employed, in the unsupplemented group 1, compared with the iron-supplemented group 2 patients (Table III). The numbers of cases, however, are small.

Summary

Antenatal patients have been randomly allocated to five prophylactic treatment groups at their first clinic visit. Thereafter their haemoglobin level was estimated at each visit, and they were removed from the trial if anaemia developed. In 350 consecutive patients the 2-4 day postpartum fasting serum folate level was measured. It was found that these levels were similar in the non-supplemented group 1 and the iron-supplemented group 2, but significantly raised in the iron plus 100 µg. of folic-acid-supplemented group 3. In the groups receiving iron plus 300 µg. (group 4) or 450 µg. (group 5) a day of folic acid the postpartum serum folates were further significantly raised ($P < 0.001$). The levels in these groups are compared with those in patients not in the trial, with patients with overt megaloblastic anaemia, and with a group of non-pregnant normal adults.

The median postpartum serum folate levels in groups 1, 2, and 3 were lower than in the normal non-pregnant adults, the level in group 4 receiving 300 µg. a day was identical, at 5 mµg./ml., with that of the normal adults, while the level in group 5 was supranormal. In group 4 84% of the patients had postpartum serum folate levels above 2.5 mµg./ml., and no cases of megaloblastic anaemia were found in group 4 or 5 before or after delivery.

It is concluded that the minimal oral requirements of folic acid in late pregnancy are close to 300 µg. a day.

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Diaphragmatic Paralysis after Herpes Zoster

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Motor complications after herpes zoster are not uncommon, the first association of muscular paralysis and zoster being reported by Sir William Broadbent (1866). Since that time there have been many reports of muscular paralyses following herpes—of the hand, abdominal muscles, face (Ramsey Hunt, 1907), calf, quadriceps, foot, and even bladder, and many other sites. A comprehensive review of the literature on motor involvement has been made by Taterka and O'Sullivan (1943).

The association between diaphragmatic paralysis and zoster was first reported by Halpern and Covner (1949). The case presented below showed not only weakness of the right arm but also diaphragmatic involvement following herpes zoster of C 5 and 6 on the right side. Recognition of this latter

relationship became important when the patient developed carcinoma of the bronchus in the right lung some months later.

Case Report

A man aged 54 first developed symptoms of rheumatoid arthritis in 1942, but was reasonably well until 1958, when his wrists, proximal interphalangeal joints, and left shoulder became stiff and painful. At that time he was given chloroquine and aspirin, with some relief. During the next five years he had various forms of treatment, including gold, steroids, A.C.T.H., and phenylbutazone.

In May 1963, whilst an inpatient with an attack of acute bronchitis, he developed a typical zoster eruption affecting C 5 and 6 on the right side. Pain and itching were the main symptoms, but he complained of weakness in the right arm and hand one week later, and dyspnoea after a further fortnight.

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