Reduction of Incidence of Prematurity by Folic Acid Supplementation in Pregnancy

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SUMMARY: Folic acid administered to pregnant Bantu, whose diet is low in folate, was associated with a significant reduction in the incidence of prematurity. No such effect could be demonstrated in White patients subsisting on an average Western diet. This suggests that folate deficiency may contribute to the "pregnancy wastage" in populations whose dietary folate intake is low, and is a further indication for folic acid supplementation during pregnancy in these groups.

Introduction

A possible relation between folate deficiency and prematurity was suggested some 25 years ago when Callender (1944) reported an increased incidence of prematurity in megaloblastic anaemia in pregnancy. This was confirmed by Gatenby and Lillie (1960), but no such association could be demonstrated by Karthigaini *et al.* (1964), Chanarin *et al.* (1965), or Giles (1966). Similarly, it is doubtful if less severe degrees of deficiency, as revealed by tests of folate nutrition, are associated with a higher incidence of prematurity (Husain *et al.*, 1963; Martin *et al.*, 1967; Whiteside *et al.*, 1968). If there is a relation between folate deficiency and prematurity it might be anticipated that folic acid administered to pregnant women with low dietary folate intake would result in a reduction of the incidence of prematurity. In the course of a study of the effect of folic acid and vitamin B_{12} supplementation in pregnancy in two groups of patients—one Bantu, whose diet is poor in folate, and the other White, subsisting on an average Western diet—it was noted that folic acid significantly reduced the incidence of prematurity in the Bantu group but not in the White patients.

Material and Methods

Subjects Studied.—The patient material has been previously described (Metz *et al.*, 1965; Edelstein *et al.*, 1966, 1968). All patients were attending antenatal clinics at the Baragwanath and South Rand Hospitals, Johannesburg. The diet of the Bantu patients consisted mainly of maize meal eaten as a porridge boiled in water. Vegetables were eaten infrequently, and then almost invariably after boiling in water for long periods. The White patients were subsisting on an average Western diet, with 75% of them taking uncooked green vegetables and fruit daily.

Procedure.—Patients were allocated by random numbers to three groups. Group 1 received 200 mg. of iron by mouth, group 2 received 5 mg. of folic acid daily by mouth in addition to the iron, and group 3 received 50 µg. of vitamin B_{12} by mouth in addition to the folic acid and iron. In the White patients supplementation was started after the 24th week. The Bantu subjects tended to present at the antenatal clinic later in pregnancy and supplementation was started after the 28th week in this group.

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Results

When multiple births were excluded, birth weights were available in 183 Bantu and 172 Whites. The distribution of the birth weights in the Bantu groups receiving various supplements is shown in Fig. 1 and in the White groups in Fig. 2. Of the 63 Bantu who received iron only, infant birth weight was less than 4 lb. (1,815 g.) in 13 (20%). By way of contrast, in Bantu who received folic acid, birth weights were 4 lb. or greater in all. No such difference was apparent in the White patients, where the number of infants of birth weights of less than 5 lb. (2,270 g.) was similar irrespective of the type of supplementation. For the Bantu patients the difference in the number of premature births, defined as those under 5 lb., between the group receiving folic acid and the group receiving iron only was highly significant, as Table I shows.

TABLE I

	Over 5 lb.	Under 5 lb.	
Iron	44	19	63
Iron + folic acid	61	4	65
Total	105	23	128

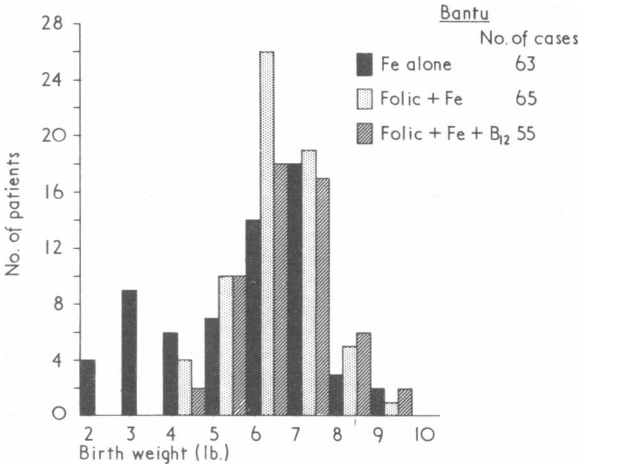

FIG. 1.—Distribution of birth weight of infants of Bantu mothers receiving various supplements in pregnancy.

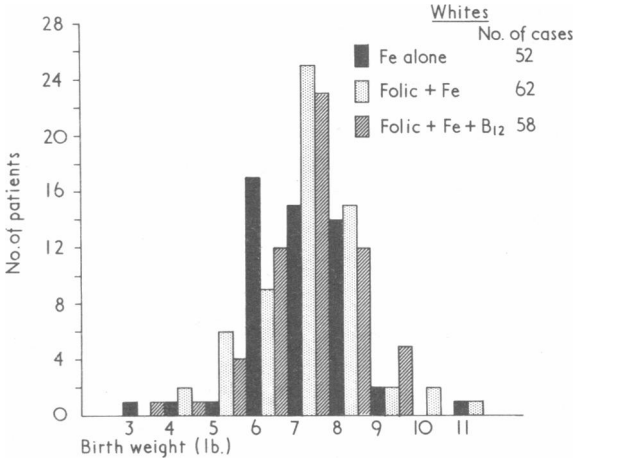

FIG. 2.—Distribution of birth weights of infants of White mothers receiving various supplements in pregnancy.

A test of independence for the above gives a continuity corrected χ^2 (1 D.F.) of 10·9 and a corresponding probability of occurrence by chance of 0·001. Since we expect that without the addition of the folic acid the high Bantu prematurity rate would persist, a one-sided test is more appropriate and the actual probability level is 0·0005.

The mean values of the various groups studied are shown in Table II. The usual Student *t* test for difference in means

TABLE II.—*Mean Birth Weight of Infants of Bantu and White Mothers Receiving Various Supplements during Pregnancy*

Group	No. of Patients	Supplementation	Birth Weight in lb.	
			Mean	S.D.
Bantu	63	Iron	5·48	1·83
	65	Iron + folic acid	6·22	1·05
	55	Iron + folic acid + B_{12}	6·38	1·13
White	52	Iron	6·92	1·28
	62	Iron + folic acid	7·03	1·33
	58	Iron + folic acid + B_{12}	6·91	1·22

would be inappropriate, since the distribution of birth weights in the group of Bantu patients who received iron only is highly abnormal. As seen in Fig. 1 it is skewed to the left, and the variance in these birth weights is significantly higher than that of the other five groups, both the result of the high prematurity rate for this group. For the other groups, however, the *t* test and its generalization to more than two groups (one-way analysis of variance) are appropriate and were performed. The mean birth weight of the Bantu group receiving vitamin B_{12} in addition to folic acid and iron was not significantly different from that of the group receiving folic acid and iron only. In the White group the differences in the mean values were not statistically significant.

Of the 13 Bantu patients with infants of birth weight less than 4 lb. ante-partum haemorrhage had not occurred in any. The incidence of ante-partum haemorrhage for the whole Bantu group was 2 out of 183.

Discussion

The aetiological role of folate deficiency in megaloblastic anaemia in pregnancy and the ability of folic acid supplementation to prevent this anaemia is well established (Lowenstein *et al.*, 1955). An association between abnormalities in tests of folate nutrition and other complications of pregnancy (accidental haemorrhage, abruptio placentae, abortion, fetal abnormalities, premature delivery) has been found by some workers but not by others (Hourihane *et al.*, 1960; MacKenzie and Abbott, 1960; Coyle and Geoghegan, 1962; Hibbard and Hibbard, 1963; Hibbard, 1964; Martin *et al.*, 1965; Menon *et al.*, 1966; Thambu and Llewellyn-Jones, 1966; Streiff and Little, 1967). Very significant, however, is the absence of controlled studies showing the prevention of these complications by folic acid supplementation. A recent review concluded that with the exception of megaloblastic anaemia "it has yet to be proven that prophylactic folic acid supplements will lessen the hazards shown to be associated with folate deficiency" (*Nutrition Reviews*, 1968, **26**, 5).

Previous attempts have been made to demonstrate a relation between tests of folate nutrition in pregnancy and prematurity. Husain *et al.* (1963) failed to show an increased incidence of premature delivery in women with excessive formiminoglutamic acid excretion. Whiteside *et al.* (1968) found evidence, suggestive of a correlation between serum folate and prematurity, but this was not confirmed by statistical analysis. Martin *et al.* (1967) reported a significant association between serum folate level and fetal weight, but the association disappeared when cases of uterine bleeding were excluded. This was not the case in the present study, where uterine bleeding was not related to the incidence of prematurity. In an earlier study Martin and Davis (1964) failed to show an effect on fetal growth in a group of Australian women treated with folic acid as early as the eighth week of pregnancy.

The reduction in the incidence of prematurity in the Bantu patients in the present study is evidence of a beneficial effect of folic acid supplementation in pregnancy, other than its prevention of megaloblastic anaemia. The demonstration of this effect in the population subsisting on a suboptimal diet is of considerable importance, but not in the group subsisting on a relatively good diet. This may explain why an association between complications in pregnancy and tests of folate deficiency has been found in some studies but not in others; subtle differences in diet, not necessarily manifest in changes in tests of folate nutrition, may be responsible.

Routine supplementation with folic acid to prevent megaloblastic anaemia is the rule in many antenatal clinics. The results of the present study suggest a further indication for supplementation in populations subsisting on a suboptimal diet—that is, the reduction of prematurity and "pregnancy wastage." The mechanism whereby folic acid reduces the incidence of prematurity is unknown. The most obvious explanation is the accepted role of folate in deoxyribonucleic acid synthesis and cell growth.

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