

Folate supplements during pregnancy

K. H. TRIGG, M.R.C.G.P., D.Obst.R.C.O.G.

E. J. C. RENDALL, M.D., M.R.C.P.

General practitioners, South-east England Faculty of the Royal College of General Practitioners

A. JOHNSON, Ph.D., M.I.S.

Medical Research Council, Statistical Research Unit

F. R. FELLINGHAM

T. A. J. PRANKERD, M.D., F.R.C.P.

Professor of Clinical Haematology, University College Hospital, London

SUMMARY. In a controlled, prospective trial, the effects of giving ferrous sulphate 50 mg daily to 76 pregnant women was compared with giving ferrous sulphate 50 mg daily plus folic acid 0.5 mg daily to 82 women in 12 general practices in South-east England.

No differences in obstetric complications were found between the two groups, although the evidence of some of the listed complications may be too rare for detection in a sample of patients of this size.

Introduction

Reports on the value of folate supplements in pregnancy are at variance with one another, (Chanarin, Rothman and Berry, 1965; Chisholm, 1966; Fletcher, Gurr, Fellingham, Prankerd, Brant and Menzies, 1971; Pritchard, Scott and Whalley, 1971; Rae and Robb, 1970; Scott, 1954).

In England, particularly in the south, anaemia which is preventable by supplements of folic acid is uncommon. Elsewhere its prevalence varies and may be related to dietary and social conditions. In some of the studies of folic acid in pregnancy there has been no demonstrable effect of folic acid in preventing complications of pregnancy and birth defects, but there is also disagreement on the relationship between folate deficiency and these complications. (Streff and Little, 1967; Thambu and Llewellyn-Jones, 1966). In the United Kingdom folate supplements are still widely prescribed in pregnancy and the present trial was undertaken in ten general practices of varying character in South-east England to investigate their effects.

Methods

General practitioners in the former South-east England Faculty of the Royal College of General Practitioners (now South-west Thames and South-east Thames Faculties) were asked if they would co-operate in a trial of ferrous sulphate versus ferrous sulphate plus folate treatment.

If agreeable, they would include in the trial pairs of consecutive patients, for whom they were providing either antenatal or complete medical maternity services. The co-operation of the obstetricians who would be responsible for the majority of the deliveries was sought, and their agreement to giving either treatment to alternate patients was obtained.

The objects of the trial were explained to the patients at the time of their potential entry and their agreement to taking either of the tablets was obtained. The doctors participating were supplied with a questionnaire which was completed with the patient on the first attendance, at six months of pregnancy, and after labour.

At the first two attendances blood was taken for haematological and chemical tests. After the first test patients were randomly allocated to one of the two treatments which was either a minimum of 50 mg of ferrous sulphate daily or a minimum of 50 mg of ferrous sulphate plus 0.05 mg of folic acid daily, and afterwards allocation was in sequence.

It was possible for the participating doctors to make the additional investigations at the routine visit of the patients for antenatal care. Furthermore, blood tests were indicated at this time and an extra quantity of blood was, therefore, taken for the additional tests. This was important, both to get volunteers among the doctors and also to avoid putting the patients to any additional discomfort or inconvenience. Blood specimens were collected in sequestrene and posted to University College Hospital where haematological measurements were made by Coulter counter. Serum iron was estimated in clotted blood by the automatic method of Young, Jocelyn, and Hicks (1965), and serum folate and red cell folate were assayed by methods of Hoffbrand, Newcombe, and Mollin (1966). Red cell folate is stable at normal temperatures for seven days and serum folate does not vary more than five per cent after postage times of up to four days (Fellingham, 1976; personal communication).

The distributions in the two treatment groups of all discrete variables were compared using chi-squared tests. The data for red cell folate, serum folate, and serum iron were transformed logarithmically before analysis to normalise their distributions. Comparisons between the means of these data, haemoglobin, and packed cell volume for the two treatment groups at first attendance have been made using Student's *t*-test; mean birth weights have been compared similarly. Comparisons of the mean changes in the haematological variables between the two attendances have been made by analysis of the differences using Student's *t*-test.

Results

Twelve practices distributed over a wide part of the South-east of England took part in the trial and no differences were found on analysis of the distribution of the social classes of the patients amongst them. A total of 158 patients were included in the trial; 76 received ferrous sulphate only, 82 received ferrous sulphate and folic acid.

Initial examination

Table 1 shows the means (\pm standard error) of the haematological variables in the two treatment groups on first attendance and at six months of pregnancy. Mean birth weights for the

TABLE 1
MEANS (\pm SE) OF HAEMATOLOGICAL VARIATES PRE-TREATMENT AND AT 6 MONTHS OF PREGNANCY
AND BIRTH WEIGHTS BY TREATMENT

<i>Variate</i>	<i>Treatment</i>	<i>Pre-treatment</i>	<i>At 6 months pregnancy</i>
<i>Haemoglobin</i> (g/100 ml)	1	12.76 \pm 0.12 (76)	12.27 \pm 0.12 (73)
	2	12.81 \pm 0.09 (82)	12.34 \pm 0.12 (74)
<i>Red cell folate**</i> (ng/ml)	1	2.39 \pm 0.02 (72)	2.38 \pm 0.02 (63)
	2	2.37 \pm 0.02 (74)	2.50 \pm 0.03 (65)
<i>Serum folate**</i> (ng/ml)	1	0.71 \pm 0.02 (73)	0.64 \pm 0.02 (64)
	2	0.71 \pm 0.02 (74)	0.88 \pm 0.03 (59)
<i>Serum iron**</i> (μ /ml)	1	2.13 \pm 0.02 (66)	2.12 \pm 0.02 (63)
	2	2.11 \pm 0.02 (74)	2.05 \pm 0.02 (63)
<i>Packed cell volume</i> <i>Per cent</i>	1	39.07 \pm 0.34 (76)	37.55 \pm 0.41 (73)
	2	39.24 \pm 0.27 (82)	37.61 \pm 0.61 (74)
<i>Birth weight</i> (gms)	1	3452.1 \pm 71.5 (72)	
	2	3366.3 \pm 60.0 (77)	

*Treatment: 1.50 mg ferrous sulphate daily; 2.50 mg ferrous sulphate and 0.05 mg folic acid daily.

**Means (\pm S.E.) of logarithmically transformed data are quoted. Figures in parentheses are the sizes of each group.

two treatments are also shown. No statistically significant differences between the two groups of patients were found in their age distributions, maturity at first and second visits, social class,

general-practitioner referral, or previous pregnancies. There were no significant differences between the mean haemoglobin, red cell folate, serum folate, serum iron, and packed cell volume of the two groups at the first consultation.

Second consultation

At the second consultation, the level of haemoglobin and packed cell volume had fallen significantly in both groups and both red cell folate and serum folate had risen significantly in the group prescribed folic acid supplements, indicating that patients in this group had been taking their folic acid and had been provided with enough to maintain normal blood levels.

No significant differences were found between the two treatment groups in the changes in haemoglobin and packed cell volume levels between the first and second visits. There were small, but significant, falls in serum iron in the group given iron and folic acid, but not in that given iron alone; the significance of this is not clear. The prevalences of pre-eclampsia, threatened abortion and antepartum haemorrhage, live and still-births, malformations, and post-partum complications were similar in the two groups.

Discussion

In this trial the administration of folic acid to a group of pregnant women produced no increase in their mean haemoglobin levels during pregnancy, and this is in accord with the other trials which have been published from the south of England. It is, however, in contrast to findings in other parts of England (e.g. Liverpool) where folate supplements have reduced the incidence of anaemia. Similar effects have been seen in other parts of the world.

No beneficial effects of folate supplements in preventing various complications of pregnancy and labour were found, but some of these may be too rare for detection in a sample of patients of this size. The findings of different trials suggest that folate deficiency follows certain geographical distributions (World Health Organisation, 1972) and may be primarily related to social living conditions.

The areas involved in South-east England in this trial appear not to be those where folate supplementation is beneficial, and the decision of whether or not to give these supplements must depend on a knowledge of the risks to the population in the area concerned. Some women, such as those with multiple pregnancies, known inadequate diet, or with haemolytic anaemia, are always at risk and should, in any case, be given folate supplement.

Acknowledgements

The following members of the South-east England Faculty of the Royal College of General Practitioners co-operated in this trial and we are grateful for their help and also to Mr. A. Todd for help with analysing the data: Drs G. A. E. Baker, Eaglefield Green; J. A. Barlas, Tonbridge; C. Clissold, Dorking; J. N. Graham Evans, Bognor; A. V. Griffiths, Horley; E. J. C. Kendall, Epsom; D. P. Mason, Camberley; D. J. E. Newley, Crawley; J. F. S. Nicholson, Canterbury; R. M. Palmer, Bognor; R. M. Powell, Horley; M. G. Ridley, Horley; J. S. Seaton, Crayford; K. H. Trigg, Merstham.

REFERENCES

- Chanarin, I., Rothman, D. & Berry, V. (1965). *British Medical Journal*, **1**, 480-485.
 Chisholm, M. (1966). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **73**, 191-196.
 Fletcher, J., Gurr, A., Fellingham, F. R., Pranker, T. A. J., Brant, H. A. & Menzies, D. N. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **78**, 781-785.
 Hoffbrand, A. V., Newcombe, B. F. A. & Mollin, D. L. (1966). *Journal of Clinical Pathology*, **19**, 17-28.
 Rae, P. G. & Robb, P. M. (1970). *Journal of Clinical Pathology*, **23**, 379-391.
 Scott, J. M. (1954). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **61**, 646-651.
 Streiff, R. R. & Little, A. B. (1967). *New England Journal of Medicine*, **276**, 776-779.
 Thambu, J. & Llewellyn-Jones, D. (1966). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **73**, 930-933.
 World Health Organisation (1972). Technical Report Series No. 503. Geneva; W.H.O.
 Young, D. S. & Hicks, J. M. (1965). *Journal of Clinical Pathology*, **18**, 98-102.