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FOLATE AND FETAL ABNORMALITIES: THE PREVENTION OF NEURAL TUBE DEFECTS

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Summary

Neural tube defects are a major cause of mortality and morbidity perinatally, in infancy, and in childhood. Recent observational studies and randomised controlled trials have confirmed that an increased maternal intake of folic acid in the periconceptional period prevents a significant proportion of neural tube defects in offspring. The challenge now is to translate this finding into effective public health practice.

I. INTRODUCTION

Birth defects affect 5% of all children (Bower et al. 1992) and yet the causes of most of them are still unknown. The recent confirmation that folic acid prevents a significant proportion of a major group of birth defects - neural tube defects - is therefore of great importance.

II. NEURAL TUBE DEFECTS

Neural tube defects (comprising anencephaly, spina bifida and encephalocoele) affect almost two in every thousand births in Australia (Bower et al. 1984). Closure of the primary neural tube in the human embryo is normally completed by 26-27 days after ovulation (40-41 days from the first day of the last menstrual period). Complete cranial non-closure results in the defect of **anencephaly, an encephalocoele** is a herniation of meninges and brain through a localised skull defect, and failure of closure occurring in the cervical, thoracic, lumbar or sacral regions is called **spina bifida.** Infants with anencephaly are stillbom or die within the first day or two of birth. About a quarter of infants with spina bifida or encephalocoele are stillbom, and almost a half do not survive the first year of life. Survival is often associated with considerable handicap, including weakness or paralysis of the lower limbs, urinary and faecal incontinence and hydrocephalus, and intellectual handicap may also be present.

Women who have had an affected infant are at an increased risk of having another affected child in a subsequent pregnancy (5% risk of recurrence), and close relatives of an affected person also have a risk greater than that of the general population (Elwood and Elwood 1980).

Because of the high mortality, the severity of handicap in the survivors, and their relatively common occurrence, neural tube defects have been intensively studied, with the aims of understanding the etiology, of improving treatment for the surviving infants, and of fmding methods of prevention.

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III. PREVENTION OF NEURAL TUBE DEFECTS

Secondary prevention of open neural tube defects is now possible by means of prenatal diagnosis of the defects, and the temlination of affected pregnancies. South Australia is the only state with a population-based screening program in Australia, where 85% of pregnant women are screened during the second trimester of pregnancy, and 80% of neural tube defects are identified (Robertson 1991). However, screening programmes do not address the issue of primary prevention, that is, preventing the formation of these defects in the first instance.

IV. EPIDEMIOLOGICAL STUDES OF DET AND NEURAL TUBE DEFECTS

Early studies in the sixties and seventies suggested a role for some aspect of diet as a cause of neural tube defects (eg Hibbard and Smithells 1965; Knox 1972; Smithells et al 1976) and led to two important studies, published in the early eighties (Smithells et al. 1980; Laurence et al. 1981). The first of these was a trial of periconceptional multivitamin supplementation (including 0.36mg of folic acid) to prevent recurrences of neural tube defects in women who had already had at least one affected infant. Controls were women not wishing to take part in the study, or who were already pregnant when referred to the study centres. Five percent of infants of unsupplemented mothers developed a neural tube defect (as expected), while only 0.6% of the infants of supplemented mothers were so affected. A continuation of this study design produced similar results (Smithells et al. 1981; Smithells et al. 1983; Smithells et al. 1989). The major criticism was the lack of random assignment of mothers to the intervention.

The study of Laurence et al. (1981) was a randomised controlled trial of periconceptional folate supplementation (4mg daily), again in women with a previous pregnancy affected by a neural tube defect. The recurrence rate was 3% in the treated group, less than half that seen in the placebo group (8%). However, there were only 111 infants in the entire study, and the difference was not statistically significant.

Because of the methodological limitations of these studies (summarised by Wald and Polani 1985), several further observational studies and trials were undertaken (see Table below).

In the Atlanta study, mothers taking multivitamins every month for the three months before pregnancy and for the first three months of pregnancy were compared with mothers not taking any vitamins over that period, and found to have a 60% lower risk of neural tube defect (Mulinare et al. 1988). A second US case-control study showed no association of either multivitamins or folic acid and neural tube defects (Mills et al. 1989). A third US study was a cohort study, in which vitamin supplementation was ascertained in early pregnancy, and the women were followed up to determine the outcome of the pregnancy. 73% reduction in risk was seen, associated with periconceptional multivitamin use, and largely confined to women taking folic acid (Milunsky et al. 1989).

Our own study in Western Australia, was also a case-control study, in which we sought information on periconceptional intake of folic acid in the diet and as supplements. Using a food frequency questionnaire, we found a significant dose-response relationship of decreasing risk of neural tube defects with increasing dietary folic acid (Bower and Stanley 1989). There was also a non-significant protective effect of periconceptional folic acid supplements (Bower and Stanley 1992). In the non-randomised trial of folate supplementation from Cuba, there were no recurrences in the supplemented CB18Tgroup, but 3.5% recurrence risk in the unsupplemented

Proc. Nutr. Soc. Aust. (1992) 17

group (Vergel 1990).

Table 1. Recent Studies of Folate/multivitamins and Neural Tube Defects

Reference and Location	Study design	Total subjects (no of cases)	Periconceptional exposure method	Outcome measure	Findings
Mulinare et al. 1988 Atlanta, USA	case-control	3176 (347)	Multivitamins	Occurrent NTD	Protective
Mills et al. 1989 California, Illinois,USA	case-control	1690 (571)	Multivitamins folic acid supps	Occurrent NTD	No effect
Milunsky et al. 1989 Boston, NE, USA	cohort	22776 (49)	Multivitamins folic acid supps	Occurrent NTD	Folic acid Protective
Bower&Stanley 1989,1992 ~~Boston, NE, USA~~ WA, Australia	case-control	308 (77)	- Dietary folate - folic acid supps	Occurrent NTD	Protective
Vergel et al. 1990 Cuba	non-randomised trial	215 (4)	Folic acid	Recurrent NTD	Protective
MRC Vitamin Research Group 1991, Multicentre, UK	RCT	1195 (27)	Multivitamins folic acid, placebo	Recurrent NTD	Folic acid Protective
Czeizel and Rode, 1984 Hungary	RCT	-	Multivitamins	Occurrent NTD	Completed results not published
Berry et al. 1990 China	RCT	-	Not decided yet	Occurrent NTD	Planning stage only

However, the very best evidence so far has come from the randomised controlled multicentre trial (Medical Research Council Vitamin Study Research Group 1991). A significant 72% reduction in risk of recurrence was seen in women taking folic acid supplements, compared with those not taking folic acid. No protective effect was seen with multivitamins.

Preliminary results from the Hungarian trial (Czeizel and Rode 1984) indicate that the risk of neural tube defects is reduced amongst those women taking the folate-containing vitamin supplements, compared with those taking the placebo.

Taken together, these studies provide strong evidence of a protective role of some aspect of nutrition, and the powerful evidence from the MRC trial is convincing that folic acid is a major candidate.

V. FOLIC ACID

Humans are wholly dependent on food as their source of this vitamin, found especially in leafy green vegetables, but also in a wide variety of fruit, vegetables, liver, and other foods.

As very little is stored in the body, inadequate intake rapidly leads to clinical signs of folate deficiency (Davis, 1986).

Maternal folate status, and hence the availability of maternal folate for the developing embryo and fetus, is dependent on a number of factors, including the dietary content of folic acid, supplementation with folic acid, the presence of folate antagonists such as some drugs, deconjugation and absorption of folic acid from the gastro-intestinal tract, metabolism and excretion of folic acid, folic acid transport in the body and across the placenta, and the interrelationships of folic acid with other vitamins and metabolic processes. It is also plausible that an abnormality may be entirely fetal, although able to be overcome by adequate maternal folate status. It is unlikely that folic acid is the only cause for neural tube defects. Other nutrients may also be important, for example vitamin B12 (Schorah et al 1980) and zinc (Sever 1982), and there may be factors unrelated to diet which account for a proportion of cases. Nevertheless, the evidence to date suggests that increased folic acid intake (either in diet or as folic acid supplementation) in the periconceptional period prevents the majority of neural tube defects.

VI. PUBLIC HEALTH IMPLICATIONS

There are still many unanswered questions, such as how much folic acid is enough, how long before pregnancy must folate intake be increased, might other nutrients in addition to folic acid be important, and how does folic acid work. Several studies point to abnormalities in folate metabolism in either the mother or the fetus (Yates et al. 1987; Steegers-Theunissen et al. 1991; Habibzadeh and Smithells 1990), although the final pathway to failure of closure of the neural tube is still unclear. This is an important area for research, as the elucidation of the underlying mechanisms may lead to the identification of high risk groups of mothers to whom preventive measures could be specifically directed.

However, there is now enough evidence to embark on efforts to increase intake of folic acid in women of child-bearing age. Because the neural tube closes so early in pregnancy, it will not be sufficient for women to only begin folic acid supplementation once pregnancy is confirmed.

Folate intake can be increased by supplementation; by increased dietary intake of folate-containing foods; and by food fortification of staple foods, such as breakfast cereals or bread. Although supplementation may be simpler and easier to address, a dietary prevention offers several advantages. Improving the dietary intake of folic acid in women of childbearing age in general avoids the problems of when to take supplements, and of unplanned pregnancy, and dietary prevention does not add to the already considerable medicalisation of pregnancy. Folate rich foods have other advantages: they tend to be high in other important nutrients (eg beta-carotene, vitamin C), low in fat and cholesterol, and are probably less likely than folate supplementation to lead to excessive intake and precipitation of other vitamin deficiencies, such as vitamin B12. There will undoubtably be difficulties in achieving either total population supplementation, or dietary intervention, and hence food fortification, such as exists with cereals in the USA and Britain, should be considered in Australia.

The confirmation that this major group of birth defects can be prevented by nutritional means is "one of the great medical advances of the century" (Elwood 1983). The challenge now is to translate this finding into effective public health practice.

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