Folate and neural tube defects

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The multifactorial aetiology of neural tube defects has stimulated many theories related to dietary factors in pregnancy. The results of the Medical Research Council Study confirm that folate has a protective effect if taken in the 3 months prior to conception and for the first timester. The dosage recommended is 5mg daily for women at risk for recurrence of spina bifida or anencephaly and 0.5mg daily for those at low risk. Dietary modification to include foods with high folate such as leafy green vegetables and wholemeal grain is not considered sufficient. Fortification of staple food items such as bread and cereals with folate is being considered in some countries. A comprehensive health education programme is essential, directed to women in the reproductive age group and to doctors involved in primary care, family planning and obstetric management. The incidence of neural tube defects could be reduced by 70% with the introduction of folate supplementation in all pregnancies.

Malformations which result from defective closure of the neural tube are anencephaly, meningomyelocoele and encephalocoele. Closure occurs in the third week of fetal development and proceeds in two directions – both cephalad and caudad. The general term, spinal dysraphism is used to refer to open and closed defects, which can be induced experimentally. An alternative mechanism of rupture of the neural tube has been proposed, and this occurs at a slightly later time in development. Anencephaly is absence of the cranial vault and brain and is incompatible with life.

Encephalocoele is protrusion of the cranial contents and is associated with high perinatal mortality or severe physical and intellectual disability in survivors.

Meningomyelocoele is a cystic protrusion of the spinal cord and results in defective function of the cord below the level of the lesion with paraplegia and incontinence. Associated hydrocephalus causes specific learning difficulties. Survival rates are 50% past 6 months of life and the disability is so significant that there are criteria for selection for treatment.

Incidence rates for these abnormalities have varied throughout the ages. There are world-wide trends, and strange parallels have been noted in seasonal peaks and sex ratios.

Perinatal mortality figures for New South Wales are available from 1958 to 1990 and show a downward trend which is partly due to true decrease in incidence which has been observed world-wide, and partly to changes in diagnostic procedures which identify cases before 20 weeks of pregnancy, thus facilitating early termination which is not notifiable to Australian Bureau of Statistics. True incidence figures from multiple data sources are available from 1965 to 1990, and show a less marked downward trend.

Epidemiological studies have shown variations by race, country, area, social class, and parental occupation. Dietary factors have occasioned wide interest.

The aetiology of neural tube defects is said to be multifactorial, and is a genetic-environmental interaction. A polygenic predisposition provides a background risk with a threshold effect which is exceeded by an environmental trigger.

The genetic component accounts for less than 10% of cases. 90% occur sporadically. There is a 5% recurrence risk after one affected case. Twin studies confirm 5% concordance rates.

Many environmental factors have been incriminated such as pesticides, heat waves, toxins, caffeine and a variety of dietary agents ranging from tannin in tea, through nitrites in meat preservatives to solanine in blighted potatoes.

Hibbard and Smithells[1] suggested in 1965 that vitamins may play a role in the prevention of neural tube defects.

This initial article was followed by studies published by Smithells et al. in 1976[2] and 1981[3]. Laurence proposed that the active agent was folic acid in 1981[4]. This suggestion was supported by the identification of high risk groups such as aboriginal women, who are known to be folate deficient, women on folate antagonists such as septrin or aminopterin in pregnancy, and those with coeliac disease.

Due to criticism of the structure of the published studies, and uncertainty about the active component of vitamin supplements, the Medical Research Council Study was proposed and started in 1983. There were ethical objections to such a study on the grounds that withholding vitamins from women at risk of having a child with a neural tube defect was wrong. The lack of information about the efficacy of supplementation and possible harmful effects of the use of multivitamins was considered to outweigh these objections and the trial

which involved 33 countries, was allowed to proceed. There was a strict protocol to be followed for all centres participating in the trial which was randomized to avoid bias, and double blind using a placebo to avoid preferential self-medication.

There were four treatment groups using a factorial design:

A – Minerals and folic acid
B – Minerals and folic acid and multivitamins
C – Minerals and placebo
D – Minerals and multivitamins (no folic acid)

This allowed the following comparisons:

A+B vs C+D tested the effect of folic acid
B+D vs A+C tested the effect of other vitamins.

Supplementation was commenced at least three months before conception and continued until 12 weeks gestation.

Blood and urine specimens were collected on entry to the study and at three-month intervals to check compliance and response to therapy. The dosage of folate was 4mg daily. The composition of the vitamin preparation was:

Vitamins
A (4000U)
B-1 (thiamin – 1.5mg)
B-2 (riboflavin – 1.5mg)
B-6 (pyridoxine – 1.0mg)
C (40mg)
D (400U)
Nicotinamide (15mg)

Minerals
Iron (dried ferrous sulphate – 120mg)
Calcium (di-calcium phosphate – 240mg).

The study was monitored using sequential analysis so that when a clear result was apparent this would be acknowledged and further recruitment of cases would cease. A clear 72% protective effect of folate supplementation was noted after 1817 women had participated in the study.

Six recurrences occurred in 593 pregnancies supplemented with folate (A+B) while 21 were noted in 602 pregnancies which did not have folate supplements (C+D).

There was no effect of either multivitamin or mineral supplementation alone.

This supports the result obtained by both Laurence in 1981[4] and by Smithells group[2]. Three further studies[5-7] yielded similar effects, while one by Mills et al. in 1989[8] did not demonstrate any protective effect of folate.

Studies of red cell and serum folate and serum zinc revealed no significant differences in levels of affected and unaffected pregnancies.

The results of the Medical Research Council Study provide vital information about the value of folate in preventing a proportion of recurrences of neural tube defects. However several questions require further clarification.

- Does this finding relate to the prevention of sporadic cases? Will the widespread use of folate supplements in pregnancy prevent 72% of all cases of neural tube defects? The study group conclude that the mechanism for recurrence is identical to that for first cases in a family.
- What dosage is effective? The original study of Smithells used 0.36mg of folate and a recent study in Hungary suggests that 0.4mg of folate may be effective.
- How can folate supplements be provided to the relevant population without harm to others? There are concerns that the use of folate may mask the symptoms of vitamin B12 deficiency. Foodstuffs rich in folate such as leafy green vegetables, wholemeal bread and yeast can be recommended in increased quantities. However, should certain staple dietary items be fortified with folate? Cornflakes and branflakes are already fortified in the United Kingdom, but representation needs to be made to the appropriate authorities in Australia for this to be approved.
- Should all women be advised to take folate tablets prior to conception? At present 5mg folate tablets only are available in Australia. The mechanism of action of folate in protecting against neural tube defects is not known. It appears to act at a certain point in the metabolic pathway in methionine synthesis related to hyperhomocysteinaemia which has an increased risk of vascular fragility.

Further studies are proceeding in this area. Widespread supplementation with folate may also prevent the occurrence of other malformations such as cleft lip and palate, tracheooesophageal fistula and gastroschisis which are thought to arise from a similar mechanism to neural tube defects because of the increased frequency in siblings of index cases.

Current recommendations in the USA suggest that all women of childbearing age who are capable of becoming pregnant should use 0.4mg of folate per day. Women who have had a baby with a neural tube defect are advised to take 4mg of folate for at least three months before conception and for the first three months of pregnancy.

Similar recommendations relevant to the Australian population, subject to the availability of the appropriate folate preparations, should be made as soon as possible.

References

1 Hibbard ED, Smithells RW. Folic acid metabolism and human embryopathy. Lancet 1965;i:1254.
2 Smithells RW, Shephard S, Schorah CJ. Vitamin deficiencies and neural tube defects. Arch Dis Child 1976;51:944-950.
3 Smithells RW, Shephard S, Schorah CH et al. Possible prevention of neural-tube defects by periconceptional vitamin supplementation. Lancet 1980;i:339–340.
4 Laurence KM, James J, Miller MJ, Tennant GB, Campbell H. Double blind randomized controlled trial of folate treatment before conception to prevent recurrence of neural tube defect. Br Med J 1981;282:1509–1511.

5 Milunsky A, Jick H, Jick SS et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA 1989;262:2874–2852.
6 Mulinare J, Condero JF, Erickson D, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. JAMA 1988;260:3141–3145.
7 Bower C, Stanley FJ. Dietary folate as a risk factor for neural tube defects; evidence from a case-control study in Western Australia. Med J Aust 1989;150:613–618.
8 Mills JL, Rhoads GG, Simpson JL et al. The absence of a relation between the periconceptional use of vitamins and neural-tube defects. N Eng J Med 1989;321:430–435.

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葉酸與神經管缺陷

摘　要

妊娠胎兒神經管缺陷的多方面病因激發了與膳食因素有關的許多學說，醫學研究委員會研究結果證實，如果在妊娠前三個月和妊娠后頭三個月進食葉酸有保護作用，他們建議胎兒有復發性脊柱裂和無腦畸型危險的婦女每日進食5毫克葉酸，而低危險的婦女每日進食0．5毫克葉酸。膳食改進包括供應含葉酸高的食物如綠葉青菜和粗麥制品等。在某些國家已開始考慮用葉酸强化主要食物，如面包和谷類食物。

一個內容廣泛包括了對生育年齡的婦女，對執行初級護理的醫生，家庭計劃和產婦的處理的健康教育計劃是重要的。所有妊娠婦女補充葉酸后可使胎兒神經管缺陷減少達70%。