POLICY REVIEW

Folic Acid in the Prevention of Neural Tube Defect - A Programme for Malaysia?

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Summary

There is good evidence that folic acid is safe and efficacious for reducing neural tube defect (NTD). All women capable of becoming pregnant should take 400 microgram daily. This can be given in the form of a daily vitamin supplement, by food fortification, or by increasing natural dietary folates. Compulsory grain fortification has been shown to reduce NTD in a population but supplementation and dietary advice have not. Malaysia should work towards a programme of grain fortification and use alternative strategies to reach sections of the population that would not be covered but several research questions need to be answered before a programme could be implemented in Malaysia.

Key Words: Neural tube defect, Folic acid, Malaysia, Preconception care, Pregnancy

Folic acid is the synthetic form of a wide range of naturally occurring folates. Compared to the naturally occurring folates, folic acid is more stable and more easily absorbed. After absorption both dietary folates and folic acid are reduced to tetrahydrofolate which is a co-enzyme for a variety of metabolic processes.

Neural Tube Defect

The two most common types of neural tube defects (NTD) are anencephaly and spina bifida. Anencephaly is invariably fatal whereas spina bifida may not be. Spina bifida is however considered to be one of the most severe and disabling congenital malformations of childhood. NTD's arise during the development of the neural tube prior to its closure at 4 weeks post fertilization, thus defects occur at a time when a woman may not realize that she is pregnant. NTD is one of the commonest congenital malformations worldwide. The birth prevalence is estimated 1 per 1000 total births but varies between populations[1].

Efficacy

The evidence for folic acid in the prevention of NTD is compelling. Epidemiological evidence began to appear in the 1980's[2-6]. Controlled trials began to appear in the 1990's and there are now 4 such trials[7-10]. These have been subjected to a Cochrane systematic review[11]. The summary relative risk reduction was 72% (95% confidence interval 47%-85%) and the absolute risk reduction was 0.8 per 1000 total births. In other words folic acid reduced the risk of NTD by 72% and an additional 0.8 per 1000 normal births annually could be attributed to folic acid supplementation. Although there is evidence for a reduction in other types of major birth defects including truncal conal cardiac abnormalities, congenital obstructive renal anomalies, congenital pyloric stenosis, and limb defects[8,10,12-14], the meta-analysis had insufficient power to answer this question. In the experimental group a small increase in conception, OR 1.12 (95% CI 1.03 - 1.22) was found. One trial also showed a reduction in vertigo, nausea and vomiting, OR 0.46 (95% CI 0.26 - 0.79). There were no

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adverse effects of supplementation, specifically no increase in spontaneous abortion or ectopic pregnancy and no reduction in stillbirth. The authors noted a trend towards increased multiple gestations but this did not reach statistical significance (OR 1.40 (95% CI 0.93 - 2.11). However, it has been suggested that caution is required as the increased perinatal mortality associated with multiple gestations may offset or partially offset any gains made by folic acid supplementation[15].

Safety

There is a minor safety issue with the administration of folic acid[16]. Both folic acid and vitamin B12 deficiencies result in a megaloblastic anaemia. Folic acid can correct the megaloblastic anaemia associated with either folic acid or vitamin B12 deficiency but if the B12 deficiency is left uncorrected it will eventually present with the typical neurological sequelae that culminate in subacute combined degeneration of the cord. Thus folic acid masks the early stages of B12 deficiency. Vitamin B12 status is part of a work-up for unexplained neurological disease in an adult. B12 deficiency is rare in women of reproductive age but one group at particular risk is the strict vegan. The importance of this issue has been debated at length and it has been concluded that the masking effect is rare when the daily intake of folic acid is below 1 mg[17-19]. This is the main rationale behind the CDC recommendation that a daily supplement should not exceed 1 mg[20].

There is also some concern that high doses of folic acid may cross the placenta and accumulate in the foetus. This is based on evidence from animal studies. However, there is no evidence from human studies in particular the large numbers of women subjected to randomised controlled trial. Nevertheless the CDC has listed pregnant women as one of the groups considered to be at risk of excessive intakes of folic acid[20]. Other reports on the potential risk of folic acid in malaria, epileptics and other situations have not been substantiated[16].

Dose

The currently recommended dose is 400 micrograms daily. This dose is derived from early uncontrolled studies but has subsequently been confirmed[21, 22]. Increasing dietary folate alone has been shown to be inadequate in achieving optimal folate status[23].

The 400 ug dose is recommended for one month before and 2 months after conception. Because 50% of pregnancies are unplanned[24-26], it is recommended that all women capable of becoming pregnant take folic acid daily either as a pill or in the form of fortified foods such as breakfast cereals.

Strategies for the administration of these policies

There are 2 main strategies for the delivery of folic acid. Supplementation by a daily folic acid pill, the first strategy, was recommended in the US in 1992 and UK in 1994[20, 26]. Other countries have followed suit. In both the US and UK there have been extensive health education campaigns to promote this policy and the effects of these have been monitored[27-39]. A US report by the CDC showed that in 1995 and 1997 respectively the percentage of women who had heard of folic acid was 52% and 63% and the percentage of women who took a supplement was 28% and 32% respectively. Knowledge that folic acid should be taken before pregnancy was very low at 7%. Over this period there was no decline in NTD[34]. In the UK following the implementation of a folic acid supplementation policy, there was a massive increase in prescriptions and over the counter sales of folic acid but no associated decline in NTD. In fact almost all the decline in NTD seen in the UK was seen prior to the adoption of this policy[40]. A study of 11 National birth defect registries failed to show any change in the rate of NTD that could be attributed to folic acid supplementation[41]. Birth prevalence may decline in response to increased prenatal diagnosis but without any change in the total incidence of NTD[42].

The failure of supplementation was behind the 1998 US introduction of compulsory grain fortification. All flours of grains including wheat, rice, corn and others were fortified at 140 micrograms per gram of grain. This level of fortification was adopted to meet the needs of the maximum proportion of the population while minimising exposure of the population to levels above 1 mg. Loss during cooking, the dietary intake of folate and additional dietary supplements containing folic acid were taken into account. Since 1998 there has been a significant decline in the prevalence of NTD[43]. The level of 140 micrograms per gram may be subject to change as there is continued lobbying of the FDA by groups including cardiologists, who would like to increase the proportion of the population whose intake is greater that 400 micrograms daily. However, more information is needed on the public health effects of higher doses. The UK is currently considering a policy of food fortification[44].

Whole grain rice, refined or unrefined can be fortified with folic acid but it is not practical since most of it

would be lost during grain washing and cooking[45]. Dry foods such as grains are particularly suited to folic acid fortification as folic acid stability is maintained. The fortification of wet foods such as soya sauce is not practical.

NTD in Malaysia

There are four studies on congenital abnormalities in Malaysia. They are all hospital based[46–49]. A study of 19,769 deliveries in Alor Star Hospital reported a birth prevalence of 1.53 per cent for major congenital malformation. The prevalence of anencephaly was 1.29 per 1000 births. A more recent unpublished study done in University Hospital Kuala Lumpur reported a birth prevalence of 1.56% for all congenital malformation present at birth or diagnosed in the first week of life. Of these 10.8 percent were due to NTD[49]. Another study described anencephaly in the hospital setting[50]. This suggests the birth prevalence of NTD is in the region of 1 per 1000 births and is not different from that reported in developed countries. From vital statistic reports there is no evidence for a decline in death due to NTD from 1991 to 1997[51]. A population-based study on the prevalence of NTD is currently underway in Perak and may be able to produce some population based data by 2003 (IRPA project 06-02-03-0586, The Epidemiology and Prevention of Major Birth Defects in Kinta, Perak). This study also aims to provide a working framework for an ongoing national birth defects registry.

In the University Hospital study the ratio of spina bifida to anencephaly was 1:2 which is the reverse of that reported in countries of predominantly European populations. Does this reverse ratio suggest other aetiologies besides low folic acid intake? Good up-to-date data on RBC folate levels in women of reproductive age are not available. The most recent published data was a study published in 1982 by Jaffar et al[52]. Serum folate levels were done on 104 women attending the antenatal clinic at Kuala Lumpur Hospital. The mean serum folate level was 5 ng/ml and 28% were found to have serum folate levels below the normal, 3 ng/ml. This compares with a mean of 7.4 ng/ml and 15% below the normal in a US national sample in 1976-80[53]. There has been considerable socioeconomic progress over the 20 years since then and this study would not be generalisable to antenatal women today. It could even be speculated that due to the year round abundance of fruit and vegetables in Malaysia, most women have higher RBC folate levels than is seen in temperate climates where the randomised controlled trials were done. This, along with the reverse ratio of spina bifida to anencephaly, raises the possibility that efficacy in the Malaysian population may be lower.

Research questions

What should we in Malaysia do about this public health issue? Do we need a folic acid programme? If so should we adopt a strategy of supplementation or food fortification?

We can't answer these questions without first asking others. Is folic acid efficacious in our population? The reverse ratio of spina bifida to anenecephaly suggests a possible difference in aetiology. This along with the lack of data on the folate status of the population suggests the systematic review may not be fully generalisable to Malaysia. Do we therefore need to do our own randomized controlled trial? Ideally all interventions should be subjected to this but trials are expensive and should not be undertaken lightly. In this case we may be able to obtain sufficient evidence from other sources. In 2 large areas of China, one in the north and one in the south, Berry at al gave folic acid to women at the time of marriage counseling. These areas were important as the northern region had a high incidence of NTD whereas the southern region had a low incidence. The women were monitored closely for folic acid intake and for the outcome of all pregnancies occurring over a 3 year period. There was a reduction in all types of NTD in both the high and low prevalence regions and this was greater in the high prevalence region so that after the intervention there was very little difference in the birth prevalence between the 2 regions[54]. In both regions the women were almost entirely from the Han ethnic group. This suggests that environmental rather than genetic factors accounted for the baseline difference and indeed the Southern region with the lower baseline prevalence was one of the wealthiest in China and had a longer growing season. Thus folic acid was effective in 2 very different settings. This provides some evidence that we might also expect folic acid to be effective in Malaysia. This study did not look at the effectiveness of folic acid on specific types of NTD and there is very little on this in the literature. However, data obtained from the US after the fortification programme was introduced showed twice the reduction in spina bifida compared with anencephaly but the reduction seen for both these conditions was statistically significant. It is still unclear whether the effectiveness of folic acid is dependant on the type of NTD.

In Malaysia a folic acid programme is likely to reduce the birth prevalence of NTD but this may be less than the 72% reduction seen in the efficacy trials. Our own RCT would quantify this difference but it would not tell us anything about effectiveness - the performance of this strategy in the clinical setting in contrast to the ideal setting of the randomised controlled trial. In our case it is effectiveness rather than efficacy that is the issue. We know that in the clinical setting supplementation has not been made to work on a long term basis but some evidence for the effectiveness of fortification now exists.

For us the more pressing questions are those that would provide evidence to support a fortification programme such as the RBC folate status of the population and the folate intake of both women capable of becoming pregnant as well as in the population as a whole. If the folate status of our population is higher than in countries where the trials were done then we could expect to see a smaller effect and of course a greater effect if out folate status was lower. How prevalent is vitamin B12 deficiency? Studies are needed to address this safety issue. If B12 deficiency is less common here then this issue will be less of a problem and a higher level of grain fortification could be used.

What type of grain does the population consume? Malaysia is a rice eating nation and while there are probably pockets of the population who eat only rice there are large segments, particularly in urban areas who eat flour based foods on a daily basis (predominantly rice and wheat based noodles and bread). Dietary surveys could answer questions on both grain intake and folate intake. The presence of sections of the population who do not eat flour does not contra-indicate the adoption of flour fortification. Other strategies could be used on these pockets of the population.

Is there another option to flour fortification? Some have suggested sugar? It is likely that the sugar intake of the population varies widely making this difficult to implement but we don't know. Is folic acid stable in sugar?

As the option of supplementation has not been shown to work in other countries do we have any reason to believe it might work better here? At the present level of evidence we would be foolish to embark on this unless we were able to show the unlikely situation where our population is more willing to take a daily supplement. Qualitative studies on the attitude and intention of the population towards supplementation may provide some information on this.

In summary, folic acid is efficacious in reducing NTD but the extent of this is uncertain in the Malaysian population and it may be reduced. There is evidence that fortification is more effective than supplementation but for fortification to be safe the level of fortification must be carefully estimated.

Fortification is the way we should go. We therefore need to establish the level of fortification needed to provide safe and effective levels of folic acid to the population.

It is hoped that those in the local research community with the skills to answer some of these questions can take them up and bring us forward in this issue.

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