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# Antenatal Prevention of Neural Tube Defects

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## 1. Introduction

Neural tube defects (NTDs) are complex congenital anomalies. Spina bifida and anencephaly which arise from failure of closure of the neural tube during embryogenesis are the most common forms of NTDs. While anencephaly is a lethal malformation, spina bifida is a common birth defect in which patients can suffer from a multitude of potential medical and surgical morbidities and increased risk of mortality throughout their life. The incidence and prevalence of NTDs varies in different parts of the world [1]. This is attributable to many factors including; geographic region, maternal age, obesity, ethnicity and socioeconomic status of the parents. However a declining trend has been seen in many countries. This in part may be explained by the availability of prenatal diagnosis, folic acid supplementation recommendations, folic acid food fortification initiatives and selective termination. Prevention of NTDs presents a complex problem as the underlying aetiologies of NTDs are an interplay of genetic, environmental and nutritional factors. Folate deficiency explains approximately 72% of NTDs cases and this chapter will primarily address the role of folic acid supplementation for the prevention of NTDs [2]. However, it is necessary to briefly review the metabolism of folate to understand how these prevention strategies were developed.

## 2. An overview of folate metabolism

Dietary folate polyglutamates need to be converted to monoglutamates before they can be absorbed. In the jejunum, polyglutamates are converted to monoglutamates by the enzyme  $\gamma$ -glutamyl hydrolyase prior to their absorption in the intestine. During absorption in the jejunum, the different monoglutamyl folates are converted to 5-methyltetrahydrofolate (5-MeTHF). 5-MeTHF is the principal circulating folate and is transported across the plasma membranes of cells and thus the principal form by which tissues are supplied with folate. Within cells, folate is involved in methylation reactions where it can either donate one carbon units for purine and thymidine synthesis or accept one carbon units from amino acids. There are three principal enzymes involved in these methylation reactions. Methylenetetrahydrofolate reductase (MTHFR) competes with thymidylate reductase (TS) and methylenetetrahydrofolate dehydrogenase (MTHFD) for one carbon units. MTHFR is controlled by S-adenosylmethionine. 5-MeTHF donates a methyl group via methionine synthase to homocysteine using Vitamin B12 as a co-factor to produce S-adenosylmethionine [3]. Homocysteine will accumulate when there are depleted amounts of folate or vitamin B12. S-adenosylmethionine is a key donor in the methylation of DNA,

proteins and lipids. It is also essential in the metabolism of certain neurotransmitters. This outlines the importance of folate metabolism in cellular function especially in rapidly dividing cells i.e. periods of rapid growth. It is here we see the importance of folate metabolism in the aetiology of NTDs.

### 3. Genetics: Variations in folate metabolism

Normal folate levels with high homocysteine levels have been observed in women who have delivered children with NTDs [4]. This is an indicator that there must be other factors contributing to the aetiology of NTDs. Several genes coding for folate dependent enzymes have been examined for mutations that could account for NTDs. One gene that codes for a folate dependent enzyme is C677T polymorphism of 5,10 methylenetetrahydrofolate reductase (MTHFR). The function of MTHFR is to regulate production of 5-MeTHF, the main plasma form of the vitamin. This thermolabile variant is associated with decreased enzyme activity [5]. The C677T thermolabile variant gene was observed in 18% of spina bifida patients versus 6% of a controlled group in a study carried out by Shields et al in Ireland [6]. Several other studies confirmed the increased risk of NTDs in the offspring of women with this variant gene. The major implication of this finding is that these are a subset of women who may have increased folate requirements [7]. Although other mutations of the MTHFR gene have been identified, along with mutations in other key genes encoding for enzymes used in folate metabolism none have been implicated yet as contributing to cases of NTDs [8].

### 4. Environmental

As described earlier the incidence of NTDs can vary with geography, socioeconomic status of the parents and there is a seasonal variation. Discordance in monozygotic twinning has also been reported in NTDs. This suggests that environmental factors may contribute to the aetiology of NTDs. A whole host of physical, chemical and infectious agents have been suggested as possible teratogens including; solvents, anaesthetics agents, X-radiation, viruses and paints [9]. One physical agent, hyperthermia has been investigated as a possible teratogen and a meta-analysis by Moretti et al in 2005 showed that maternal hyperthermia during critical periods of neural tube development is associated with an increased incidence of NTDs (OR 1.95) [10]. Of course one cannot forget the possibility of susceptible gene-environment interactions which could help explain the geographical and seasonal variations seen in the incidence of NTDs.

### 5. Nutritional

Folic Acid supplementation had been shown to prevent NTDs. There had been an explosion of scientific and clinical data since the first seminal work by Smithells et al more than thirty years ago [11]. The United Kingdom Medical Research Council Trial and the Hungarian Periconceptional folic acid supplementation randomised control trial in the early nineties outlined how folic acid supplementation could decrease the occurrence of NTD by 50-70% [2, 12]. This led to universal recommendations of periconceptional folic acid supplementation. A recent meta-analysis by the Cochrane collaboration identified five trials

which examined the prevalence of NTDs in women receiving folic acid supplementation, those receiving folic acid had a significantly reduced risk of having baby with a NTDs (risk ratio 0.28 95% confidence intervals (CI) 0.15 to 0.52) [13]. Indeed the evidence from these five trials is so overwhelmingly in favour of folic acid supplementation there has been a paucity of supporting trials since the year 2000. The recommendations are to take 400µg of folic acid daily (either from dietary sources or supplements) for at least one month before conception (World Health Organisation). This dosing regimen has been largely based on the association between maternal red cell folate (RCF) levels and the risk of NTDs.

## 6. Red cell folate and serum folate and its relationship to NTD

Irish researchers have made substantial contributions to the understanding of NTD epidemiology. In a large case-control study based on over 56,000 women attending the maternity hospitals in Dublin from 1986 to 1990, the folate and vitamin B12 levels of blood samples taken at the first ante-natal visit were noted as independent risk factors for neural tube defect [14]. Later, data representing the blood folate concentrations of NTDs cases (n = 84) and selected controls (n = 266) was used to calculate the degrees of risk of an NTDs birth [15]. Cases and controls were similar with regard to maternal age. All controls were representative of normal births. The red cell folate (RCF) level in early pregnancy emerged as a premier indicator of such risk. The overall NTDs rate was 1.9/1000 births in this study. They showed that the risk of NTDs is associated with RCF levels in a continuous dose-response relationship. The risk is reduced as RCF levels increase. With a RCF level of <150µg/l the risk of NTD is 6.6/1000 but if the RCF level is increased beyond 400µg/l the risk falls to 0.8/1000. The RCF levels can be increased over a 6 month period with doses of 400µg of folic acid which can reduce the risk of NTDs by 47% [15]. This dose is also considered safe. However, in the context of food fortification programmes it may be worth reviewing this recommendation. There is no consensus on the minimal effective dose of folic acid. Table 1 shows the distribution of RCF in cases and controls and NTDs risk in each category.

RED CELL FOLATE ng/mL	RISK OF NTD PER 1000 BIRTHS
0-149	6.6
150-199	3.2
200-299	2.3
300-399	1.6
>400	0.8

Table 1. Overall risk of a neural tube defect pregnancy associated with low red cell folate status.

The largely European drive for improved periconceptional education and folic acid supplementation has not seen the reduction in NTDs predicted. A large international cohort study involving ten countries and covering more than 13 million births concluded that recommendations alone did not improve trends of incidence of NTDs[16]. Countries which had implemented food fortification programmes were excluded from this study. This underlines the entire problem with the prevention of NTDs. For folic acid to work it must be taken within the first four weeks of pregnancy, before the woman knows she is pregnant!

## 7. Food fortification

Many countries have identified new strategies to increase serum folate levels in women of reproductive age. In the US, Canada, South Africa and Chile they have adopted national flour fortification policies and have seen a substantial decrease in the numbers of new cases of NTDs. In March 1996, the U.S. Food and Drug Administration (FDA) issued a final rule, effective January 1998, that required all enriched cereal-grain products (flour, rice, breads, rolls and buns, pasta, corn grits, corn meal, farina, macaroni and noodle products) to be fortified with folic acid 0.14mg folic acid /100g flour and 0.24 mg/100g pasta in addition to the iron, thiamin, riboflavin and niacin already added to these enriched cereal-grain products. Mandatory food fortification has been the solution to NTDs in the USA, and has had a dramatic effect on the folate status there [17, 18]. Further evidence to support the process of food fortification has emerged. Jacques et al. looked at blood folate status in a control group before fortification and a group after fortification. They found that the mean plasma folate (for non-users of B-vitamin supplementation) increased from 4.6µg/L before fortification to 10µg/L after folic acid fortification. They also noted that with fortification there was a decrease in the prevalence of high homocysteine levels from 18.7 to 9.8% [19]. The U.S. Centres for Disease Control and Prevention reported that there has been a three-fold increase in the serum folate status of women aged 15-44 years who did not use supplements[18]. Another report published in 2000 looked at data collected from the Framingham Offspring Cohort Study. It was found that among non-supplement users, folic acid intake increased by a mean of 190µg/day and total folate intake increased by a mean of 323µg/day dietary folate equivalents in the exposed participants[20]. In Canada a mandatory fortification policy was also adopted; specific cereal grain products had to be fortified with folic acid at a level of 0.15mg/100g by November 1<sup>st</sup> 1998. Persad et al looked to see if folic acid supplementation or fortification changed the annual incidence of open NTDs in Nova Scotia. The study looked at the total number of births and stillbirths with NTDs and the number of terminated pregnancies affected with NTDs from perinatal and fetal anomaly databases. They reported that the incidence of open NTDs (spina bifida, anencephaly, encephaloceles) decreased by 54% after the Canadian fortification program was implemented. In 1991 to 1997 the mean annual rate was 2.58 per 1000 births and from 1997 to 2000 was 1.17 per 1000 births [21]. De Wals et al demonstrated similar results, showing a decline in the prevalence of NTDs from 1.58 per 1000 pregnancies before fortification to 0.86 per 1000 pregnancies thereafter giving a 46% reduction (95% CI 40-51) [22]. Mandatory fortification has also been introduced in other countries in Central and South American and in the Middle East. In Chile, the addition of folic acid to wheat flour commenced in January 2000. A study looking at the prevalence rate of spina bifida and anencephaly there demonstrated a decrease in the years 2001 and 2002 [23]. The decrease was approximately 51% for spina bifida and 46% for anencephaly. These results showed an obvious benefit in folic acid fortification and do not significantly differ from those published from other folic acid fortified populations in Canada and the USA. The main strength of this paper is that termination of pregnancy is illegal in Chile and therefore the observed data is complete and not influenced by termination of pregnancy such as occurs in other countries. In the USA the level of folic acid fortification, at 140ug/gm of flour, was chosen to be sufficient to prevent NTDs and to provide less than 1mg/day additional folate, a limit set by the Institute of Medicine (IOM) in 1998. There is a concern that excessively high levels might



delay the diagnosis of a haematological or neurological impairment due to vitamin B12 deficiency, which could potentially be masked by high serum folate. Food fortification policies in Europe have been delayed due to difficulty in determining the effective dose and concerns about safety. This helps explain the disparity in reduction of NTDs in Europe when compared to the USA and Canada [24]. An Irish study carried out in the late nineties indicated effectiveness and safety at a dose between 100 $\mu$ g and 200 $\mu$ g[25].

## **8. The cases for high dose folic acid**

### **8.1 Epilepsy and Anti-Epileptic Drugs (AED)**

The association of epilepsy and NTDs is well known. The risk of a woman with epilepsy on AEDs of having a child affected with a NTDs is 1-2% [26]. The known anti-folate mechanism of action of AEDs (especially valproate and carbamazepine) would intuitively indicate a recommendation of folic acid supplementation and is supported by a study in Hungary showing that the risk of congenital abnormalities could be reduced but not eliminated by folic acid supplementation[27]. However, the benefits have not been clearly demonstrated by a large prospective study in the United Kingdom [28]. A Cochrane review on the effectiveness of pre-conception counselling for women with epilepsy did not outline any consensus on the recommended dose, which varies in different countries from 0.4 $\mu$ g to 5mg[29].

## **9. Obesity**

Many countries have seen a substantial rise in the prevalence of obesity in women of reproductive age in the last twenty years. It is an important observation and of critical value when interpreting the effects this may have on the observed rates of NTDs. Several studies have reported an increased risk of NTDs in the offspring of obese women. This risk can vary from no risk at all as demonstrated in one study[30] to a 3 fold increase in risk in a study by Shaw et al in 1996[31]. A recent meta-analysis by Rasmussen et al in 2008 identified 12 studies (4 cohort and 8 case controls) which investigated the relationship between maternal obesity and the risk of NTDs[32]. The odds ratio for a NTD-affected pregnancy was 1.22 (95% CI 0.99-1.49) for overweight women, 1.70 (95% CI 1.34-2.15) for obese women and 3.11 (95% CI 1.75-5.46) for severely obese women. This meta-analysis controlled for confounding factors such as date of publication, diabetes and folic acid intake. There are three main hypotheses for this increased risk of NTDs in obese women. Firstly, the association of NTDs and the teratogenic effects of hyperglycaemia may be a possible explanation [33]. Altered glucose metabolism in these women leads to hyperinsulinaemia, which has been shown to be associated with NTDs. This is similar to the mechanisms causing the increased NTD-affected pregnancies in diabetic patients. A second possible explanation for the association of obesity and NTDs is that obese women have a higher dietary requirement for folic acid. It is well established that higher plasma and red cell folate levels are associated with a lower risk of NTDs. A study carried out by Werler et al and published 1996 showed that obese women, specifically those greater than 70 kgs, were less responsive to the WHO recommended 400 $\mu$ g dose than women of a normal weight[34]. Further investigations of women with a higher BMI showed overall lower serum folate levels and advised that obese women should take 750 $\mu$ g of folic acid to reach satisfactory RCF levels[35]. The final

hypothesis is that these findings simply reflect that prenatal diagnosis of NTDs in women who are obese is limited. Therefore more NTD-affected pregnancies would result in live births and this more likely to be identified in the birth defects surveillance systems which were used to identify the cases for the meta-analysis. This factor may have led to an over estimation of the risk associated with maternal obesity.

## 10. Conclusion

This chapter outlines the aetiologies and strategies for preventing neural tube defects. It is clear from international data that we should be striving for national policies for food fortification programmes to effectively reduce the incidence of neural tube defects. Future studies focus on identifying those who may have an increased folate requirement either due to a genetic predisposition or co-morbidities.

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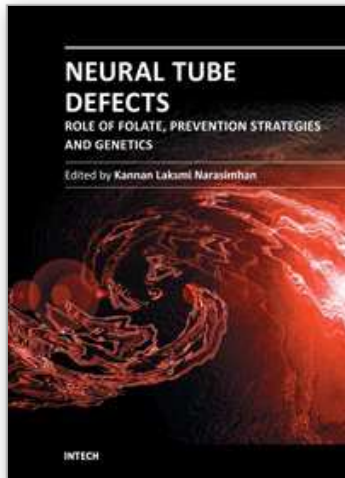
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