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Strategies for Prevention of Neural Tube Defects

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1. Introduction

Neural tube defects (NTDs) are congenital malformations of the brain and spinal cord caused by the failure of neural tubes to close between 21 and 28 days after conception (Sadler, 2005). Any disruption of neurulation during or prior to this time may result in a defect or failure of neural tube closure. Non-invasive prenatal diagnostic testing by ultrasound and maternal serum screening, which should be offered at 16 to 20 weeks gestation and 15 to 20 weeks gestation, respectively, will identify 95% of spina bifida and 100% of anencephaly cases. After 15 weeks of pregnancy, invasive prenatal diagnostic testing with ultrasound-guided amniocentesis can evaluate the fetal karyotype and measure amniotic fluid alpha-fetoprotein and acetylcholinesterase, to assist in differentiating between open or closed lesions (Chodirker et.al., 2001). The majority of cases can be categorized as either anencephaly (lack of closure in the region of the head) or spina bifida (lack of closure below the head).

Folate deficiency before conception and during early pregnancy is one potential cause of NTDs. Folate is the general term for water soluble B vitamin predominantly found in green leafy vegetables. Adequate folate intake is required for normal metabolism, cell division, neural function and growth. Humans are unable to synthesize folate and depend on an adequate and constant intake. Both observational and interventional studies, including randomized, controlled trials, have demonstrated that adequate consumption of folic acid periconceptionally can prevent 50-70% of NTDs (Czeizel & Dudas, 1992).

Currently, 57 countries have regulations for mandatory fortification of wheat flour with folic acid, (Flour Fortification Initiative, 2009) and health agencies in many countries have officially recommended the periconceptional consumption of folic acid in the range of 400 to 500 µg in young women of reproductive age who are capable of conceiving or planning to conceive (Centers for Disease Control and Prevention [CDC], 1992; Bower et al., 1995). The prevalence of spina bifida and anencephaly in the United States has declined significantly since the onset of fortification of enriched grain products with folic acid. The latest prevalence of spina bifida and anencephaly rates in the United States, reported in 2006, was 3.05 and 1.56 per 10,000 live births, respectively (Neural tube defect ascertainment project, 2010). On the other hand, the incidence of spina bifida in countries in which the fortification

of enriched grain product with folate is not compulsory or endorsed officially, was 5.32 per 10,000 live births (Annual report 2007 with data 2005, 2009). The primary objective of this review article is to discuss the strategies for prevention of NTDs.

2. Definition and classification

NTDs are common and severe congenital malformations of the central nervous system occurring secondary to a lack of closure of the neural tube. The following three groups are categorized based on the severity of the defects (Copp & Harding, 2004).

2.1 Severe form

The severe form of the NTD spectrum includes open defects resulting from the failure of neural tube closure, in which the interior of the brain or spinal cord communicates directly with outside, and includes the following:

- *Craniorachischisis*: There is an almost complete absence of neural tube closure, affecting both the brain and spine. This malformation results from a failure of the initiating event of neurulation in the early embryo.
- *Excencephaly*: This is a brain defect resulting from a failure of cranial neural tube closure. Although this appearance is seen only in embryos and early fetuses, the persistently open cranial neural folds have an everted appearance.
- *Anencephaly*: Exposed cranial neural folds may degenerate with advancing gestation. This is a catastrophic malformation in which the brain is severely degenerated and the skull vault is absent.
- *Myelomeningocele*: This results from a failure of the closure of the spinal neural tube, most often in the lumbosacral region. In *spina bifida cystica*, a meningeal sac containing the open spinal cord herniates through a vertebral defect. In *myeloceles*, the open spinal cord is directly exposed as a flat open lesion.

2.2 Moderate form

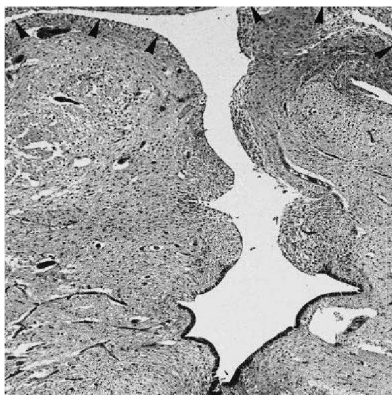
The moderate form of NTD includes *encephaloceles* and *meningoceles*. These defects result from herniation of the brain or meninges through an opening in the skull or vertebral column, respectively. These defects appear to be primary abnormalities of skeletal development, not neural tube closure, as the brain and spinal cord appear to have closed normally prior to herniation.

2.3 Mild form

The mild end of the NTD spectrum is represented by a third group of dysraphic defects in which there are closed abnormalities of the spinal cord, usually in the low lumbar and sacral regions. The following types are included:

- *Diplomyelia*: This is a side-by-side or anteroposterior duplication of the spinal cord.
- *Diastatomyelia*: A midline septum divides the spinal cord longitudinally into two usually unequal portions extending up to 10 thoracolumbar segments.
- *Hydromyelia*: The central canal is overdistended (Fig. 1).

- *Lipomeningocele*: The dysraphic spinal cord is accompanied by fatty tissue deposits.
- *Spina bifida occulta*: This is defined as a defect in the posterior bony components of the vertebral column without involvement of the cord or meninges.



Source; Modified from Takano, T. & Becker, L.E. (1997).

Fig. 1. A coronal section of the spinal cord in a patient with a meningocele. Note the overdistended and deformed central canal showing hydromyelia. Hematoxylin and eosin staining.

3. Clinical features and management

3.1 Craniorachischisis, exencephaly and anencephaly

These malformations are incompatible with survival beyond birth and today are observed almost exclusively on ultrasound examination during pregnancy.

3.2 Myelomeningocele

Myelomeningoceles involve all of the underlying layers, including the spinal cord, nerve roots, meninges, vertebral bodies and skin. The spinal cord may be exposed because of a complete failure of neural closure, or may be covered by a membrane. Although myelomeningocele may be situated at any longitudinal level of the neuroaxis, lumbosacral involvement is the most common (Fig. 2). Varying degrees of paresis of the legs, usually profound, and sphincter dysfunction are the major clinical manifestations. Fifty to seventy percent of neural tube defects can be prevented if a woman consumes sufficient folic acid daily before conception and throughout the first trimester of her pregnancy (Gleeson et al., 2006). Maternal serum alpha-fetoprotein determination and ultrasound examination are now routinely used to identify fetuses that have or are likely to have spina bifida or anencephaly (Drugan et al., 2001). Alpha-fetoprotein is a component of the fetal cerebrospinal fluid, and it may leak into the amniotic fluid from the open neural tube. Closed lesions often do not lead to increased alpha-fetoprotein concentrations. The management of a child with a myelomeningocele requires the concerted efforts of a multidisciplinary team involving many specialists. Treatment includes surgical reduction of the myelomeningocele and other associated defects, prevention of infection, covering of the myelomeningocele, control of hydrocephalus, management of urinary dysfunction, and treatment of the paralysis and abnormalities of the hips and feet (Gleeson et al., 2006).



Fig. 2. A lumbar myelomeningocele in a newborn, showing a large meningeal sac (asterisk). The midline sagittal view from a computed tomography study.

3.3 Meningocele

A meningocele is a protrusion of the meninges without accompanying nervous tissue, and it is not associated with neurological deficits. The mass usually is evident as a fluid-filled protrusion covered by skin or a membrane in the midline. When careful examination of patients with a suspected meningocele reveals significant neurological abnormalities such as the equinovarus deformity, gait disturbance or abnormal bladder function, the diagnosis of a meningomyelocele is appropriate. A meningocele can be found in the cranial (Fig. 3) or high cervical area.



Fig. 3. A cranial meningocele in a newborn. Note the meningeal herniation through a small opening of the frontal skull (arrow) into the nasal cavity. The midline sagittal view from a magnetic resonance imaging study.

3.4 Encephalocele

An encephalocele is a herniation of the intracranial contents through a midline skull defect. The cranial meningoceles contain only leptomeninges and cerebrospinal fluid, whereas encephaloceles also contain brain parenchyma. The amount of compromised and deformed neural tissue and the degree of resultant microcephaly determine the extent of cerebral dysfunction (Gleeson et al., 2006). Severe intellectual and motor delays typically occur in

association with microcephaly. A prenatal diagnosis of encephaloceles may be established by the determination of an increased amniotic alpha-fetoprotein content and ultrasound studies (Graham et al., 1982). Surgical corrections of all but the smallest encephaloceles are necessary.

3.5 Diplomyelia

This malformation is compatible with normal spinal function, and neurological deterioration suggests the presence of diastematomyelia or tethering.

3.6 Diastematomyelia

Patients with diastematomyelia present with congenital scoliosis, hydrocephalus, or cutaneous lesions such as hairy patch, dimple, hemangioma, subcutaneous mass, or teratoma (Kothari & Bauer, 1997). A progressive myelopathy, with deformities of the feet, scoliosis, kyphosis, or discrepancy in leg length, also may develop. Resection of the spur in diastematomyelia frequently does not result in any clinical improvement.

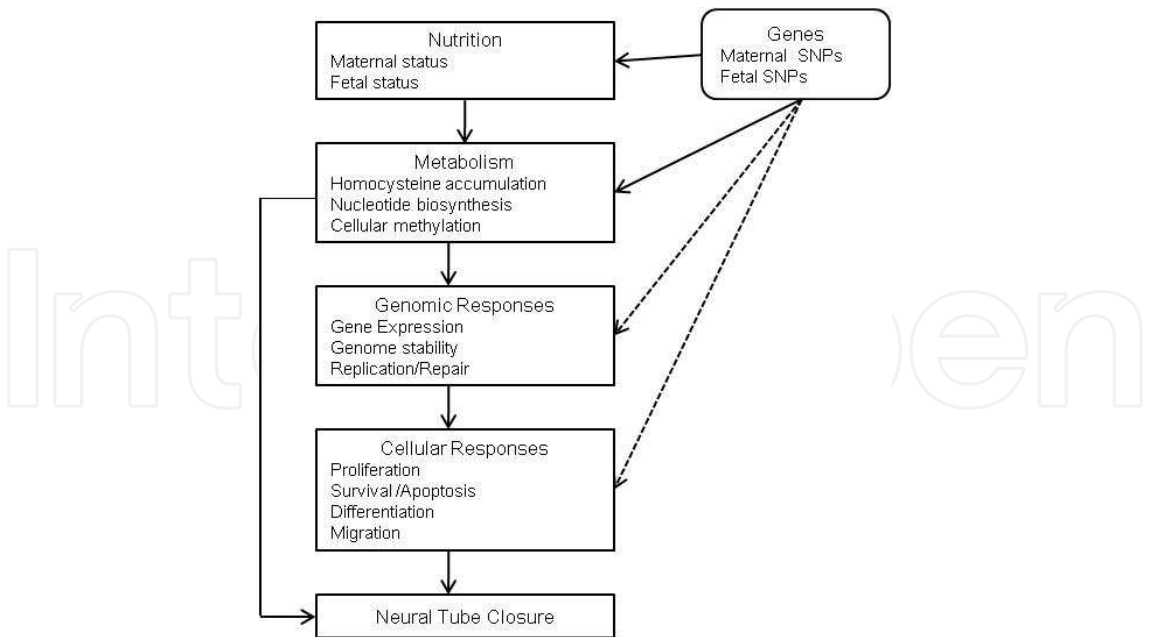
3.7 Spina bifida occulta

This occurs in at least 5% of the population, but most often is asymptomatic. This defect is often found incidentally on radiographic studies or is diagnosed because of a subtle clinical finding, such as a tuft of hair or a cutaneous angioma or lipoma in the midline of the back marking the location of the defect (Guggisberg et al., 2004).

4. The mechanism of folate deficiency and NTDs

In 1976, Smithells et al. (1976) suggested that folate deficiency was a cause of NTDs because women with NTDs infants had low blood folate levels. Later, they reported that periconceptional vitamin supplementation, including folic acid, reduced the recurrence of NTDs (Smithells et al., 1983). Further studies provided a growing body of evidence. Folic acid exists as polyglutamates in green leafy vegetables and other natural sources. It consists of a pteridine ring, p-aminobenzoic acid, and glutamine acid. Although folate deficiency is an established risk factor for NTDs, the exact mechanism is not clear.

Beaudin and Storver (2007) showed the pathway linking alterations in folate status with NTDs (Fig. 4). They summarized that disruption of folate metabolism could result in homocysteine accumulation, impaired nucleotide biosynthesis, and impaired cellular methylation. These metabolic impairments evoke genomic responses such as alterations in gene expression, genomic instability, reduced mitotic rates, and impaired DNA repair. Impairments in metabolism and/or genomic responses may influence cellular responses critical to proper neural tube closure, including cell proliferation, survival, differentiation, and migration. SNPs in folate-related genes can influence both maternal and infant folate status, or alternatively, Aminopterin (4-aminopteroic acid; APN) can also directly disrupt metabolism. APN is an antineoplastic drug with immunosuppressive properties used in chemotherapy and a synthetic derivative of pterin, and works as an enzyme inhibitor by competing for the folate binding site of the enzyme dihydrofolate reductase. Its binding affinity for dihydrofolate reductase effectively blocks tetrahydrofolate synthesis. This results in the depletion of nucleotide precursors and inhibition of DNA, RNA, and protein synthesis.



Source: Beaudin, A.E. & Stover, P.J. (2007)

Fig. 4. Pathway linking alterations in folate status with NTDs

5. Strategies for prevention of NTDs

The prevalence of NTDs has declined considerably during the past three decades, due to advances in the refined resolution of ultrasonography for fetal examination, the clinical availability of serum alpha-fetoprotein measurements, termination of affected pregnancies, and the consumption of folic acid supplements among reproductive-aged women. Included in these factors, successful mandatory fortification programs have been documented in several countries, including the United States, Canada, and Australia (Abeywardana et al., 2010; De Wals et al., 2008; Pfeiffer et al., 2008).

5.1 Countries of fortification of enriched grain product with folate

5.1.1 Mandated folic acid fortification programs

In 1992, the U.S. Public Health Service recommended that all women of reproductive age in the United States who were capable of becoming pregnant should consume 400 µg of synthetic folic acid daily from fortified foods and/or supplements and that they should consume a balanced, healthy diet of folate-rich food in order to reduce the risk of NTDs (CDC, 1992). The Food and Drug Administration mandated the addition of folic acid to all enriched cereal grain products by January 1998 (Food and Drug Administration, 1996). In 2009, the U.S. Preventive Services Task Force (2009) published updated guidelines reinforcing these recommendations.

Canada introduced a fortification program in 1998, mandating the folic acid fortification of enriched white flour, as well as some corn and rice products, with ranges from 95 to 309 µg/100 g for different products (Ray et al., 2002). In Australia, the Australian National Health and Medical Research Council recommended a periconceptional daily supplement intake of 500 µg folic acid for women of childbearing age in 1993, and voluntary folic acid fortification of certain foods was permitted (National Health and Medical Research Council,

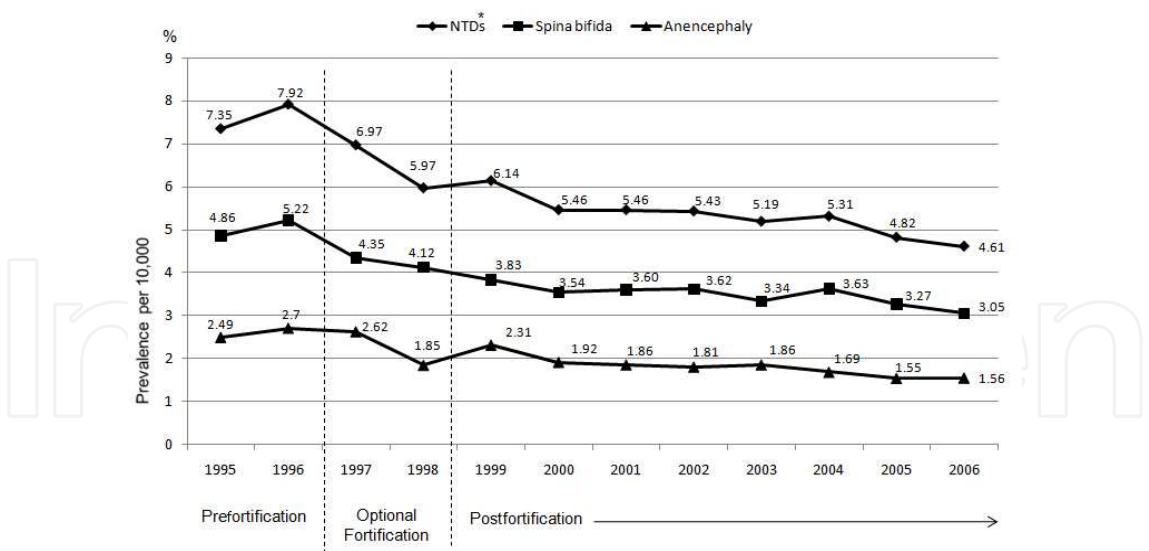
1994). In June 2007, the Australian Food Regulatory Ministerial Council agreed to mandatory fortification of bread-making flour with folic acid. The standard, September 2009, requires the mandatory addition of 200-300 µg folic acid per 100 grams of bread-making flour (Food Liaison, 2007).

The percentage of the world’s wheat flour produced in large roller mills that is fortified has increased from 18% to 30%. By 2015, the target date of the World Health Organization millennium Development Goals, the Flour Fortification Initiative goal is for 80% of the world’s roller-mill wheat flour to be fortified (CDC, 2010).

5.1.2 The effect of fortification

According to the Morbidity and Mortality Weekly Report, if 50%-70% of NTDs can be prevented through daily consumption of 400 µg of folic acid, assuming an annual prevalence of 300,000 NTDs, worldwide folic acid fortification could lead to the prevention of 150,000 - 210,000 NTDs per year (CDC, 2010).

Numerous studies have evaluated the effect of folic acid fortification on primary prevention of NTDs. A significant, worldwide decline in the prevalence of NTDs was noted in the period following folic acid fortification. In the United States, during 1995-1996, an NTD affected approximately 4,000 pregnancies. The number declined to 3,000 pregnancies in 1999-2000, following the mandated fortification of enriched cereal grain products with folic acid (CDC, 2004). From the prefortification period of 1996-1996 to the early postfortification of 1999-2000, the prevalence of spina bifida and anencephaly decreased dramatically (CDC, 2008). The latest prevalence of spina bifida and anencephaly rates in the United States, reported in 2006, was 3.05 and 1.56 per 10,000 live births, respectively, based on birth defects surveillance data (Neural tube defect ascertainment project, 2010) (Fig. 5).



Source by neural tube defect ascertainment project of the National Birth Defects Prevention Network at Centers for Disease Control and Prevention.

*NTDs: Spina bifida + Anencephaly

Fig. 5. Prevalence of spina bifida and anencephaly in the United States, 1995-2006

Australia presented similar findings. The prevalence of NTDs dramatically declined from 20 per 10,000 births in the prefortification period to 5 per 10,000 births in the postfortification

period. A declining trend of 26% was seen during this period (Abeywardana et al., 2010). Chan et al. (2008) reported a decline in the total prevalence of NTDs from 2.06 per 1,000 births in the prefortification period to 1.23 per 1,000 births in the mandatory fortification period (RR: 0.60, 95% confidence interval (CI): 0.48-0.74; $p < 0.001$). Sayed et al. (2008) showed that the prevalence of spina bifida decreased from 1.41 per 1,000 births in the prefortification period to 0.98 per 1,000 births in the mandatory fortification period (RR: 0.69, 95% CI: 0.49-0.98). Ten studies suggested that food fortification could reduce the incidence of NTDs by 20 to 50%.

The effect of folic acid fortification on the incidence of NTDs has also reported in Jordan. Seventy-eight NTDs were recorded among 61,447 births between 2000 and 2006 at a Jordan hospital. Of the cases, spina bifida was the most common type of anomaly (87.2%), followed by encephalocele (11.5%), and anencephaly (1.3%). The incidence of NTDs decreased from 1.85 (95% CI: 1.2-2.4) per 1000 births before fortification (2000-2001) to 1.07 (95% CI: 0.7-1.5) during the fortification period (2002-2004), and to 0.95 (95% CI: 0.5-1.5) after full fortification (2005-2006), a 49% reduction (Amarin & Obeidat, 2011). Thus, the folic acid fortification strategy was clearly successful in some countries.

5.1.3 Blood folate levels after fortification

The mandatory fortification of standardized enriched cereal grain products in the United States has resulted in a substantial increase in blood folate concentrations. The percentage of the population with low serum folate (< 3 ng/mL) declined from 21% in the period before fortification (1988-1994) to $< 1\%$ of the total population in the period immediately following fortification (1999-2000) (Pfeiffer et al., 2008). In a study based on data from the National Health and Nutrition Examination Survey (NHANES), the mean serum folate concentration for women aged 15-44 years who did not use supplements increased from 10.7 nmol/L to 28.6 nmol/L shortly after the initiation of fortification in the United States, representing an almost threefold increase (CDC, 2000). In the most recent analysis of NHANES data, the CDC reported a 16% decline in serum folate concentrations among women aged 15-44 years from 1999-2000 to 2003-2004; red blood cell folate concentrations decreased 8% over the same time periods (CDC, 2007). The reason of these different decreased rate may that red blood cell folate concentrations reflect body stores at the time of red cell synthesis and are considered a better measure of long-term folate status (> 3 months) than serum folate concentrations, which reflect recent dietary intake (Scientific Advisory Committee on Nutrition, 2006).

In Australia, researchers examined the impact of mandatory fortification of flour with folic acid on the blood folate levels in 20,592 Australians, including in women of childbearing age between 2009 and 2010. In 2010, there was a 31% increase in mean serum folate levels (from 17.7 nmol/L to 23.1 nmol/L), and a 22% increase in mean red blood cell (RBC) folate levels (from 881 nmol/L to 1071 nmol/L) after mandatory fortification with folic acid of wheat flour used in bread making among women of childbearing age (Brown et al., 2011). The introduction of mandatory fortification with folic acid has significantly reduced the prevalence of folate deficiency.

5.2 Countries with voluntary fortification of enriched grain products with folate

Countries where the fortification of enriched grain products with folate is not compulsory or officially endorsed report low folate status among reproductive-aged women and high

incidences of NTDs. Japan is one such country, although 440 µg of dietary folate with balanced meals was recommended to all Japanese women of reproductive age by the Ministry of Health (2000) to prevent birth defects. In 2008, the National Nutrition Survey in Japan reported that the mean dietary intake of folate, vitamin B₆, and vitamin B₁₂ of non-pregnant women aged 18-29 years was less than the recommended dietary allowance (RDA) (Ministry of Health, Labour and Welfare, 2008). Another study showed (Mito et al., 2007) that more than 80% of Japanese women aged between 17 and 41 had inadequate (i.e., less than the RDA of 240 µg/d) folate intake in 2002. This failure of women to meet the RDA for folate intake may have led to the increase in the prevalence of spina bifida from 1.96 per 10,000 live births (1974-1980) to 5.32 (2001-2005) (Annual report 2007 with data 2005, 2009).

In China, women who are planning marriage or pregnancy are advised to take 400 µg of supplemental folic acid every day, starting before conception, through to the end of the first trimester of pregnancy, but this is not mandatory (Ren et al., 2006). Northern China has one of the highest reported NTD birth prevalence rates in the world. The prevalence of NTDs was 4.5 per 1,000 in 2002 (Zhang & Wang, 2004), and only 35.8% of the affected population was aware of folic acid; fewer than 15% of women reported taking folic acid periconceptionally, with the percentage being significantly lower than the average among rural farming women with less education (Ren et al., 2006). The low level of awareness as well as the low reported rate of periconceptional supplementation may explain the high prevalence of NTDs.

6. Feature approaches

There have been three main approaches to reduce the incidence of NTDs: health promotion to improve the knowledge and awareness of folic acid, ensuring the use of fortified folic acid and folic acid supplements, and reducing the number of obese women, which is also a known environmental factor (Waller et al., 1994; Werler et al., 1996).

6.1 Health promotion to improve knowledge and awareness regarding folic acid

The USA, Canada, and Australia have implemented food fortification programs successfully with resultant improvement in serum folate levels and reduction in incidences of NTDs. Education campaigns can be effective and public health campaigns aimed at informing and influencing behavioral change in all individuals. Rofail et al. (2011) examined pre- and post-campaign awareness, knowledge, and consumption data for women of reproductive-age in Australia. Awareness of folic acid improved post-campaign, with the percentage improvement between pre- and post-campaigns ranging from 6 to 41%. Women's knowledge of the association between folate and spina bifida increased from 8% before the program began to 67% two-and-a-half years later. The proportion of women taking periconceptional folic acid supplements increased from 13% to 30% over the same period (Bower et al., 1997). Since the introduction of this promotion, the prevalence of NTDs in Western Australia, which was about two per 1,000 births from 1980 until 1995, fell by 30% in 1996 (Bower et al., 2002). The estimated increase in mean serum folate concentration was 19% after educational campaigns to increase periconceptional folic acid use (Metz et al., 2002). The ultimate goal of any folic acid awareness campaign is to promote use of folic acid supplements, to increase the blood folate levels of women, and to prevent the occurrence of NTDs.

An U. S. national survey showed differences in folic acid awareness and knowledge among age groups (CDC, 2008). In 2007, approximately 61% of women aged 18-24 years reported being aware of folic acid, compared to 87% of women aged 25-34 years and 89% of women aged 35-45 years. Women aged 18-24 years were also less knowledgeable about the need for folic acid consumption before pregnancy (6%), compared to women aged 35-45 years (16%). In addition, approximately 33% of women who were aware of folic acid had received the information about folic acid from their health-care providers, followed by finding information in a magazine or newspaper (31%) and receiving it through radio or television (23%). Official health education initiatives have promoted folic acid supplementation and a diet rich in folates through mass media, including TV, newspapers, and magazine articles worldwide (CDC, 2010). Special attention and targeted approaches must concentrate on this age group. Public health campaigns aimed at increasing awareness, knowledge, and periconceptional use of folic acid should concentrate on using appropriate intervention methods worldwide.

6.2 Encouragement to increase women's dietary intake of folic acid and use of folic acid supplements

Many women of childbearing age in the United States do not maintain a healthy diet prior to, during, or after pregnancy. Numerous studies have reported that women in the United States do not consume the recommended 400 µg of folic acid (Hilton, 2007; Rinsky-Eng & Miller, 2002). In Japan, more than 80% of Japanese women between 17 and 41 years of age had inadequate folate intake - less than the recommended daily allowance of 240 µg/d (Mito et al., 2007; Watanabe et al., 2008). Other studies have also shown that most women of reproductive age in the U.S. are not getting enough vitamin C or B6, in addition to folic acid (Cena et al., 2008 ; Yang et al., 2007).

As previously indicated, consuming folate-rich foods or ingesting folic acid, a synthetic compound available through dietary supplements and through fortified foods, can increase folate levels. Folic acid is approximately 1.7 times more bio-available than folate, and therefore, has a greater efficiency in making an impact on folate levels (Neuhouser & Beresford, 2001).

In the U.S, the percentage of women of childbearing age who took daily supplements containing folic acid increased from 28% in 1995 (prefortification) to 32% in 2003 (postfortification) (Green-Raleigh et al., 2006), and to 40% in 2007 (US Department of Health and Human Services [USDHHS], 2010). One of the Healthy People 2010 objectives was to increase to 80% the proportion of all women of childbearing age who consume 400 µg of folic acid daily to reduce the risk for serious birth defects (USDHHS, 2010). Although a worldwide campaign contributed to progress toward this goal, approximately 60% of childbearing-aged women are still not consuming a daily supplement containing folic acid.

One should note that supplementation alone is not an effective approach because one-third to one-half of all pregnancies in the United States is unplanned (Custer et al., 2008). Women often do not know that they are pregnant during the crucial first 4 to 8 weeks of pregnancy. Neural tube development occurs during this time, hence the importance of ensuring adequate folic acid intake. Women aged 18-24 years have the highest rate of unintended pregnancies in the United States (Finer & Henshaw, 2006) but remain the least aware of and

knowledgeable about folic acid; they are also the least likely to report consuming a supplement containing folic acid. Recent studies have indicated that only 39% of southern Australian subjects (Chan et al., 2008), and 13.5% of Canadian subjects (French et al., 2003), knew they should take folic acid before pregnancy. Fortifying foods with folic acid has been a highly effective and uniform intervention, because fortification makes folic acid accessible to all women of childbearing age, without requiring substantial behavioral changes.

6.3 Reduce the number of obese or overweight women

Overweight status and obesity have become serious global public health issues. Nearly two thirds of reproductive-aged women in the United States are currently overweight or obese (≥ 25 kg/m²). In the NHANES, the prevalence of obesity (BMI ≥ 30 kg/m²) in women aged 20-49 years continues to be high, exceeding 30% after 1999 (Flegal et al., 2010). In the latest NHANES data from 2007-2008 of 877 women aged 20-39 years, the prevalence of overweight status (BMI ≥ 25 kg/m²) and obesity were 59.5% and 34.0%, respectively.

The worldwide trend of increasing obesity may lead to increasing the incidences of NTDs. A population-based case-control study by Shaw et al. (1996) indicated an increased risk for NTD-affected pregnancies among obese women with BMIs >29 kg/m², compared to women of normal pre-pregnancy BMIs (OR: 1.9, 95% CI: 1.3-2.9), when adjusted for maternal age, education, gravidity, use of vitamins, and use of alcohol. Rasmussen et al. (2008) conducted a metaanalysis of 12 published reports, including 4 cohort and 8 case-control studies conducted from 2000 through 2007, on the relationship between maternal obesity and the risk of NTDs. Unadjusted odds ratios for an NTD-affected pregnancy were 1.22 (95% CI: 0.99-1.49), 1.70 (95% CI: 1.34-2.15), and 3.11 (95% CI: 1.75-5.46) among overweight, obese, and severely obese women, respectively, compared with normal-weight women. Based on the results of this metaanalysis, maternal obesity was associated with a 1.7-fold increased risk of NTDs, and severe obesity was associated with a >3 -fold increased risk. A possible mechanism may involve problems with glucose metabolism, because obese women are more likely to have pre-pregnancy diabetes mellitus, which is a well-known risk factor for NTDs (Becerra et al., 1990; Werler et al., 1996). However, the reasons for this association are not yet known.

The risks associated with high BMI are best addressed before conception because weight loss during pregnancy is not recommended. Counseling to support improvements in diet and physical activity is a first-step intervention. All women with a BMI of 25 kg/m² or greater should be offered specific strategies to improve the balance and quality of their diets, to decrease caloric intake, and to increase physical activity.

7. Conclusion

NTDs are life threatening and cause life-long disabilities. They are a worldwide problem, affecting an estimated 300,000 or more fetuses or infants each year. Experimental and epidemiological evidence has shown that periconceptional dietary supplementation with folic acid can result in an estimated 50-70% decrease in the prevalence of NTDs. To reduce more incidences of NTDs, each reproductive-aged woman must try to consume food fortified with folic acid and folic acid supplements and maintain adequate BMIs before conception. Special attention or renewed educational approaches must target reproductive-

aged women. Public health campaigns aimed at increasing awareness, knowledge, and periconceptional use of folic acid using appropriate intervention methods worldwide continues to be the most effective strategy.

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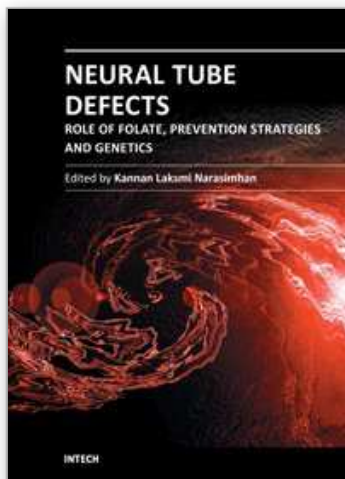
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Neural Tube Defects - Role of Folate, Prevention Strategies and Genetics

Edited by Dr. Kannan Laksmi Narasimhan

ISBN 978-953-51-0317-2

Hard cover, 200 pages

Publisher InTech

Published online 16, March, 2012

Published in print edition March, 2012

The book Neural Tube Defects - Role of Folate, Prevention Strategies and Genetics has several eminent international authors and the book is a resource for anybody who is interested in this very important subject. The authors are distinguished and the chapters are a product of their extensive research.

How to reference

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Hiroko Watanabe and Tomoyuki Takano (2012). Strategies for Prevention of Neural Tube Defects, Neural Tube Defects - Role of Folate, Prevention Strategies and Genetics, Dr. Kannan Laksmi Narasimhan (Ed.), ISBN: 978-953-51-0317-2, InTech, Available from: <http://www.intechopen.com/books/neural-tube-defects-role-of-folate-prevention-strategies-and-genetics/strategies-for-prevention-of-neural-tube-defects>

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