

Primary Prevention of Neural Tube Defects

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1. Introduction

Neural tube defects (NTD) are serious birth defects of the brain and spine, occurring when the neural tube doesn't form or close completely. They are among the most frequent congenital malformations, affecting 300,000 pregnancies worldwide. Two forms of NTDs, spina bifida and anencephaly, account for 90% of all cases (Centers for Disease Control, CDC, 1989).

Studies had proven that supplementation of women of childbearing age with folic acid can prevent up to 70% of all cases of NTDs (Laurence et al 1981, MRC Vitamin Study Research Group 1991). These researches led to international recommendations that all women of childbearing age consume 400 micrograms of folic acid daily for the prevention of neural tube defects at least 1 month before and throughout the first trimester of pregnancy (CDC 1992, Institutes of Medicine 1998, WHO 2002). Three potential approaches were advocated to increase level of folic acid consumption among the general population: fortification of food supply, improvement of dietary habits and use of dietary supplements (CDC, 1992). In some countries such as Canada and the USA, these recommendations led to the fortification of all enriched grain products with folic acid. This action decreased the occurrence of spina bifida by 31% and anencephaly by 16% (CDC 2004) and thus was considered as a partial success. As for the change in eating habits, meeting dietary recommendations for grain intake is an important step to achieving the recommended daily intake for folic acid. Studies have shown that non pregnant women of childbearing age reported an average daily consumption of 128 mcg of folic acid, representing only 32 percent of the daily recommended amount (Yang et al. 2007). These facts imply that most women still need to daily consume a dietary supplement containing folic acid at the recommended dose (400 µg) in order to prevent pregnancies with NTDs. Despite all this, several studies have shown a low consumption of folic acid supplements worldwide: numbers vary from prevalence as low as 7.5% in Lebanon (Nasr Hage et al 2011) to the highest percentage of 40 % in Canada and the USA (Morin et al. 2002; Petrini et al, 2008). These percentages remain far from the "Healthy people 2010" goal aiming that a minimum of 80% of women of childbearing age consume at least 400 mcg of folic acid daily in the periconception period. Levels of awareness and knowledge have been studied extensively in women of childbearing age in order to explain the low prevalence of folic acid intake with variable results in different countries. Although these levels of awareness and knowledge were thought to explain low levels of folic acid consumption, a systematic review of the literature showed that variable interventions on folic acid increased women's awareness from 60% to 72% and knowledge

from 21% to 45%. At the same time, levels of folic acid consumption increased only from 14% to 23% showing a positive but suboptimal impact (Chivu et al. 2007). As Green and Kreuter say “changes in knowledge and awareness alone cannot be assumed to translate into changes in behavior” (Green and Kreuter, 1991). There is still a gap between awareness and behavior on one side and usage of folic acid on the other side. This gap could be explained by determinants of behavioral change such as unplanned pregnancies, perceived barriers for taking folic acid pills, lack of time, level of education, age group and culture.

This chapter will discuss the preventive role of folic acid in the development of neural tube defects and the recommendations concerning its consumption. Factors related to folic acid knowledge, attitude and behavior will be analyzed as well as suggestions made for effective strategies aiming to improve its usage among women of childbearing age.

2. Role of folic acid in the prevention of NTDs

2.1 Folic acid as a vitamin

Folate, also known as vitamin B9, is a water-soluble B vitamin that occurs naturally in food. It is an essential nutrient that humans can not synthesize. Folic acid is the synthetic form of folate that is found in supplements and added to fortified foods. Folate is found naturally in a wide variety of foods particularly leafy green vegetables such as spinach, asparagus and lettuce, grains such as beans, peas and lentils, fruits such as orange, cantaloupe and melon, kidney, liver, egg yolk and yeast. Most folates have many molecules of glutamic acid; they have to be converted to monoglutamate to be absorbed in the intestine. The synthetic form has one molecule of glutamic acid making it more bioavailable than the natural form. Folate is critically important for fetal development. It has a role in DNA synthesis, acts as a cofactor for many essential cellular reactions and is implicated in the metabolism of several amino acids especially in the conversion of homocysteine to methionine; thus, the need for folate increases during periods of rapid tissue growth such as in pregnancy. When folate is insufficient, DNA synthesis is impaired and cells are unable to successfully achieve mitosis. In addition, the methylation process of proteins, lipids and myelin is inhibited (Rosenblatt, 1995).

2.2 Mechanism of NTD prevention with folic acid

The mechanism by which folic acid prevents NTDs remains unknown. Many theories have been proposed. Genetic, nutritional, environmental factors or a combination of these play a role in the development of NTDs. The genetic theory of methylation was proposed by Blom et al (Blom et al, 2006). Problems during embryogenesis in the methylation of DNA, proteins and lipids are related to the development of NTDs. A mutation in the gene coding for the methylenetetrahydrofolate reductase enzyme, responsible of the generation of a methyl group essential for biosynthesis of methionine and nucleotides, is believed to contribute to fetal nervous system malformation such as spina bifida (Mills et al, 1995). This mutation accounts for one-fourth of NTDs suggesting that the protective effect of folate, reaching a 70% reduction in NTDs, involves other environmental factors or gene-environment interactions (Posey et al, 1996). Other genes involved in the methylation cycle through remethylation or transsulfuration of homocysteine were also involved in the development of NTDs (Boyles et al, 2005). Besides the methylation theory, two other theories were proposed as genetic explanations for the relationship between folic acid and NTDs: the role of the

genes codifying to enzymes needed for nucleotide biosynthesis such as the polymorphism in methylenetetrahydrofolate dehydrogenase, and the role of the genes codifying proteins involved in the transport, capture and cell retention of folate (DeMarco et al, 2006; Beaudin and Stover, 2009). The role of nutrition in the development of NTDs has been studied. The relationship between folic acid deficiency and NTDs may be linked to lower gene expressions due to alteration in the methylation and synthesis of DNA (Zeisel, 2009). The daily consumption of folic acid reduced the level of homocysteine, a risk factor in the development of NTDs (Boyles et al, 2005).

2.3 Evidence for prevention of NTDs with folic acid

Early studies in the sixties and seventies suggested a role for diet in NTDS (Hibbard and Smithells 1965; Knox, 1972; Smithells et al 1976). In early eighties, two randomized controlled trials showed a reduction in the recurrence of NTDs with folic acid supplementation but these studies were criticized for their methodological limitations (Laurence et al 1981; Smithells et al, 1980). Further observational studies conducted in the eighties suggested that the consumption of folic acid by women of childbearing age is protective against NTDs in newborns (Bower and Stanley, 1989; Milunsky et al, 1989; Mulinar et al, 1988). This was confirmed by a randomized multicenter controlled trial showing that daily supplementation of women in childbearing age with folic acid reduced by 72% the risk of recurrence of NTDs (MRC Vitamin Study Research Group 1991). The conclusive proof of the preventive effect of folic acid for women with no NTD history came from a randomised controlled study conducted in Hungary that showed no NTD cases occurred among 2104 women taking folic acid as compared with six cases among 2052 pregnancies in the group not taking folic acid (Czeizel and Dudas, 1992). A meta-analysis study published in 2010 reviewed all observational and randomized studies evaluating the first occurrence and recurrence of NTDs and related mortalities in pregnancy. It concluded that folic acid intake reduced the recurrence of NTDs by 70% and the first occurrence of NTD by 62% (Blencowe et al, 2010).

2.4 Recommendations for folic acid consumption in pregnancies

All the data confirming the protective effect of folic acid against NTDs led to international recommendations concerning folic acid consumption in women of childbearing age. The Institutes of Medicine and CDC recommend the maternal consumption of 400 micrograms of synthetic folic acid daily at least 1 month before conception and during the first few months of pregnancy (CDC, 1992; Institute of Medicine, 1998). The Canadian college of medical geneticists recommended that a minimum dose of 0.8 mg/day of folic acid along with a well-balanced diet should be prescribed for women planning a pregnancy, starting before conception and for at least 10-12 weeks of pregnancy (Van Allen et al, 1993). Similar guidelines were issued by the Canadian college of obstetricians and gynecologists.

The EUROCAT published a report about the "prevention of neural tube defects by periconceptional folic acid supplementation in Europe" (EUROCAT special report, updated version December 2009). In most European countries where a policy exists, periconceptional folic acid supplements are recommended at a daily dose of 0.4 to 0.5 mg and the dose of 4 to 5 mg is reserved for women who have had a previous pregnancy

complicated with NTDs. Table 1 (adapted from the EUROCAT report) summarizes periconceptional folic acid supplementation policies around Europe.

Because half of all pregnancies in the United States are unplanned (Finer and Henshaw 2006), and because NTDs occur often before a woman knows she is pregnant, the Centers for Disease Control and Prevention (CDC) recommends that all women who can become pregnant consume the recommended amount of folic acid daily, regardless of their pregnancy intentions (CDC, 2004).

Country	Folic acid policy	
	Status	Year current policy introduced
Austria	Unofficial	1998
Belgium	Unofficial	-
Croatia	Unofficial	-
Denmark	Official	1997
Finland	Official	2004
France	Official	2000
Germany	Unofficial	1994
Hungary	Official	1996
Ireland	Official	1993
Italy	Official	2004
Malta	Dietary	1994
Netherlands	Official	1993
Norway	Official	1998
Poland	Official	1997
Portugal	Official	1998
Slovenia	Official	1998
Spain	Official	2001
Sweden	Official	1996
Switzerland	Official	1996
UK	Official	1992
Ukraine	Official	2002

Table 1. Folic acid supplementation policy in European countries (until December 2007)

3. Community interventions to increase folate intake

Three ways were advocated in order to increase folate intake in women of childbearing age: improvement of dietary habits, fortification of food supply with folic acid and the use of folic acid supplements (CDC, 1992)

3.1 Improvement of dietary habits

Studies have shown that the average consumption of folate by women is not more than 200µg/day (Gregory et al, 1990; Subar et al, 1989). Yang and colleagues calculated the average daily dietary intake of folate and folic acid by women of childbearing age in the

USA in 2001-2002. They found that the average daily consumption was 128 $\mu\text{g}/\text{day}$, representing 32% of the daily recommended amount (Yang et al, 2007). Knowing the importance of grain intake in achieving the recommended intake for folic acid, Briefel and Johnson reviewed national data in the USA on grain intake; they found that, in 1999-2000, only 24% of the population met the recommendation for daily servings of grains (Briefel and Johnson, 2004). The German Nutrition Report 2004 stated that the average daily intake of all women in Germany was 215 $\mu\text{g}/\text{day}$, still below the reference value of 400 $\mu\text{g}/\text{day}$ (EUROCAT, 2009). Another study done by Heinz showed that 81% of women 18-40 years of age had a daily folic acid consumption of less than 150 μg (Heinz et al, 2001 as in EUROCAT, 2009). In Hungary, a dietary survey conducted in 2003-2004 showed that the average daily folic acid intake is 132.3 $\mu\text{g}/\text{day}$ (EUROCAT, 2009). The average daily natural folate intake of most women in different European countries ranges from 230 to 280 $\mu\text{g}/\text{day}$ (Flynn et al, 2009). A review done by Kumaniyka and his colleagues in 2000 on dietary behavioral changes in relation with nutrients such as fruits, vegetables and grains highlighted the difficulty of sustaining these behavioral modifications (Kumaniyka et al, 2000). These studies show that achieving the recommendations for folic acid consumption by food folates alone requires major dietary modifications unlikely to be achieved by women of childbearing age. Furthermore, one study tried to compare the effectiveness of the 3 suggested interventions for meeting the recommendations on folic acid. A 12-week trial evaluated the changes in red blood cell folate in response to one of the following interventions: folic acid supplementation (400 $\mu\text{g}/\text{day}$), natural food folates (400 $\mu\text{g}/\text{day}$), fortified food (400 $\mu\text{g}/\text{day}$), qualitative dietary advice and control diet. The study showed that the only interventions increasing significantly blood folate were food fortification and folic acid supplements. The increase in natural food folates did not translate into higher levels of blood folate, most probably because of the low bioavailability and stability of natural folates compared to the synthetic form (Cuskelly et al, 1996).

3.2 Fortification of food with folic acid

Regulations for mandatory food fortification with folic acid are currently in place in 53 countries (CDC, 2010). In 1996, the United States Food and Drug Administration (FDA) issued a mandate to fortify all enriched grain products with folic acid, to be fully implemented in 1998. Food items covered by this mandate were mainly flour, corn meal, pasta and rice and they were fortified with 140 $\mu\text{g}/100\text{g}$ of cereal grains. At this level of fortification, women are expected to consume an average of 100 μg daily of folic acid from fortified cereal grain products (FDA, 1996). Folic acid food fortification became mandatory in Canada and Costa Rica in 1998, with the fortification respectively of 150 μg and 180 $\mu\text{g}/100\text{g}$ of enriched flour and uncooked cereal grains (Chen and Rivera, 2004; Ray, 2004). In 2000, the Chilean ministry of health mandated that folic acid should be added at a level of 2.2mg/kg to wheat flour (Hertrampf and Cortés, 2004). In June 2004, the Brazilian government introduced mandatory fortification of wheat and maize flour with 150 $\mu\text{g}/100\text{g}$ (Almeida and Cardoso, 2010). A number of Middle Eastern countries, as well as Indonesia now fortify their flour. South Africa issued a mandate on food fortification in 2003 with 150 μg of folic acid added to 100g of cereal grains (Sayed et al, 2008). The Australian government had agreed to fortification of flour and bread with folic acid, starting September 2009. In Europe mandatory fortification of a staple food with folic acid has been seriously considered in 8 countries (Denmark, Germany, Ireland, Northern Netherlands, Norway, Poland,

Switzerland and the UK), but debates are still going on. Until now, no European country has agreed to mandatory food fortification with folic acid (EUROCAT, 2009). At the same time, food voluntarily fortified with folic acid (such as breakfast cereals) is available in many European countries. These countries do not implement mandatory folic acid supplementation because, according to them, expected additional health benefits are not scientifically proven in clinical trial, because of feared health consequences and because of the issue of freedom of choice (Eichholzer et al, 2006).

Studies have shown a positive impact of food fortification on blood folate concentrations and a reduction in the prevalence of NTDs in the USA (Boulet et al, 2008), in Canada (Godwin et al, 2008) and in Chile (Nazer et al, 2007).

Measuring blood folate concentrations constitutes one way to evaluate the effect of food fortification programs. Folate deficiency is defined as a serum folate concentration $<7\text{nmol/l}$ (3ng/ml) or a red blood cell folate concentration $<315\text{nmol/l}$ (140ng/ml) (Crider et al, 2011). In The USA, median serum folate increased from $12.6\mu\text{g/l}$ in 1994 to $18.7\mu\text{g/l}$ in 1998 after food fortification (Lawrence et al, 1999). In Canada, a study conducted on 38,000 women in Ontario showed an increase in red blood cell folate from 527nmol/l to 741nmole/l after food fortification ($p<0.001$) (Ray et al, 2002). In Chile, the mean serum concentrations and red blood cell folate increased respectively from 9.7 and 290nmol/l to 37.2 and 707nmol/l ($p<0.0001$) after mandatory fortification (Hertrampf et al, 2003).

The main purpose for folic acid fortification was to reduce the occurrence of NTDs and the associated mortality and morbidities. Many studies around the world evaluated the impact of food fortification on the prevalence of NTDs. In the USA, a report published by the CDC in 2004 found a reduction of 27% in spina bifida and anencephaly between 1995-1996 and 1999-2000 (CDC, MMWR 2004). Different studies in the USA with different methodologies showed a decrease in the prevalence of NTDs between 19-32% after mandatory food fortification, reaching 23 to 54% for spina bifida and 11% to 16% for anencephaly (Boulet et al, 2008; Honein et al, 2001; Mathews, 2008; Williams et al, 2002). In Canada, studies have shown an even greater impact of food fortification than the impact shown in the USA. De Wals and colleagues examined the NTD trends before and after food fortification in seven of ten Canadian provinces (De Wals et al, 2007, 2008). They showed a 46% reduction of NTDs and the magnitude of the decrease was higher for spina bifida (53%) than for anencephaly (38%) (De walls et al, 2007). Similar results were found in Chile, Argentina and Brazil with a reduction in the prevalence of NTDs by 19 to 55 % (Lopez-Camelo et al, 2010). In South Africa, Sayed and his colleagues found a significant decline of 30.5% in the prevalence of NTDs (41.6% for spina bifida and 10.9% for anencephaly) following food fortification in 2003 (Sayed et al, 2008). The differences found in the magnitude of the decline in NTD prevalence after food fortification among different countries depend on many factors such as the initial prevalence of NTDs, the initial folate status of the population, the consumption of fortified food by the population and the presence of birth defects surveillance systems (Crider et al, 2011).

3.3 Folic acid supplements

The third way suggested for increasing women consumption of folic acid is the use of supplements. In order to be effective, these supplements should be taken at least 1 month

before conception. This fact constitutes a limitation for the reliance on supplements as a primary public health program since in many countries, a high level of pregnancies are unplanned such as in the USA where up to 50% of pregnancies are unplanned. International studies have shown a low level of compliance with folic acid supplements intake. In the USA, the percentage of women of childbearing age who consume folic acid supplements is low, slightly increasing from 28% in 1995 to 33% in 2005, up to 40% in 2007 (CDC, 2008). Even in the Netherlands, where the percentage of planned pregnancies is estimated at 85%, only 36% of women take folic acid supplements during the periconceptional period (Meijer and De Walle, 2005). These low levels of intake were seen in different countries with the highest percentage of intake seen in Canada and the USA (40%) and the lowest percentages in Korea (10.3%), Thailand (9.7%) and Lebanon (7.5%) (Kim et al, 2009; Morin et al, 2002; Nasr Hage et al, 2011; Nawapun and Phupong, 2007; CDC, 2008).

4. Women's knowledge and awareness concerning folic acid

Of interest is the relationship between knowledge, awareness and adequate intake of folic acid. Awareness concerning folic acid is usually evaluated in response to the question "have you ever heard or read anything about folic acid?"; levels of awareness reported in the literature are very variable. In the USA, the March of Dimes Birth Defects Foundation reported national levels of awareness of 52% in 1995, increasing to 84% in 2005 (March of Dimes Birth Defects Foundation, 2005). The analysis done by the CDC showed that from 2003 to 2007, levels of awareness were stagnant around 80% (79% in 2003 and 81% in 2007) (CDC, 2008). In Canada, awareness reached a percentage of 95% (French et al, 2003). Even in countries where folic acid intake is very low, women have usually high levels of awareness such as in Lebanon where 60% of women knew about folic acid but only 7.5% of them were using supplements adequately (Nasr Hage et al, 2011). Still in some countries, the number of women who have heard of folic acid is low, reaching 18% in Turkey (Turgul et al, 2009). Even though levels of awareness are acceptable in general with some exceptions, the gap lies in knowledge concerning the benefits of folic acid in NTDs prevention, the nutritional source of natural and synthetic folates and the adequate period of folic acid intake. National percentages in the USA showed that in 1995 only 4% of American women knew that folic acid help reduce the risk of birth defects. These numbers reached 24% in 2004 before decreasing to 19% in 2005. The same report stated that only 2% of American women identified the adequate period for folic acid intake, percentages reaching 12% in 2004 and dropping to 7% in 2005 (March of Dimes Birth Defects Foundation, 2005). A CDC report showed that knowledge concerning the adequate period of intake raise slightly to 12% in 2007 (CDC, 2008). In Canada where the levels of awareness and intake are relatively high, only 25% of women studied in Vancouver knew that folic acid could prevent birth defects (French et al, 2003). As expected, low levels of knowledge were also found in countries with low levels of folic acid intake such as in Thailand where 25% of surveyed women knew that folic acid was something important and in Lebanon where 14% knew about the role of folic acid in NTD prevention and 25% knew about the adequate period for supplementation (Nasr Hage et al, 2011; Nawapun and Phupong, 2007). These numbers show that low intake of folic acid supplements is, at least partially related to lack of knowledge. This relationship was suggested by French and colleagues showing that 78% of the women in their study

indicated that, with knowledge of the benefits of folate, they would use folic acid supplements to reduce the risk of birth defects (French et al, 2003). Another survey done in 2009 by the Gallup organization showed that when women were told the health benefits of taking a multivitamin with folic acid, 66% stated they were “willing” to buy and take a multivitamin and 22% stated they were “somewhat willing” (North Carolina Folic acid Council, 2009). A systematic review of the literature showed that variable interventions on folic acid increased women’s awareness from 60% to 72% and knowledge from 21% to 45%. At the same time, levels of folic acid consumption increased only from 14% to 23% showing a positive but suboptimal impact (Chivu et al. 2007).

5. Folic acid intake

5.1 Determinants of folic acid intake

Studies measuring levels of folic acid intake looked for the factors related to behavior in order to explain low levels of usage. Daily folic acid intake is shown to be related to race/ethnicity, income, marital status, a positive attitude toward taking a physician’s advice, knowledge about the relationship between folic acid and birth defects, planning for the pregnancy, earlier pregnancies and earlier discussion between the women and her physician about vitamins (Ahluwalia et al, 2007; Carmichael et al, 2006; Cleves et al, 2004; French et al, 2003; Rosenberg et al, 2003). Studies also found that younger age is related to a lower intake of folic acid supplements (Morin et al, 2002; CDC, 2008; Timmermans et al, 2008).

Studies in the USA showed that African-American and Hispanic women were less likely to use folic acid supplements than Caucasian women (Ahluwalia et al, 2007; Carmichael et al, 2006; Cleves et al, 2004). Half of Hispanic women, and one third of African-American women aged 18-24 years, as compared to Caucasian women were taking folic acid supplements. An Irish study showed that women from Asia/Middle East, Eastern Europe, Africa and South America were less likely to use folic acid supplements than those from Western Europe and that the highest intake was among women from North America, Australia and New Zealand (McGuire et al, 2010). Ethnicity was also a factor influencing the uptake of folic acid supplements in the Netherlands, where non-western women were less likely to use supplements than western women (Timmermans et al, 2008).

The relationship between low income and a lower intake of supplements has been highlighted in the literature. In their report published in 2008, Petrini and colleagues showed that the lowest prevalences of folic acid intake were seen in those with an annual household income of <\$25,000 compared to those with >\$50,000; these prevalences varied from 24% to 32% between the years 2003 and 2007 for women with the lowest income, and from 38% to 43% between 2003 and 2007 for women with the highest income (CDC, 2008). In Australia, a low income of less than 30,000\$ was also associated with low levels of supplements intake (Forster et al, 2009). Lower socio-economical status was related to an inadequate behavior concerning folic acid supplements (no intake or less than recommended intake) in 2 studies conducted in Ireland and The Netherlands (McGuire et al, 2010; Timmermans et al, 2008). At the same time, high level of education in women of childbearing age was associated with a high level of folic acid intake (Nasr Hage et al, 2011; Nawapun and Phupong, 2007; CDC, 2008).

Being married was frequently identified as a factor of high folic acid intake. Cleves and colleagues found that married women were almost twice more likely than single women to take a daily supplement (Cleves et al, 2004). In the Netherlands, 42% of married women used folic acid supplement as compared to 10% of single women ($p < 0.001$) (Timmermans et al, 2008). Another factor related to folic acid usage is the planning of pregnancy. Studies have shown that women who intended their pregnancies were 3 times more likely to use adequately folic acid supplements than women with unintended pregnancies (Rosenberg et al, 2003). In Europe, countries such as Norway and Ireland, studies have shown a higher chance of folic acid usage among women with planned pregnancies compared to unplanned pregnancies (McGuire et al, 2010; Nilsen et al, 2006). A planned pregnancy was also a factor related to supplements consumption in non-western countries such as Lebanon and Korea (Kim et al, 2009; Nasr Hage et al, 2011). The impact of this factor increases with the proximity of the planned conception, with women who indicate their desire to become pregnant at some time in the future but with no specific plan, being no more likely to take a daily folic acid supplement than women never wanting to become pregnant (Cleves et al, 2004). The number of pregnancies was also found as a determinant of folic acid intake with women having had anterior pregnancies more likely to take folic acid supplements than women with their first pregnancy (Carmichael et al, 2006; Nasr Hage et al, 2011; Nilsen et al, 2006). Only one study conducted in Australia by Forster and his colleagues showed that having had other pregnancies is correlated with lower levels of folic acid intake (Forster et al, 2009). National studies in the USA showed that the pregnancy status was also a factor influencing positively the chance of folic acid intake (CDC, 2008).

Age is a very important factor in relationship with folic acid for many reasons. In the USA, women in the age of 18-24 years account for one third of all births. At the same time, studies have shown that this age group had the least awareness and knowledge about folic acid and the lowest reported daily use of supplements (Morin et al, 2002; CDC, 2008; Timmermans et al, 2008). Furthermore, women in this age group have multiple risk factors for inadequate folic acid consumption. They have a high rate of unintended pregnancies, reaching 80% of all pregnancies in this age group (Finer and Henshaw, 2006) and they adopt risky sexual behaviors, not using systematically birth controls in about 1 in 5 women (Chandra et al, 2005). In this age group, women have also the lowest median annual household income (DeNavas-Walt et al, 2006) and often haven't completed college. They engage in unhealthy dietary behavior and often fail to meet dietary intake recommendations (Anding et al, 2001). All these behavioral, economical, educational and nutritional factors contribute to the low level of folic acid consumption in this age group and to the increased risk of pregnancies affected by NTDs. One study found that women aged 14-19 years were twice as likely to have a pregnancy with NTD as women 25-29 years of age (Reefhuis and Honein, 2004). It is of noteworthy to highlight the fact that all these studies in this age group were conducted in western countries where sexual activities and pregnancies in young, single women are socially accepted in opposition to more conservative societies where data on this subject is lacking.

An interesting study conducted by Ahluwalia and his colleagues showed that certain psychosocial factors as well as advice from a health care provider help women to make decisions about folic acid use (Ahluwalia et al, 2007). In this study, regular use of multivitamins was positively associated with perceived benefits and negatively associated with perceived barriers.

5.2 Strategies to improve folic acid use

In the years following the folic acid recommendations, many educational and promotional campaigns using different means of communication have been used to promote folic acid intake during the periconceptional period with variable results. A systematic review of the literature on interventions designed to improve knowledge, awareness and consumption concerning folic acid was conducted in 2007 (Chivu et al, 2007). Among consumers, the interventions studied were printed and audio-visual media (radio, TV, internet) and printed media with other channels such as counseling, free distribution of folic acid pills, advertisements, magnetized reminders, food labels (folate logo and messages from nutritionists on food packs), slide presentations and reminder phone calls. Among health professionals, the interventions studied consisted of printed materials, training, professional publications, letters, personal communication, incentives (coffee mugs, note pads) and reminder in the patient history form. The review showed that health professionals increased their knowledge about folic acid advised dose from 13 to 58% before intervention to 51% to 70% after intervention and about the recommended period for folic acid usage from 57% to 80% before intervention to 79% to 85% after intervention ($p < 0.0001$). Also, 19% to 62% of health professionals were recommending folic acid to women after the intervention, as compared to 13% to 45% before the intervention. As for women, awareness concerning folic acid increased on average from 60% to 72%, knowledge increased from 21% to 45% and consumption increased from 14% to 23%. Even though variable interventions increased women's knowledge and awareness of folic acid, there were still wide discrepancies between awareness/knowledge and consumption. Studies have shown that, according to social marketing theory, mass media positively influences people's awareness and knowledge, whereas behavior is more influenced by things such as health professionals' counseling and interpersonal communication (Roger, 2003).

Many European countries have launched official educational campaigns on folic acid and its role in the prevention of NTDs. In Belgium, the ONE (Office Of Birth and Childhood) in association with ASBBF (Association Spina Bifida Belge Francophone) ran a campaign including leaflets, a website, information on radio and television and letters to gynecologists and family physicians about the benefits of periconceptional folic acid. After the campaign, a study was conducted in 2006 on 195 women in the first week after delivery. It showed a percentage of folic acid consumption before and during pregnancy of only 12% (EUROCAT, 2009). In Denmark, the Danish Veterinary and Food Administration published leaflets addressing women planning pregnancy and distributed them to clinics, hospitals, pharmacies and drugstores in 1999 and again in 2001. At the same time, a study on compliance with folic acid guidelines was launched in 2000 until 2002 and was able to evaluate the impact of the health education campaign on folic acid usage. This study showed an increase in the proportion of women complying with the recommendation after the campaign. However, even at the end of the period, only 22% of the women with planned pregnancies were following the recommendations on folic acid supplementation (Knudsen et al, 2004). In Germany, there are no official governmental guidelines on periconceptional folic acid and no official health education campaigns. However, in Munich, a non official campaign on folic acid took place from 1996 to 1998. The impact of this campaign was evaluated by measuring periconceptional folic acid intake. This study showed an increase of intake from 2% in 1996 to 5% in 1998. Still, the percentages reached for folic acid

consumption were excessively low (Egen, 1999 as cited in EUROCAT, 2009). In Ireland, since the recommendations on the consumption of folic acid tablets were issued in 1993, many promotional campaigns were undertaken at the national level through periodic media campaigns. At a more local level, health promotion units and public health departments promoted folic acid through a variety of channels, usually on an on-going basis. Studies evaluating the impact of these campaigns showed that even though women's awareness and knowledge concerning the role of folic acid in NTD prevention have reached high levels (95% and 77% respectively in 2002), the consumption of periconceptional folic acid was very low and not improving, being 21% in 1998 and reaching only 23% in 2002 (Ward et al, 2004). In Sweden, since 2007, the Board of the National Food Administration is sending annual letters to all women 18-45 years of age with information on the link between folic acid and the risk of NTDs, in addition to an offer of free folic acid tablets. No Study was conducted in Sweden to evaluate the efficacy of this campaign (EUROCAT, 2009).

6. Health professionals' knowledge and behavior concerning folic acid

Some studies found that health professionals play a major role in folic acid usage by women of childbearing age. The survey conducted by the March of the Dimes Foundation showed that 42% of women, aware of folic acid but not consuming it, would take a multivitamin if advised to do so by a health professional (March of the Dimes, 2004). In the 2004 Health Styles Survey, 91% of women 18-45 years of age agreed to take a multivitamin daily to prevent NTDs if their doctor encouraged them (Williams et al, 2006). In order to evaluate health professionals' knowledge and practice, the CDC initiated a national study in USA in 2001 among obstetricians/gynecologists, family/general physicians, nurse practitioners, certified nurse midwives, physician assistants and registered nurses (Williams et al, 2006). The study showed that more than 85% of the health care professionals knew about the adequate time to use folic acid supplements and that these supplements were necessary beyond what is available in diet. At the same time, 42% of the health professionals surveyed did not know the correct folic acid dosage. Nurse practitioners were most likely and family/general doctors were least likely to recommend supplements. The strongest predictor for recommending supplements was the personal intake of multivitamins by the health professional. Since incorporating messages about folic acid into preventive health care messages is critical to increasing folic acid consumption, health professionals were asked if they addressed folic acid intake during well-women visits. More obstetricians/gynecologists than family/general practitioners said they mentioned folic acid regularly to women (65% v/s 50% respectively). The conclusion of this study was that even though knowledge among health professionals concerning folic acid was good, this knowledge did not necessarily translate into counseling patients about its benefits.

Consistent with these results, 2 other studies conducted in the USA showed that even though health care providers were aware of the importance of folic acid in the prevention of NTDs, only half of them discussed folic acid on a regular basis with women of childbearing age (Hauser et al, 2004; Power et al, 2000). A pilot study conducted in Ontario, Canada showed that 43% of family physicians did not mention folic acid supplementation as a topic for discussion with women of childbearing age, with women actually planning pregnancies or with women in the first trimester of pregnancy (Perleman et al, 1996). The same study showed that up to 40% recommended folic acid to an already pregnant woman, and 10%

recommend it only to pregnant women. Only 14% of physicians in this study had correct knowledge of the appropriate dosages and timing for folate supplements and only 17% of all contacted physicians recommended folate to any women of childbearing age. In Puerto Rico, 88% of primary care physicians demonstrated an inadequate knowledge about folic acid supplements with older physicians and women physicians demonstrating greater knowledge than other physicians in the study (Mirinda et al, 2003). In Israel, 2 studies evaluated physicians' knowledge and practice concerning folic acid. The first study showed that 94% of physicians recommended folic acid to their patients but knowledge in this study was insufficient since only 2% correctly estimated the efficacy of folic acid in decreasing NTDs, 12% knew about the adequate timing and 47% about the correct dosage of folic acid supplements (Abu-Hamad et al, 2008). Another study conducted among women and physicians in Israel showed that 87% of gynecologists recommended preconception folic acid compared to 60% of family physicians ($p < 0.05$) (Auriel et al, 2011). In Germany, a study done in 1996 showed that only 38% of gynecologists in Munich recommended preconceptional folic acid, 8% recommended folic acid at the beginning of pregnancy, 17% recommended folic acid only in cases with family history of NTDs and 37% did not give any recommendation at all. Following an interventional campaign in 1998, 74% of gynecologists recommended preconceptional folic acid. However, there were still 15% of gynecologists who recommended folic acid with the beginning of pregnancy and 11% only in case of a family history (Egen, 2000 as in EUROCAT, 2009).

7. Conclusion

There is strong evidence that most NTDs are preventable by increasing folate status before conception. Responses to this evidence have been variable around the world. Many governments have issued recommendations regarding the necessity for women to take folic acid, from at least 1 month before conception and during the first 3 months of pregnancy. Up to 53 countries around the world issued regulations for mandatory folic acid fortification of staple food. These countries had the most reduction in NTD prevalence according to registries. Even though this was a success story, it was considered as a partial success since the reduction seen with fortification was less than the reduction seen in studies using folic acid supplements. This was the reason behind the recommendations for folic acid supplements during the periconceptional period, at the dose of 400-500 μ g/day for women with no history of NTDs and at the dose of 4-5 mg/day in case of family history or previous personal pregnancies with NTDs. Health education campaigns on local and national were launched in many countries with variable results. These campaigns have been mainly effective on increasing the knowledge and awareness of women concerning folic acid. Still, the actual intake of folic acid is quite low during the periconceptional period. All these facts show that women's behavior is complex and influenced by many determinants. A package of different measures including actions targeting women and health professionals are needed in order to improve intake of folic acid by women of childbearing age.

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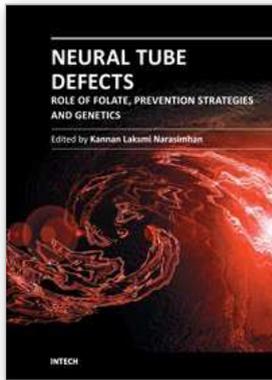
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