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Prevention of NTDs – Proposal of a New Concept

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1. Introduction

Neural tube defects (NTDs) are a heterogeneous group of serious congenital structural abnormalities of the brain and spine due to inadequate formation and/or closure of the developing brain and lower spine in the first month of pregnancy. Anencephalus, spina bifida, and encephalocele are the main manifestations of NTDs. The most serious form of NTDs is an anencephalus incompatible with life. Although NTDs can be detected by increased levels of alpha-fetoprotein and especially by ultrasound investigations early in pregnancy (Holzgreve et al., 1994), the prenatal diagnosis is often missed. After prenatal detection of NTDs, careful and comprehensive counseling of the parents is needed. Some parents select to carry the affected child to term, others decide to have a termination of pregnancy within the legal frameworks of their countries. If an anencephaly is recognized only late in gestation or even only at birth, the psychologic shock for the parents is usually prominent, and in their desperation to have at least some positive aspect in an otherwise hopeless situation parents have even requested in these rare situations to have organs transplanted from anencephalic donors (Holzgreve et al. 1987). NTDs have multiple etiologies and the role of folate, other vitamins and various micronutrients as factors in their etiology has been investigated from different angles for a long time now (Holzgreve et al., 1991, Simpson et al., 2010, 2011). A number of observational and interventional studies have demonstrated that folic acid (FA) supplementation before and in early pregnancy reduces the risk of having a NTD-affected offspring (Laurence et al., 1981; Milunsky et al. 1989; Smithells et al., 1980; Vergel et al., 1990).

Two intervention trials examining the effect of FA supplementation on NTD occurrence and recurrence, published twenty years ago, supported the evidence of the protective role of FA in NTD prevention (Czeizel et al., 1992; Medical Research Council [MRC], 1991). In these two trials, daily FA supplementation, alone, or in combination with other micronutrients, had started before conception and continued throughout the first trimester of pregnancy. Both studies reported a considerable reduction in NTD prevalence. These results were later confirmed in a public health campaign trial in China. Berry et al. (1999) observed a risk reduction between 40% and 85% in China among women who supplemented 400 µg/day FA. The wide range of decrease depends on the different baseline rates of NTD prevalence

in the geographic areas included in the study (Northern region of China with high NTD prevalence, Southern region of China with low NTD prevalence).

Periconceptional supplementation with FA is internationally recognized as an effective measure for prevention of NTD-affected pregnancies. Although not all forms of NTD will be avoidable by additional FA, it is estimated that 70% of NTDs can be circumvented by adequate folate status prior to conception. Health authorities worldwide recommend that all women capable of becoming pregnant should improve their folate status to reduce the likelihood of having an NTD-affected child. Means to achieve this aim include modification of eating habits by choosing more food naturally rich in folate, increasing consumption of FA-fortified food and/or taking FA-containing supplements. Recommendations of the various governmental and non-governmental organizations are nearly identical, advising women of reproductive age to have about 400 – 500 μg FA daily from supplements, fortified foods, or both in addition to a varied diet in order to reduce occurrence of NTD. Women should follow this counsel at least four weeks prior conception and during the first three months of pregnancy (Australian Government, Department of Health and Ageing, National Health and Medical Research Council, 2006; Centers for Disease Control [CDC], 1992; Commission of the European Communities, 1993; German Nutrition Society, Austrian Nutrition Society, Swiss Society for Nutrition Research, Swiss Nutrition Association, 2002; Health Council of the Netherlands, 2008; Institute of Medicine [IOM], 1998; Scientific Advisory Committee on Nutrition [SACN] UK, 2006; US Preventive Task Force [USPTF], 2009; World Health Organization [WHO], 2002).

The U.S. Food and Drug Administration [FDA] had directed that all enriched cereal grain products were to be fortified with FA by January 1, 1998 with the objective to raise FA intake in the population (FDA, 1996). Meanwhile, more than fifty countries in North and South America, the Caribbean, the Middle East, North and Sub Saharan Africa and Oceania followed this strategy of public health policy and have regulations for food fortification programs including FA (Berry et al., 2010). Member states of the European Union have not chosen this policy, partly due to health risks possibly associated with high intake of FA and to the consumer's choice among fortified and non-fortified food (Osterhues et al., 2009).

Concentrations of plasma folate, red blood cell [RBC] folate and total homocysteine [tHcy] are biomarkers for evaluating folate status. Plasma folate concentration depends mainly on actual folate intake whereas RBC folate concentration is an indicator of long-term folate status as erythrocytes accumulate folate only during erythropoiesis. Taken into account the average life span of erythrocytes in the human body (about 120 days), folate concentration in erythrocytes changes slowly. As shown by Daly et al. (1995) in a large Irish cohort study, a woman's risk of having an NTD-affected offspring is inversely associated with maternal RBC folate concentration in early pregnancy. Although the precise optimal effective RBC folate concentration cannot be calculated from the study, the data allow associating RBC folate concentration above 906 nmol/L with the lowest risk for a NTD-affected pregnancy.

The objective of this chapter is to give a short overview of the effect of recommendations on folate status and FA intake and the consequences for NTD prevalence. In countries with mandatory FA food fortification a concomitant decline in NTD prevalence is observed. In countries without this measure only a marginal decrease in NTD prevalence can be

recognized. A reason might be futile educational work. An alternative concept to improve folate status is therefore needed and presented in this chapter. Combining FA supplementation with oral contraceptives [OC] would be a good policy in this context. The rationale behind this concept is based on steady state conditions and elimination kinetics of folate, on the rapid conception among prior OC users who want to become pregnant, and on the high percentage of unplanned pregnancies. Although the majority of studies showed that FA, the synthetic form of the B-vitamin folate, was effective in preventing NTDs, there is evidence to suppose that natural folate like 5-methyltetrahydrofolate [5-MTHF] might have the same effect. Replacement of FA by the natural folate form [6S]-5-methyltetrahydrofolate in supplementation should therefore be considered, too.

2. Folate status and folic acid intake in the post-recommendation era

Numerous studies have been published in the last decade to document variation in folate status and folic acid intake in the post-recommendation period. As mandatory fortification is not yet implemented in all countries worldwide, data for some selected countries both with and without mandatory fortification are presented.

2.1 Data representative of countries with national fortification programmes

The United States were the first to implement mandatory food fortification with FA. In 1996, the U.S. FDA included FA in the pre-existing list of vitamins and minerals which have to be added to grain products in order to restore the micronutrient content of processed food. This regulation became active in 1998, directing that enriched grain has to be fortified with 140 µg FA per 100 g (FDA, 1996). A subsequent increase of daily FA intake by about 100 µg was predicted.

Jacques et al. (1999) and Choumenkovitch et al. (2001) analyzed the effect of this regulation on folate status in the Framingham Offspring Cohort. An increase in plasma folate concentration after fortification was seen in individuals who did not use B-vitamin supplements (117% increase) as well as in those taking B-vitamin supplements (61% increase) (Jacques et al., 1999). Mean RBC folate concentration was also significantly higher after fortification compared to the pre-fortification value in supplement user (+38%) and non-user (+24%) (Choumenkovitch et al., 2001).

Data from three National Health and Nutrition Surveys (NHANES) 1988-2005 show that FA fortification significantly raised folate status in the U.S. population compared to the pre-fortification period (Ganji & Kafai, 2006). Geometric mean RBC folate concentrations were higher in the post-fortification period than in the pre-fortification period (1999-2000: +58.2%; 2001-2002: +56.5%). Similar results were obtained for the geometric mean serum folate concentrations (1999-2000: +149%; 2001-2002: +129.8%). A small decline in serum folate was observed between NHANES 1999-2000 and NHANES 2001-2002. This finding might be explained by a reduced FA content in fortified food in NHANES 2001-2002 compared to NHANES 1999-2000. At the beginning of the fortification period products might had more overage of FA compared to later years (Ganji & Kafai, 2006).

The data of NHANES 2003-2004 and 2005-2006 were used to calculate FA consumption of non-pregnant U.S. women of childbearing age (15-44 years) in the post-fortification period.

The total daily FA intake was estimated by adding the FA value from foods reported in 24-h dietary recalls and the FA content of supplements taken by the subjects. The median intake of FA was 245 $\mu\text{g}/\text{day}$. Less than a quarter of the total group ($n=2617$) achieved the recommended amount of $\geq 400 \mu\text{g}/\text{day}$ FA. The strongest determinant of realizing the recommended FA level was the use of supplements containing FA. The lowest proportion of supplement user was found among young women aged 15-24 years. The median intake of FA in supplement user ($n=647$) was 502 $\mu\text{g}/\text{day}$, and more than two thirds (72%) of this group were able to fulfill the recommended intake. Median FA consumption and percentage achieving recommendation was significantly lower in the non-user group ($n=1,970$; 163 $\mu\text{g}/\text{day}$ FA; 1.4% of the subjects with recommended intake) (Tinker et al., 2010). The marginal intake of FA supplements by young women was reported before by CDC on the basis of national, random-digit-dialed telephone surveys of a proportionate stratified sample of women of childbearing age (CDC, 2008).

Data from other countries support the benefit of fortification on folate status (and NTD prevalence, see 3.1). In Canada, fortification became mandatory at the end of 1998. An increase in RBC folate concentration in women of reproductive age (18-42 years) was observed shortly after the implementation of this regulation (Ray et al., 2002). In Iran, FA fortification became active in 2008. Abdollahi et al. (2011) evaluated the effect of fortification on folate status in postpartum women recruited from hospitals. While intake of dietary folate was stable over time (2006: 198.3 $\mu\text{g}/\text{day}$; 2008: 200.8 $\mu\text{g}/\text{day}$), a significant increase in total folate intake was observed after fortification (2006: 198.3 $\mu\text{g}/\text{day}$; 2008: 413.7 $\mu\text{g}/\text{day}$). Mean serum folate concentration was higher in the post-fortification era than in the pre-fortification era (2006: 13.6 nmol/L; 2008; 18.1 nmol/L). In Australia, fortification with FA was mandated in September 2009. Between April 2009 and April 2010, a significant 31% rise in mean serum folate concentration (17.7. nmol/L vs. 23.1 nmol/L) and a significant 22% increase in mean RBC folate concentration (881 nmol/L vs. 1071 nmol/L) was observed in a sample of inpatients and outpatients living in South Australia, Victoria and Western Australia (Brown et al., 2011).

Worldwide, the number of countries with mandatory FA fortification is rising. Fortification results in an improvement of folate status and folic acid intake in the populations from these countries including women of childbearing age. Nevertheless, as shown by the U.S. data, the major part of the targeted group is not compliant with the recommended intake of FA (400 $\mu\text{g}/\text{day}$) by fortified food alone. This supports the need to take supplements containing FA additionally to fortified food. However, the proportion of women supplementing FA is still low.

2.2 Data representative of countries without national fortification programmes

Up to now, mandatory fortification is not introduced in any European country, although products fortified with FA on voluntary basis are available in some of these countries. Data of folate status and folic acid intake will be presented for some, but not all European countries.

In Germany, a wide range of FA fortified foods is available. In the German National Health Interview and Examination Survey 1998 (Bundesgesundheitsurvey [BGS]), RBC folate and

serum folate concentration were analyzed in 1,244 women of childbearing age (18 and 40 years). Median RBC folate was 266.3 nmol/L and median serum folate was 7.6 nmol/L without significant difference between the age groups. A high proportion of the participants showed suboptimal RBC folate concentrations and only 13% of the women had RBC folate concentrations above the cut-off value for NTD prevention (906 nmol/L) according to Daly et al. (1995) (Thamm et al., 2002). Data of the German National Nutrition Survey II showed a mean folate equivalent intake of 318 µg/day in women aged 19-24 years, 311 µg/day of women aged 25-34 years, and 285 µg/day for women aged 35-50 years (Max-Rubner-Institute [MRI], 2009). Periconceptional use of FA supplements is low in Germany, ranging between 4% and 6% (Egen, 1999; Heinz, 2001). Information campaigns had only a small effect on supplementation. The intake of FA was monitored in two small cross-sectional studies before and after such a campaign. 9.3% of the women interviewed in childbed used FA supplements after the campaign compared with 3.8% before (Egen & Hasford, 2003).

Two recent published studies investigated the folate status and FA supplement use in Irish women. In a large population-based cohort (n= 61,252), data on FA supplementation were available for 61,056 women. 85% of these women reported FA intake at any time during the periconceptional period. However, less than a third (28%) used FA according to the recommendation. Noteworthy is the increase in the proportion of women with correct FA supplementation over the years (2000: 17%; 2006: 36%) (McGuire et al., 2010). McNulty et al. (2011) investigated the association between FA intake and RBC folate concentrations in pregnant Irish women at 14 wk gestation (n=296) in a hospital-based trial. 84% of the participants stated FA supplement use at any time in the first three months of pregnancy. But only 19% of the total sample followed the recommendation correctly, using FA prior to conception and during the first trimester of pregnancy. Serum folate and RBC folate concentration was higher in subjects who started supplementation before or during the first six weeks of pregnancy compared to those who started later in pregnancy. RBC folate concentrations above 906 nmol/L were achieved by 73% of the women using FA already prior to conception, by 62% of the women starting in the first 6 weeks of pregnancy, and by 47% beginning supplementation after the sixth week of gestation.

Inskip et al. (2009) also noticed a poor compliance with recommendation in British Women recruited for the Southampton Women's Survey. Among those women who became pregnant, 2.9% reported to follow the recommendations taking ≥ 400 µg/day FA compared to 0.66% in those women who did not conceive.

To sum up, in countries without mandatory fortification folate status of pregnant women or women of childbearing age is suboptimal and use of FA supplements prior to and during early pregnancy is still very low. On average, less than 10% of the women of reproductive age take FA according to the recommendation although health education initiatives were conducted in most countries. Best compliance with the recommendation in European countries is noticed for the north of the Netherlands and a Danish area where about 30% of the women obey the recommendation (EUROCAT, 2009b; EUROCAT 2009c).

3. Prevalence of NTD in countries with and without national food fortification programmes

The rate of NTDs varies widely depending on the geographic region considered. Worldwide, about 300,000 babies are estimated to be born with a NTD every year (Botto et al., 1999). In Europe, at least 4,500 NTD-affected pregnancies happen per year (EUROCAT, 2009a).

Current data on NTD prevalence will be given separated between countries with national FA fortification programmes and without such programmes.

3.1 Data representative of countries with national fortification programmes

In the United States, the numbers of annual NTD-affected birth in a pre-fortification period (1995-1996) were compared with those in a post-fortification period (1999-2000). The data indicate a 26% decline in spina bifida and anencephaly affected live births and stillbirths in the post-fortification period (CDC, 2004). Racial and ethnic disparities were observed. Hispanic women had the highest rate of NTDs. Updated data were presented in the course of the CDC’s Public Health Grand Rounds in February 2010 and verified the previous calculations of the CDC. According to the new data, the prevalence of NTDs dropped by 37% in a 2-year post-fortification period (2005-2006) compared to a 2-year pre-fortification period (1995-1996), at least partially attributed to the FA fortification programme as a public health strategy (CDC, February 2010).

López-Camelo et al. (2010) reported the variation in birth prevalence of NTDs in 77 hospitals in Chile, Argentina, and Brazil associated with FA fortification programmes in these countries. This paper is a publication of the Latin American Collaborative Study of Congenital Malformations (Éstudio Colaborativo Latino Americano de Malformaciones Congénitas [ECLAMC]). ECLAMC investigates the risk factors and the occurrence of congenital anomalies in South American hospitals since the late 1960s and early 1970s, using a case-control approach. Pre- and post-fortification rates of NTDs within each hospital were used to calculate prevalence rates by country. In Chile, FA fortification policy was implemented in January 2000, in Argentina in November 2003, and in Brazil in June 2004. A statistically significant decrease in birth prevalence estimates for NTDs after fortification was documented in all the three countries. A summary of the results is shown in table 1.

	Chile				Argentina				Brazil			
	before		after		before		after		before		after	
	fortification		fortification		fortification		fortification		fortification		fortification	
	1998-2000		2001-2007		2002-2004		2005-2007		2003-2006/2005		2007/2005-2007	
	isolated	total	isolated	total	isolated	total	isolated	total	isolated	total	isolated	total
Anencephaly	0.52	0.63	0.26	0.37	0.69	0.86	0.29	0.37	0.90	1.12	0.45	0.69
Spina bifida-total	0.73	1.02	0.24	0.46	0.82	1.27	0.33	0.66	0.86	1.45	0.69	1.42

Table 1. Birth prevalence estimates for NTDs (isolated and total) before and after implementation of FA food fortification in three Latin American countries, live born babies/1,000 births (modified according to Lopèz-Camelo et al., 2010)

These findings were confirmed by a study recently published by Orioli et al. (2011) in a cross-sectional study of Brazilian live births. Spina bifida birth prevalence in each state of Brazil was estimated from the Live Births Information System (Sistema de Informações sobre Nascidos Vivos [SINASC]) for both a pre-fortification and a post-fortification period (2004 and 2006). The authors observed a significant 39% decline in spina bifida birth prevalence in 2006 compared to 2004.

In Iran, flour fortification with FA started in 2008. In a hospital-based study, Abdollahi et al. (2011) noticed a 31% reduction in NTD birth prevalence in a post-fortification period (December 2007 to December 2008; 2.19 cases per 1,000 births) compared to a pre-fortification period (September 2006 to July 2007; 3.16 cases per 1,000 births) in the north of Iran. Jordan has initiated national food fortification programmes including wheat flour fortification with FA in April 2002. Amarin & Obeidat (2010) conducted a hospital-based study to evaluate the effect of FA fortified foods on the incidence on NTD in live born babies. Fortification has led to a concomitant significant fall in the number of NTDs in the north of Jordan (pre-fortification period 2000-2001: 1.85 cases per 1,000 births; post-fortification period 2005-2006: 0.95 cases per 1,000 births). A similar downward trend could be seen in Oman, where flour fortification with FA started in 1996 (Alasfoor et al., 2010). Spina bifida incidence varied from 2.34 to 4.03 per 1,000 births between 1991 and 1996 and dropped to 0.29 per 1,000 births in 2006.

In summary, national fortification programmes are associated with a notable fall in NTD prevalence. But the reduction in NTD is not completely attributed to FA fortification as there was a declining trend in some countries before fortification. In addition, one has to bear in mind whether total prevalence or live birth prevalence is reported. Live birth prevalence published by Lopez-Camelo et al. (2010), Abdollahi et al. (2011), or Amarin & Obeidat (2010) is not the best variable to deduce progress in prevention of NTD from FA fortification. Other factors than FA may be responsible for the decline like high-quality prenatal screening and medical termination of pregnancy following diagnosis of NTD. It may be that reporting the live birth prevalence therefore underestimates the total prevalence of NTD and in consequence overestimates the effect of FA fortification on NTD prevention.

3.2 Data representative of countries without national fortification programmes

Prevalence of NTDs over time across Europe is monitored by the European Surveillance Registry for Congenital Anomalies and Twins [EUROCAT]. EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies started in 1979. EUROCAT is also a WHO-collaborating center for the epidemiological surveillance of congenital anomalies. Nowadays, 21 countries¹ contribute data to EUROCAT. None of these countries has implemented regulation for mandatory FA food fortification. About 31% of the births in the European Union are covered by EUROCAT (Boyd et al., 2011). Both terminations of pregnancy and births are registered. Total prevalence rates are calculated, including all cases affected by NTD (live births, stillbirths, fetal deaths from 20 weeks of gestation, and terminated pregnancies of any gestational age)

¹Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom (EUROCAT, 2009a)

divided by the number of all births, still and live, in the registry population. Live birth prevalence includes live born cases only.

In Europe (2004-2008), the total prevalence of NTDs was 0.96 per 1,000 births. The live birth prevalence in the same period was 0.24 per 1,000 births. The lowest live birth prevalence is observed in Spain (0.08/1,000 births), the highest in Malta (0.96/1,000 births). Portugal has the lowest total NTD prevalence (0.20/1,000 births) and France the highest (1.46/1,000 births). As an estimated 72% of NTD-affected pregnancies are interrupted, discrepancies between live birth and total NTD prevalence are primarily attributed to the termination of an NTD-affected pregnancy following prenatal diagnosis (EUROCAT, 2009d).

Data on the trend in prevalence of NTDs are extracted from the EUROCAT Central Registry database 1980-2007 (EUROCAT, 2009a). According to the EUROCAT report (EUROCAT, 2009a) a declining trend in NTD prevalence was observed in the years 1992-2007. This tendency is attributed to a slightly, but significantly decreasing trend for anencephaly whereas there is no significant reduction trend for spina bifida. However, changes in NTD rates in the period considered vary among the European countries, partly due to differences in collecting and reporting data. A significant fall in NTD since 1992 has been found in Ireland. No variation has been observed in the UK. In the Continental Europe, represented by France, Belgium, Switzerland, Northern Netherlands, Denmark, Germany, Austria, Norway, Poland, Hungary, Ukraine and Finland, a significant reduction in NTD prevalence has only been observed in the Northern Netherlands. In South Europe, exemplified by Italy, Croatia, Portugal, Malta, and Spain, NTD prevalence dropped significantly since 1992.

In Europe, there are geographical discrepancies in the prevalence and trend in prevalence in NTD. The decline in Ireland can not only be explained by FA supplementation as reduction has started already before the implementation of a national policy, but rather by an improvement of the general diet. Similar downward trends were observed in other non-European countries without or prior to mandatory fortification. For example, data from South Australia, Victoria and Western Australia show a fall in total prevalence years before onset of mandatory fortification in 2009. Abeywardana et al. (2010) reported a decreasing prevalence for NTDs in these states from 1992 to 2005 with the main reduction already occurring between 1992 and 1998.

4. Natural folate like [6S]-5-methyltetrahydrofolate as an alternative to folic acid in NTD prevention

4.1 Background information

The term folate refers to a group of biologically active metabolites of this water-soluble B-vitamin. Folates occur naturally in biological systems in different chemical forms (mono- and polyglutamate forms, different one-carbon units bound). Folate, in the form of tetrahydrofolate (THF), acts as a coenzyme required for the transfer and processing of one-carbon units. The vitamin is thereby involved in numerous metabolic reactions including nucleotide synthesis, aminoacid metabolism, methylation reactions, and gene expression. FA is a synthetic form of the vitamin that does not occur in nature. It is commonly used in pharmaceuticals, supplements and fortified food products because of its high stability (Pietrzik et al. 2010).

As folates are absorbed in the monoglutamate form, polyglutamates have to be hydrolyzed to monoglutamates in the gut by the mucosal brush border conjugase prior to absorption. Most folate monoglutamates are taken up by a saturable carrier-mediated active mechanism. Only a small percentage is absorbed by a non-saturable diffusion-mediated process. In the mucosal cell, the monoglutamates are converted to 5-methyltetrahydrofolate (5-MTHF). This form can be taken up by the liver where it is retained or released to the systematic circulation or bile. Before being stored in tissue or acting as a coenzyme, monoglutamates has to be converted to the polyglutamates. Release from tissue into circulation depends on previous hydrolyzation to the monoglutamate form (Pietrzik et al. 2010).

FA is absorbed by passive diffusion. It is reduced via dihydrofolate to THF by the enzyme dihydrofolate reductase in order to become metabolically active. THF is then metabolized to 5-MTHF in the human mucosal cell and/or liver. As the capacity of conversion is limited, unmetabolized FA can appear in the systemic circulation, even after low-dose application (Pietrzik et al., 2010). A physiological function of FA itself is not known and is not to be expected as FA does not occur in nature. The underlying mechanism by which FA reduces the risk of NTD is unknown. Obviously, the beneficial role of FA in NTD prevention bases on upgrading the pool of active folate forms.

4.2 Potential health risk associated with FA

There is evidence that harmful effects might be associated with intake of FA. High intake of FA may delay the diagnosis of vitamin B12 deficiency by masking the hematological manifestation of this deficit. Megaloblastic anemia is one symptom of a severe vitamin B12 deficiency due to secondary folate deficiency. High doses of FA can result in the recovery of hematological symptoms, thereby complicating the diagnosis of vitamin B12 deficiency and allowing neurological complications in these patients to progress. This problem is specially addressed to the elderly. The IOM therefore sets a tolerable upper intake level of 1,000 µg/day of FA from supplements or fortified food for adults (19 years and older) (IOM, 1998). Furthermore, concerns have been raised that FA blunts antifolate therapy, i.e. reducing seizure control by phenytoin and affecting the efficacy of methotrexate. In addition, high folate status may trigger the promotion of malignant and premalignant lesions. Unmetabolized FA in the human systemic circulation, observed even after application of low-dose FA, is discussed to interfere with the transport, metabolism und functions of natural folates and may have a negative effect on natural killer cell toxicity. Twinning, miscarriage and epigenetic hypermethylation are further possible side effects which are put up for discussion (Kelly et al., 1997; Pietrzik et al., 2010; Smith et al., 2008; Troen et al., 2006).

4.3 Folate status and NTD risk associated with dietary folate

Observational studies indicate that the risk of an NTD-affected pregnancy is inversely associated with the intake of food folate in unsupplemented women (Shaw et al., 1995; Werler et al., 1993). As reviewed in detail by Eskes (2002), several, but not all studies showed lower serum folate or RBC folate concentrations in early pregnancy in women with NTD-affected pregnancy compared to controls.

Brouwer et al. (1999) investigated the effect of additional dietary folate from vegetables and citrus fruits on folate status. In a placebo-controlled, parallel group nutrition intervention trial in 66 healthy male and female subjects three treatments were used: 1) a high folate diet (total folate intake: 560 µg/day) plus a placebo, 2) a low folate diet (total folate content: 210 µg/day) plus supplemental FA and placebo on alternate days (FA intake: 250 µg/day), and 3) a low folate diet (total folate intake: 210 µg/day) plus placebo. Baseline folate status was measured by plasma folate, RBC folate and homocysteine [tHcy] concentrations. These parameters did not differ significantly among these three groups. After four weeks of intervention, plasma folate and RBC folate increased and tHcy decreased in both the high folate diet and the FA groups. Changes in folate indices assumed the same proportions in the high folate diet and the FA group. However, achieving a high folate diet as used by Brouwer et al. (1999) in their study requires major modifications in dietary behavior. This is unlikely to be realized by most subjects in everyday life over a longer period of time.

4.4 Studies with the natural folate form [6S]-5-methyltetrahydrofolate

Most dietary folate and FA are metabolized to 5-MTHF as described before (see 4.1). Since some years, 5-MTHF has been available commercially, both in the natural form [6S]-5-MTHF and as the racemic mixture [6RS]-5-MTHF. However, the [6R]-isomer of the racemic mixture is presumed to be biologically inactive and therefore without nutritional significance. In addition, adverse effects of the [6R]-isomer on storage are under discussion (Mader et al., 1995; Willems et al., 2004). Thus, interventional trials with the racemic mixture of 5-MTHF as conducted by Fohr et al. (2002), Litynski et al. (2002), and Willems et al. (2004) are not considered in this chapter.

[6S]-5-MTHF is the biologically active diastereoisomer, also known as L-5-MTHF. It is available as a calcium salt, and in this form used in some vitamin supplements and pharmaceuticals. Only studies with [6S]-5-MTHF administered to healthy adults in physiological doses will be reviewed in the following sections.

4.4.1 Bioavailability studies with [6S]-5-methyltetrahydrofolate in physiological doses in healthy adults

Prinz-Langenohl et al. (2009) compared the bioavailability of [6S]-5-MTHF and FA in a short-term study, using a methodological approach which is standard in pharmacology for testing the pharmacokinetics of active drug ingredients. Twenty-four healthy females of childbearing age received a single oral dose of FA (400 µg) as reference and equimolar amount of [6S]-5-MTHF (416 µg as calcium salt) as test in a randomized, double-blind, crossover design. Plasma folate was monitored at various time points up to 8 h after application. Parameters to compare the bioavailability of both treatments included the concentration time-profile (area under the curve of the plasma folate concentration versus time [AUC]), the maximal plasma folate concentration [C_{max}] and the time to reach the maximum. Plasma folate concentration peaked significantly higher and within a shorter period of time with [6S]-5-MTHF than with FA. These findings confirm the result of a previous trial conducted by Prinz-Langenohl et al. (2003). In that randomized, double-blind, four period cross-over study, 21 healthy young females received a single oral dose of 400 µg FA and 416 µg [6S]-5-MTHF (as calcium salt) either without or with FA pre-saturation (1

mg/10 days prior to the study day). The volunteers were pre-saturated with FA in order to minimize difference in volunteers' baseline plasma folate concentrations. Plasma responses were measured up to 8 h after vitamin intake. With respect to the primary variables of bioavailability, AUC and C_{max} , the authors concluded that [6S]-5-MTHF is more effective in increasing plasma folate in comparison to FA depending on the procedure of FA pre-loading. This finding is in line with the results of Pentieva et al. (2004). Pentieva et al. (2004) compared the bioavailability of [6S]-5-MTHF with that of FA by monitoring plasma folate responses for a 10-h period after administration of the two vitamin forms. Both interventions were given in an oral single dose (500 µg) to 13 males pre-saturated with FA in a randomized, double-blind, placebo-controlled, crossover trial. No differences in the bioavailability endpoints AUC and C_{max} were observed between [6S]-5-MTHF and FA.

4.4.2 Intervention studies with [6S]-5-methyltetrahydrofolate in physiological doses in healthy adults

Several studies suggest that long-term intervention with [6S]-5-MTHF in a physiological low dose has at least the same effect on folate indices in healthy subjects as has FA. A long-term study in New Zealand compared the changes in blood folate in women of childbearing age ($n=104$) supplemented with either [6S]-5-MTHF (113 µg/day, calcium salt), FA (100 µg/day), or placebo for 24 wk (Venn et al., 2002). In this randomized, double-blind, parallel-group trial, RBC folate and plasma folate concentrations increased to a similar extent under both vitamin treatments. A second study with a similar design was published one year later by this working group (Venn et al., 2003). Venn et al. (2003) confirmed in a group of middle-aged volunteers of both genders ($n=167$) that the increase in RBC folate and plasma folate concentrations did not differ significantly between the FA (100 µg/day) and the [6S]-5-MTHF (113 µg/day) groups supplemented for 24 wk. In addition, they were able to show that [6S]-5-MTHF was significantly more effective than FA in lowering plasma tHcy. Lamers et al. (2004) compared the tHcy-lowering and plasma folate rising effect of [6S]-5-MTHF and FA during 24 wk of supplementation. Female subjects ($n=144$) were randomly allocated to one of the four intervention groups: 400 µg/day FA, 416 µg/day [6S]-5-MTHF, 208 µg/day [6S]-5-MTHF, or placebo. In comparison to the placebo group, tHcy decreased by 15%, 19%, and 19% in the three vitamin groups. The differences between the groups were not significant. The increase in plasma folate was significant compared to placebo (151%, 164%, and 101%). However, supplementation with the low-dose [6S]-5-MTHF resulted in a significant lower increase relative to the two other folate groups. A second long-term study with the same treatment regime and identical duration (24 wk) was performed by Lamers et al. (2006). The primary objective was to investigate the effect of treatment on RBC folate and plasma folate concentration in healthy females ($n=144$). The increase in RBC and plasma folate was significantly higher in the group receiving 416 µg [6S]-5-MTHF than in the two other folate groups. Whereas plasma folate reached a plateau after 12 wk supplementation in all groups, a steady state for RBC folate was not observed. The authors concluded that [6S]-5-MTHF is more effective in increasing RBC folate when given in doses equimolar to FA. In addition, they recommended to extend the preconceptional period of supplementation to 12 weeks or more; consequently one would make sure to reach the most preventive RBC folate concentration according to Daly et al. (1995). Houghton et al. (2006) conducted a randomized, placebo-controlled study with healthy women ($n=72$) to assess the

effectiveness of [6S]-5-MTHF, FA, and placebo in upholding RBC folate concentration during lactation. After delivery, the lactating women were assigned to receive [6S]-5-MTHF (416 µg/day), folic acid (400 µg/day), or placebo for 16 wk. At the end of the treatment period, RBC folate concentration in the [6S]-5-MTHF group was higher than in the two other groups after adjustment for baseline concentrations at 36 wk gestation. In conclusion, the authors classified [6S]-5-MTHF to be as effective as, or even more than FA in maintaining RBC folate concentrations during lactation.

The main characteristics of the studies described are summarized in Table 2.

Authors (year)	Design	Subjects	Intervention	Outcome variable	Main result
<i>Short-term bioavailability studies</i>					
Prinz-Langenohl et al. (2003)	randomized, double-blind, crossover	young females (n=21)	single dose: 400 µg FA and 416 µg [6S]-5-MTHF with /without FA preload	plasma folate	[6S]-5-MTHF as effective as FA in increasing plasma folate
Pentieva et al. (2004)	randomized, double-blind, crossover, placebo-controlled	young males (n=13)	single dose: 500 µg FA and 500 µg [6S]-5-MTHF with FA preload	plasma folate	[6S]-5-MTHF as effective as FA in increasing plasma folate
Prinz-Langenohl et al. (2009)	randomized, double-blind, crossover	young females (n=24)	single dose: 400 µg FA and 416 µg [6S]-5-MTHF without FA preload	plasma folate	[6S]-5-MTHF as effective as FA in increasing plasma folate
<i>Long-term intervention studies</i>					
Vern et al. (2002)	randomized, double-blind, parallel-group, placebo-controlled	young females (n=104)	24 wk: 100 µg FA/d or 113 µg [6S]-5-MTHF/d or placebo	plasma folate, RBC folate	similar increase in plasma folate and RBC folate in the folate groups; no plateau in plasma or RBC folate reached after 24 wk
Venn et al. (2003)	randomized, double-blind, parallel-group, placebo-controlled	middle-aged males and females (n=167)	24 wk: 100 µg FA/d or 113 µg [6S]-5-MTHF/d or placebo	plasma folate, RBC folate, tHcy	similar increase in plasma folate and RBC folate in the folate groups; [6S]-5-MTHF more effective in lowering tHcy than FA
Lamers et al. (2004)	randomized, double-blind, parallel-group, placebo-controlled	young females (n=144)	24 wk: 400 µg FA/d or 416 µg [6S]-5-MTHF/d or 208 µg [6S]-5-MTHF/d or placebo	tHcy, plasma folate	both doses of [6S]-5-MTHF effective as FA in lowering tHcy; plasma folate increase in all groups, but lower in low-dose [6S]-5-MTHF than in the two other folate groups

Authors (year)	Design	Subjects	Intervention	Outcome variable	Main result
Lamers et al. (2006)	randomized, double-blind, parallel-group, placebo-controlled	young females (n=144)	24 wk: 400 µg FA/ d or 416 µg [6S]-5-MTHF/ d or 208 µg [6S]-5-MTHF/ d or placebo	RBC folate, plasma folate	increase in RBC folate higher in high-dose [6S]-5-MTHF than in the two other folate groups, no plateau in RBC folate reached in the three folate groups after 24 wk; increase in plasma folate higher in high-dose [6S]-5-MTHF than in the two other folate groups, plateau in plasma folate reached after 12 wk
Houghton et al. (2006)	randomized, double-blind, parallel-group, placebo-controlled	lactating healthy women (n=72)	16 wk: 400 µg FA/ d or 416 µg [6S]-5-MTHF/ d or placebo	RBC folate	[6S]-5-MTHF at least as effective as FA in maintaining RBC folate

FA, folic acid; tHcy, total plasma homocysteine; [6S]-5-MTHF, [6S]-5-methyltetrahydrofolate; RBC, red blood cell

Table 2. Interventional studies: effect of [6S]-5-MTHF supplementation in physiological doses on folate parameters in healthy adults.

In conclusion, short-term and long-term studies with healthy adults and women of childbearing age have shown that the natural folate form [6S]-5-MTHF administered in doses equimolar to FA is at least as effective as FA in improving folate status indices. A placebo-controlled trial to explore the effect of [6S]-5-MTHF given in the periconceptional period on the occurrence of NTDs as primary endpoint would be unethical. However, the inverse relation between RBC folate concentration as a surrogate endpoint and the risk of NTD has been calculated by Daly et al. (1995). Based on this observation [6S]-5-MTHF is considered to be an adequate alternative to FA supplementation in prevention of NTDs. In contrast to FA, the natural form of folate has never been linked to adverse effects as discussed for FA (Pietrzik et al., 2010).

5. Rationale for a new prevention concept – combining oral contraceptives with folic acid or folates

Although public is informed about the advantages mentioned above since more than two decades, the recommendations on NTD prevention by FA are marginally translated into practice in the majority of the European countries. Impact on NTD prevalence in Europe is small in contrast to countries with mandated FA food fortification. Therefore, an additional concept is needed to raise folate status in European women, taking into account both the steady state conditions of blood folate, the problem of unplanned pregnancies, and faster conception as expected.

5.1 Steady state conditions and elimination kinetics of red blood cell folate

Improvement of folate status should begin already in the preconceptional period to start pregnancy in an optimal folate status. Several intervention trials have investigated the time-effect of long-term supplementation on folate status indices in healthy adults. Bakker et al. (2009) studied RBC folate, plasma folate, and tHcy concentration in 27 healthy women in a 8-wk period of supplementation with 500 µg/day FA followed by a 12-wk period without supplementation. Serum folate and RBC folate concentrations significantly increased by supplementation compared to the control group (no supplementation). The authors assumed that a steady state was not reached in the 12-wk intervention period. In addition, Bakker et al. (2009) observed that serum folate and plasma tHcy returned to baseline after a 12-wk wash-out period following FA discontinuation. In contrast, RBC folate concentration remained significantly higher in the prior vitamin intervention group compared with the control group at the end of the wash-out phase. Other studies showed that low dose FA or [6S]-5-MTHF supplementation over 24 wk resulted in plasma folate steady state, but not in RBC folate steady state (Lamers et al., 2006; Venn et al., 2002). RBC folate seems to cumulate slower than plasma folate as erythrocytes take up folate only during erythropoiesis and have an average life span of 120 days.

Pietrzik et al. (2007) published a working model for appearance and elimination kinetics of RBC folate, assuming that steady state conditions of RBC folate can be calculated based on linear pharmacokinetics and the biological half-life of RBC folate (8 wk). This model predicts that a mean steady state of RBC folate would be achieved after 5 half-life periods (40 wk) after starting low-dose folate supplementation. In addition, Pietrzik et al. (2007) hypothesized that the period of time for the elimination of RBC folate after supplementation cessation is equal to the period of time needed to reach steady state in RBC folate by supplementation.

The latter assumption was partly confirmed by a study which assessed the pharmacokinetic effect on plasma folate and RBC folate during 24 wk of daily treatment with 451 µg [6S]-5-MTHF (as calcium salt) or with 400 µg FA, both in combination with an OC followed by 20 wk elimination phase with OC mono-application. Healthy women (n=172) between 18 to 40 years of age were randomly assigned to one of the treatments. Subjects were not allowed to consume FA-fortified food and vitamin supplements. Plasma and RBC folate increased by supplementation over 24 wk and decreased in the elimination phase reaching nearly baseline values after 20 wk in the MTHF group (FDA, 2010a).

Hao et al. (2008) evaluated the changes in RBC folate and plasma folate concentrations in young Chinese women (n=1108) treated with different doses and dosing schedules of FA for six months (100 µg/day FA, 4 x 25 µg/day FA, 400 µg/day FA, 4 x 100 µg/d FA, 4000 µg/day FA, 4000 µg/wk FA) in a randomized, double-blind, parallel group trial. Folate status was measured at baseline, three times during the intervention, and after a wash-out period of three months following the discontinuation of FA supplementation. Plasma folate plateaued between three and six months in all intervention groups. Three months after cessation of FA administration, plasma folate remained higher than baseline. A plateau in RBC folate was not observed over the treatment period. The concentrations of RBC folate at the end of the wash-out period were significantly higher than those at baseline only in the groups who had received ≥ 400 µg/day FA. However, the practical aspect of the high dose group is missing as women would not be exposed to 4000 µg of FA with respect to NTD occurrence reduction.

Houghton et al. (2011) conducted a study to evaluate the long-term effect of FA supplementation on RBC folate in healthy female subjects of fertile age. 144 women were randomly assigned to receive 140 µg FA/day, or 400 µg FA/day, or placebo for 40 wk. RBC folate concentration as primary endpoint of the trial was measured at different time points during the study (baseline, 6, 12, 29, and 40 wk after start of supplementation). The statistical analysis of the data was restricted to subjects with a supplement compliance of $\geq 70\%$. RBC folate concentration increased in both FA groups throughout the intervention period, but RBC folate did not stabilize in neither of the two groups. The authors concluded that the time required to reach steady state is even longer than assumed by Pietrzik et al. (2007).

To substantiate the different hypothetical assumptions, a study is needed with FA supplementation as recommended, an intervention period of sufficient duration to achieve RBC folate steady state, and a wash-out period monitoring RBC folate concentration till return to baseline values.

5.2 Planned and unplanned pregnancy

Recommendations and health education campaigns to raise folate status with respect to NTD prevention address fertile women. Success depends on the fact that pregnancies are planned. However, pregnancies are often unplanned, subsuming that they are unintended, untimed and/ or unwanted. Blumenthal et al. (2011) and Finer & Henshaw (2006) identified a number of risk factors for an unplanned pregnancy including young age of the women, poor education of women, low-income, racial origin, domestic violence, poor access to contraceptive supplies, lack of knowledge about contraception, and being unmarried. Failure of OC and other contraceptive methods also contributes to unplanned pregnancy. According to Finer and Henshaw (2006) nearly half of the unintended conceptions occur during a month when contraceptive methods were used. Typical failure rates for oral formulations of hormonal contraceptives range from $<3\%$ to 5% mainly due to failures in compliance followed by vomiting and diarrhea (Barjot et al., 2006; Frye, 2006).

Data on the proportion of planned or unplanned pregnancies have a high variability between the countries. Moreover, evidence is limited because data are often based upon small-scale, non-representative surveys with different design.

Ray et al. (2004) published a systematic overview of 52 survey studies worldwide regarding the pre- and periconceptional use of folic acid supplements. In 19 of these studies, information about the proportion of unplanned pregnancies was available which ranged from 10 to 78%. Data from the National Survey of Family Growth (NSFG) 2002 combined with birth, abortion and population data from other sources indicate that nearly half (49%) of the pregnancies in the United States are unintended (Finer & Henshaw, 2006). In a Chinese study, about 72% of the women had not planned their pregnancy (Gong et al., 2010).

In Europe, more than half of the pregnancies are unplanned (EUROCAT, 2009a). The data of the country specific reports (EUROCAT, 2009b, 2009c) can be summarized as follows:

No information is available for Austria, Belgium, France, Malta, Slovenia, Ukraine, and Portugal. The percentage of pregnancies that are planned in Switzerland and Poland is thought to be very low. In Denmark, the compliance with contraception is rather high. Therefore, the rate of planned pregnancies is assumed to be somewhat higher than in the United States where about half of the pregnancies are planned. In one regional study in Denmark pregnant women attending a university hospital ($n=3516$) were recruited in the period 1994 to 1996. In this study 68% of the women confirmed that the pregnancy was planned. The study population was judged to be a representative subsample of the Danish population. In a small study in Finland, 547 women were interviewed during their first prenatal care visit in the year 2000. About 36% to 86% of the women had planned the pregnancy. The wide range depends on the different interpretation of the concept of a planned pregnancy. In Ireland, studies have shown that the percentage of women planning their pregnancy has been stable from 1996-2002 at 40-45%. There is little knowledge in Croatia about the rate of planned pregnancies, but 75% of pregnancies are assumed to be planned. Proportion of Italian planned pregnancies ranges between 61% and 64%. The proportion of Norwegian pregnancies that are planned is supposed to be between 50% and 75%. The situation in Sweden is assumed to be comparable to that in Norway. Basing on the data of one survey conducted from 1994 to 2006 in Barcelona, 50-75% of the Spanish pregnancies seem to be planned. Studies in the UK indicate that 60-75% of the pregnancies are planned. In the Netherlands, the proportion of planned pregnancies is high (85%) and not related to the socio-economic status of the women. In Hungary, 67.4% of pregnancies were found to be planned. In Germany, four studies were conducted in which women were asked after delivery whether or not their pregnancy was planned. According to these studies 66-72% of the women confirmed their pregnancy to be planned.

The data of planned and unplanned pregnancies in European countries according to EUROCAT (2009b, 2009c) are presented in table 3.

A study recently published, but not included in the EUROCAT report, indicate that in Germany 47% of the pregnancies in the Eastern federal states (newly formed German states, formerly GDR) and 29% in the Western federal states (old German states, BRD) are unplanned. Especially young women (16-19 years) in Germany have a high percentage of unplanned pregnancies (75%) (Rieback & Kreyenfeld, 2009).

The data indicate that a major percentage of pregnancies are unplanned. This fact is relevant for prevention of NTD because women, not planning a pregnancy, may be uninterested in prenatal instructions or will not receive preconceptional health information by their gynecologist, i.e. advice and information about NTD prevention by improving folate status preconceptionally. As shown by Gong et al. (2010) the proportion of Chinese women who took FA prior to conception was higher for those who had planned their pregnancy. Similar results are reported for Irish women. Less than recommended or no FA supplementation was associated with unplanned pregnancy (McGuire et al., 2010). As indicated in the systematic reviews of Ray et al. (2004) and Stockley & Lund (2008), unintended pregnancy is the most important factor for lack of compliance with the recommendations.

Country	Percentage estimates of planned pregnancies	Percentage estimates of unplanned pregnancies
Austria	No data available	No data available
Belgium	No data available	No data available
Croatia	75%	25%
Denmark	50%-68%	32%-50%
Finland	36%-86%	14%-64%
France	No data available	No data available
Germany	66%-72%	28%-34%
Ireland	40%-45%	55%-60%
Italy	61%-64%	36%-39%
Malta	No data available	No data available
Netherlands	85%	15%
Norway	50%-75%	25%-50%
Poland	Thought to be very low	Thought to be very high
Portugal	No data available	No data available
Spain	50%-75%	25%-50%
Slovenia	No data available	No data available
Sweden	50-75%	25%-50%
Switzerland	Thought to be very low	Thought to be very high
UK	60%-75%	25%-40%
Ukraine	No data available	No data available

Table 3. Planned and unplanned pregnancies in Europe (EUROCAT, 2009b, 2009c)

5.3 Pregnancy after discontinuation of an oral contraceptive

Oral contraceptives represent a commonly used method of reversible conception control in industrialized countries. In the German BGS 1998, for example, 30% of the women between 18 and 45 years of age in the Western federal states and 47% in the Eastern federal states reported use of OC (Knopf & Melchert, 1999). Ovulation returns rapidly after stopping OC as shown by Cronin et al. (2009). In a prospective, non-interventional cohort study of 59,510 users of OC in seven European countries the rate of pregnancy over time was monitored in those participants who stopped use of OC because of a planned pregnancy (n=2,064). 21.1% of the prior OC users became pregnant one cycle after OC cessation. The rate of pregnancy increased to 45.7% after three cycles, and 79.4% after 13 cycles. Nearly half of the women who did not become pregnant in the first 13 cycles after OC cessation did so in the second year. 26 cycles after OC cessation, overall pregnancy rate was 88.3%. The age of the women only had a minor influence on the rate of pregnancy up to the age of 35 years.

The findings of this study have important consequences with respect to the periconceptional improvement of folate status. First of all, a considerable part of the prior OC users may become pregnant before being able to transfer the recommendations of NTD prevention in practice. Moreover, achieving the preventive level of RBC folate is nearly impossible when becoming pregnant sooner than expected (≤ 3 months after stopping OC), assuming that the women are counseled by the gynecologist before stopping OC and act according to the recommendation already while using OC.

6. Conclusion

Optimization of folate status by consumption of food naturally rich in folate and/or fortified with FA, and FA supplementation is possible. A daily intake of 400 µg/day FA is recommended to women of childbearing age and/or women planning to get pregnant. However, as reviewed in this chapter compliance with recommendations is poor even in countries with mandatory food fortification. Impact on total NTD prevalence is marginal in countries without mandatory FA food fortification. Regarding this unsatisfactory development in prevention of NTD, an additional concept is needed.

Combining OC with folate could be such an alternative. At first glance, this concept does not make sense as women, using OC, will prevent conception and therefore do not represent the target group of the recommendation. However, referring to the information given in section 4 and 5 of this chapter several advantages of this approach are obvious.

Firstly, fortifying OC with FA will minimize the risk of a NTD-affected baby if pregnancy will happen due to failure of this contraceptive method. As shown by Barjot et al. (2006) and Frye (2006) the failure rate of OC is up to 5% mainly due to inconsistencies or mistakes in taking the OC, vomiting and diarrhea. Failure of contraceptive methods is one reason for an unplanned pregnancy. Secondly, unplanned pregnancy is one predictor of low compliance to the FA recommendation as reviewed by Ray et al. (2004) and Stockley & Lund (2008). Combining OC with folate would result in a protective maternal folate status for OC users being advantageous to those conceiving under OC therapy. Thirdly, as shown by Cronin et al. (2009) conception may happen in a short period after cessation of OC use: more than a 20% of prior OC users got pregnant one cycle after discontinuation in this study, and 50% were pregnant 3 cycles after stopping use of OC. There is reasonable doubt that women transfer the recommendations into practice directly after discontinuation of OC, provided that knowledge about NTD prevention by FA exists. But the timing of FA supplementation is critical because the neural tube closes within 28 days after conception. Even if the women starts with FA supplementation directly after discontinuation of OC, the supplementation period might be too short to achieve protectable serum folate and RBC folate concentrations. At least 12 wk of supplementation are needed to get a steady state in plasma folate concentrations (Hao et al., 2008; Lamers et al., 2006), the medium by which the fetus is supplied with nutrients. A more extensive supplementation period is necessary to reach the plateau in RBC folate concentrations (Hao et al., 2008, Houghton et al., 2010; Lamers et al., 2006; Venn et al., 2002). A combined FA/OC would guarantee a good folate status for a certain period of time (3 months or more) after cessation of OC as RBC folate concentration decreases slowly (Bakker et al., 2009; Hao et al., 2008; Houghton et al., 2010). Fourthly, use of OC is the most common method of contraception worldwide. By combining OC with folate, the majority of the targeted group will be set into a good folate status. Fifthly, only the targeted group, women of childbearing age, will receive the product under medical care. Discussion on potential risks of high FA exposure for the whole population by mandatory fortification is therefore less relevant. In addition, there is evidence from several studies that [6S]-5-MTHF has the same beneficial effect on NTD compared with FA, but is less likely to have health risks as discussed for FA. Therefore [6S]-5-MTHF should be preferred to FA for combining with OC.

Thus, combining OC with [6S]-5-MTHF or FA is a reasonable and promising approach to minimize NTD prevalence. In 2010, the U.S. FDA approved two OC products combined with [6S]-5-MTHF (FDA, 2010a, 2010b) which have been introduced in the U.S. market in 2011. These OCs are not only approved for the primary indications of an OC, but also secondarily for improving folate status to reduce the risk of a NTD-affected pregnancy in those women who conceive while using the product or shortly after discontinuation. The concept of a combined OC-folate product would be ingenious and useful in European and other countries, too.

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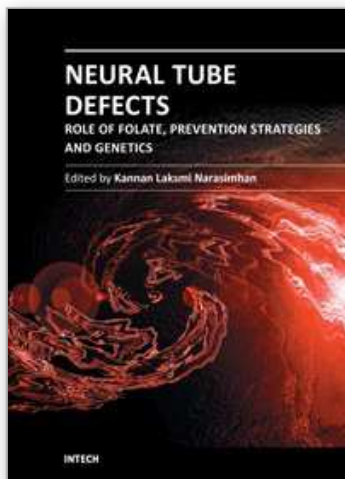
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