Review Article

Periconceptional Folic Acid and Multivitamin Supplementation for the Prevention of Neural Tube Defects and Other Congenital Abnormalities

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The pioneering studies of Smithells et al. showed the reduction of recurrent neural-tube defects (NTD) after periconceptional folic acid-containing multivitamin supplementation. The Hungarian Periconceptional Service was established in 1984, and this primary health care system offered a chance to organize a randomized controlled trial to check whether the supplementation of a multivitamin containing 0.8 mg of folic acid during the periconceptional period is appropriate for the reduction of a first occurrence of NTD in the family. This found a reduction of approximately 90% of primary NTD. An unexpected finding was a significant reduction in the rate of congenital abnormalities overall: 20.6 per 1000 in the ‘multivitamin’ group, and 40.6 per 1000 in the ‘trace-element-like’ placebo group (RR = 0.53, 95% CI: 0.35–0.70). When the 6 cases of NTD were excluded, this difference in the rates of major congenital abnormalities between the two study-groups remained very highly significant (p < 0.0001). Cardiovascular malformations and urinary tract defects were particularly affected. These findings were confirmed in the Hungarian cohort-controlled trial and by observational studies in other countries. Two questions remain to be answered. Is folic acid better alone or with multivitamins? What is the optimal dose of folic acid? Overall, the Hungarian experiences of periconceptional care have shown not only primary prevention of several severe congenital abnormalities but also a good cost-benefit balance. Birth Defects Research (Part A) 85:260–268, 2009. © 2009 Wiley-Liss, Inc.

Key words: Folic acid, multivitamins, neural tube defects, congenital abnormalities, primary prevention

INTRODUCTION

The Hungarian Periconceptional Service (HPS) was launched in 1984 (Czeizel, 1999). It embraces all the methods for the prevention of structural birth defects (i.e., congenital abnormalities [CAs]) and preterm birth known at that time. We prefer to use the term periconceptional rather than preconceptional, because prenatal care usually begins between the 8th and 12th weeks of pregnancy. Thus, the most sensitive and vulnerable early period of fetal development, from the 5th to the 10th gestational weeks calculated from the first day of the last menstrual period (i.e., from the 3rd week after conception until the 8th week), is not covered by the standard medical health service, leaving embryos without medical care and generally unprotected. Thus, our periconceptional service covers 1 to 3 months before conception and 1 to 3 months after conception followed by prenatal care.

R. W. (Dick) Smithells (1924–2002) and his co-workers first reported the possible prevention of the recurrence of neural tube defects (NTD) by periconceptional administration of a multivitamin supplement containing folic acid (0.36 mg), on the basis of the preliminary results of their intervention study (Smithells et al., 1980). I wanted to incorporate this new primary preventive method into the HPS protocol and to test the efficacy of a folic acid--
containing multivitamin in a randomized controlled trial (RCT) for the prevention of a first affected child with an NTD in the family—an occurrence or primary case of NTD. When the HPS was inaugurated, I wrote to Smithells asking him to arrange a dialogue with the manufacturers of Pregnan Forte F, the formulation which was used in his study. However, they were unwilling to produce two kinds of tablet that were outwardly the same for the study and control groups in my Hungarian study. In the 1980s, of the only two multivitamin formulations available in Hungary, Polyvitaplex 10 contained only 0.1 mg of folic acid, whereas Polyvitaplex 8 contained none at all. However, in the 1970s we had collaborated with Hoffmann-La Roche (Basel, Switzerland) in the teratological study of diazepam, and it transpired that they were planning to market a new micronutrient combination (Elevit prenatal) for pregnant women in 1984. Hoffman-La Roche looked skeptically on Dr. Smithells’s hypothesis regarding the NTD-preventive effect of folic acid with multivitamins, but suggested a collaboration to investigate possible adverse effects of their new product.

The Hungarian Periconceptional Service

The HPS begins 3 months before a pregnancy is planned and continues for the first 3 months after conception. It comprises the provision of information and counseling, examinations, and interventions in three stages by qualified nurses (Table 1).

1. Reproductive health check-up
   a. Family history of prospective mother and father, and obstetric history of females
   b. Case history and available medical records of females (e.g., epilepsy, diabetes)
   c. Vaginal and cervical smear screening for sexually transmitted infections/disorders
   d. Sperm analysis to detect subfertility and pyosperm (i.e., pus cells in the semen as indicators of sexually transmitted infections)
   e. Psychosexual assessment
   f. Blood screening of women to detect rubella seronegativity, or lack of previous exposure to varicella (vaccination will be offered), or HIV positivity; in addition, carrier screening for cystic fibrosis, and, more recently, predictive genetic diagnostic tests

2. Preparation for conception. This three-month period allows sufficient time for ceasing the consumption of tobacco, alcohol, and narcotic or recreational drugs that are hazardous to germ cells, and later, the fetus. This is also the optimal time to commence periconceptional folic acid or multivitamin supplementation.

   a. Undertaking of all additional investigation/treatment necessitated by conditions and disorders detected at the preconception check-up
   b. Appropriate investigation and treatment of women shown to suffer from hormonal dysfunction
   c. Optimal timing of conception in relation to ovulation.
   d. Early pregnancy confirmation using pregnancy tests and ultrasound scanning
   e. Postconceptional multivitamin supplementation
   f. Avoidance of teratogenic and other risks
   g. Referral of pregnant women to prenatal care clinics

2. The 3-month preparation for conception period
   a. Protection of germ cells: avoidance of tobacco, alcohol or narcotic consumption, and taking of unnecessary drugs
   b. Discontinuation of oral contraception, and removal of IUDs (condoms are provided)
   c. Occupational history of females
   d. Menstrual history; measurement of basal body temperature for detection of hormonal dysfunction (and commencement of further investigation and treatment, if necessary)
   e. Start of preconceptional multivitamin supplementation
   f. Recommendation that dental status be checked
   g. Guidelines for physical exercise
   h. Guidelines for healthy diet

The Hungarian Randomized Controlled Trial

The Hungarian RCT was carried out at the HPS coordinating center in Budapest, using a multivitamin supplement (Elevit prenatal) containing 12 vitamins including folic acid (0.8 mg), vitamin B12 (4.0 μg), B6 (2.6 mg), B2 (1.8 mg), C (100.0 mg), four minerals (calcium, phosphorous, magnesium, iron) and three trace elements (copper, manganese, zinc). The Ethical Committee of the Hungarian Ministry of Health would not sanction use of a true placebo, and accordingly a placebo-like combination of trace elements (including the three trace element compo-
nents included in the formulation of Elevit prenatal) was used. The Hungarian RCT was launched on February 1, 1984, and recruitment ceased on April 30, 1991. Pregnancy outcomes, and in particular data on informative offspring (e.g., livebirths, stillbirths, malformed fetuses prenatally diagnosed and terminated), were evaluated until the end of April 1992. All participants were supplied with one of two types of apparently identical capsules, free of charge, according to a randomization scheme. We used three different methods to check the intake of supplements for at least one month preceding conception and at least 2 months following conception, but vitamin levels in the blood of participants could not be checked because of lack of financial support.

The final data set included 5502 women whose pregnancies were confirmed. We were unable to evaluate the outcome of pregnancy in 49 (0.9%) women. The proportion of women receiving full (70.5% vs. 71.8%), partial (20.3% vs. 20.6%), or no supplementation (9.2% vs. 7.7%), did not differ significantly between the “multivitamin” and “placebo-like trace element” groups (p = 0.14). The mean maternal age was identical (26.9 ± 3.4 years [±SD]) in the two groups, and 88.3% of women in the multivitamin group and 89.9% of females in the trace element group were primiparous.

Drs. J. D. Erickson and G. P. Oakley Jr., of the Centers for Disease Control and Prevention, (Atlanta, Georgia) were interested in our trial, and they organized a scientific advisory committee (Figure 1), of which Dr. Smithells was a member, to assist in the evaluation of our data. We found no NTD cases among the informative offspring in the multivitamin group, but 6 NTD cases among the informative offspring of the trace-element group (p = 0.01) (Table 2). Thus, the Hungarian RCT demonstrated that a multivitamin containing 0.8 mg of folic acid prevented approximately 90% of primary NTDs (Czeizel and Dudas, 1992).

While the Hungarian RCT was being conducted, the results of two other ongoing intervention trials were published. The final results of the Smithells U.K. study were published in two papers, dealing with Yorkshire (Smithells et al., 1989), where a 91% reduction in recurrent NTDs was observed, and Northern Ireland (Nevin and Seller, 1990), where an 83% reduction was observed. The Hungarian RCT was performed in parallel with the MRC Vitamin Study (MRC Vitamin Study Research Group, 1991), which also commenced in Hungary in 1984. The MRC Vitamin Study compared the efficacy of administering folic acid (4 mg) alone, other vitamins without folic acid, folic acid with other vitamins, and minerals alone, in preventing a recurrence of NTD. Hungary was one of seven countries that collaborated in this study and contributed 43% of the participants. The MRC Vitamin Study found that a pharmacological dose (4 mg) of folic acid supplementation alone reduced NTD recurrence by 71% (0.8% vs. 4.3%; RR, 0.29; 95% CI, 0.12–0.71).

In 1992, on the basis of these results, the U.S. Public Health Service recommended periconceptional folic acid (0.4 mg) supplementation for all women seeking to become pregnant (Centers for Disease Control and Prevention, 1992). However, at that time there was no scientific evidence to support the recommended dose (in the Smithells study, 1980, 1989 0.36 mg folic acid was a component of the multivitamin preparation used and had not been individually tested). Subsequently, the efficacy of this amount of folic acid in preventing primary NTDs was evaluated in a Chinese intervention study (Berry et al., 1999). These researchers found that folic acid (0.4 mg) daily was sufficient to reduce the risk of NTD in areas with a high rate of NTD (6.5 per 1000) by approximately 79%, whereas in areas with low rates of NTD (0.8 per 1000) NTDs were reduced by 41%.

Furthermore, the Hungarian RCT also generated an unexpected finding. Periconceptional multivitamin supplementation was also associated with a significant reduction in the rate of informative offspring with CA. The rate of major CAs was 20.6 per 1000 in the multivitamin group and 40.6 per 1000 in the trace-element group (RR, 0.53; 95% CI, 0.35–0.70). When 6 NTD cases were excluded, this difference in the rates of major CA between the two study-groups remained highly significant (p < 0.0001). Thus, periconceptional multivitamin supplementation reduced not only the occurrence of NTD, but also the rate of other major CAs. Smithells encouraged me to publish these results as soon as possible (Czeizel, 1993).

The detailed analysis of the final data set from the Hungarian RCT, which was based on our personal medical examination of all children born to participants in the RCT, indicated a significant reduction in two further groups of CA: those of the urinary tract and the cardiovascular system (Czeizel, 1996) (Table 3). The reduction was most marked in the case of obstructive CAs of the urinary tract and conotruncal cardiovascular malformed-
tions, including ventricular septal defects (3 vs. 10; RR, 0.29; 95% CI, 0.09–0.97). There was also some reduction in the prevalence at birth of congenital limb deficiencies, congenital pyloric stenosis and Down syndrome in the multivitamin group, but this difference between the two groups in the RCT was not significant. There was no difference in the rate of cases with unclassified multiple CAs in the multivitamin and trace element groups.

There are two frequent types of orofacial cleft: cleft palate and cleft lip with or without cleft palate, with a birth prevalence in Hungary of approximately 0.5 and 1 per 1000 births, respectively. There was no reduction in the birth prevalence of these two types of orofacial cleft following multivitamin supplementation with a low (0.8 mg) dose of folic acid (Table 3).

For ethical reasons, we were unable to continue the Hungarian RCT. Therefore a cohort controlled trial (CCT) was designed to collect additional data, to confirm or reject the efficacy of periconceptional folic acid-containing multivitamin supplementation in preventing CAs other than NTD.

The Hungarian Cohort Controlled Trial

Supplemented women were recruited via the HPS coordinating center in Budapest, and the 31 HPS subsidiary centers between May 1, 1993, and April 30, 1996. The examinations of newborn infants with CAs were performed until April 30, 1999, to allow for a 12-month infant follow-up period. All participants were supplemented with the same folic acid (0.8 mg)-containing multivitamin (Elevit prenatal) during the periconceptional period. Women in the supplemented cohort were followed until the 14th week of gestation, and a cohort of unsupplemented women was recruited from the Regional Prenatal Care Clinics at the 14th week of pregnancy. None of these women had received supplementation with folic acid, folic acid–containing multivitamins, or

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Table 3
The Efficacy of Periconceptional Folic Acid–Containing Multivitamin (Micronutrient) Supplementation in the Primary Prevention of Some Major Groups of Congenital Anomalies

<table>
<thead>
<tr>
<th>CA groups</th>
<th>RCTa (n = 5447)</th>
<th>CCTb (n = 5527)</th>
<th>Pooled data (n = 5527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract CAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal a/dysgenesis</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cystic kidney</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Obstructive CAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvicoureteric junction</td>
<td>4</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Other locations</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.21 (0.05–0.95)</td>
<td>0.71 (0.33–1.50)</td>
<td>0.56 (0.30–1.04)</td>
</tr>
<tr>
<td>Cardiovascular CAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conotruncal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>8</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Subtotal</td>
<td>10</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>50</td>
<td>31</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.42 (0.19–0.98)</td>
<td>0.60 (0.38–0.96)</td>
<td>0.57 (0.39–0.85)</td>
</tr>
<tr>
<td>Congenital limb deficiencies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal transverse</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.19 (0.03–1.18)</td>
<td>0.33 (0.01–3.71)</td>
<td>0.25 (0.05–1.16)</td>
</tr>
<tr>
<td>Congenital pyloric stenosis</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.24 (0.05–1.14)</td>
<td>0.00 (0.00–26.8)</td>
<td>0.20 (0.04–0.90)</td>
</tr>
<tr>
<td>Anal/rectal atresia/stenosis</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.31 (0.02–2.52)</td>
<td>0.20 (0.02–1.69)</td>
<td></td>
</tr>
<tr>
<td>Orofacial clefts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft lip± palate</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.77 (0.22–2.69)</td>
<td>1.63 (0.31–2.88)</td>
<td>0.99 (0.37–2.63)</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>5</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.39 (0.07–1.99)</td>
<td>1.00 (0.33–1.73)</td>
<td>0.76 (0.33–1.73)</td>
</tr>
<tr>
<td>Unidentified multiple CAs</td>
<td>5</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.16 (0.35–3.81)</td>
<td>0.79 (0.40–1.48)</td>
<td>0.89 (0.47–1.68)</td>
</tr>
</tbody>
</table>

aData from Czeizel (1996).

bData from Czeizel et al. (2004).

CA, congenital anomaly; RCT, randomized controlled trial; CCT, cohort-controlled trial; OR, odds ratio; CI, confidence interval.
any multivitamins either before conception or in the first trimester of pregnancy. Each pregnant woman in the unsupplemented cohort was matched to a pregnant woman in the supplemented cohort on the basis of age, socio-economic status and place of residence. As in the Hungarian RCT, the informative offspring of women from both cohorts were evaluated for CAs at three stages (during pregnancy, at birth, and during the first year of life). These evaluations, based on well-defined diagnostic criteria, were performed “blind”. As in the RCT, the pediatric examinations (which included a cardiologic assessment) were similar in the two CCT study groups (Czeizel et al., 2004).

Differences in the mean maternal age (27.4 ± 3.9–4.0 years [±SD]), birth order, schooling level, and employment status were avoided by matching participants in the supplemented and unsupplemented cohorts. However, when the final data set of 3056 supplemented and unsupplemented matched pairs was evaluated, the cohort of supplemented pregnant women recruited via the HPS appeared to have a higher rate of morbidity (e.g., diabetes mellitus, epilepsy) and previous unsuccessful pregnancy outcomes (miscarriages and CA, including NTD) compared with the cohort of unsupplemented pregnant women recruited through the regional prenatal care clinics. This finding may have been due to the good reputation of the HPS in establishing optimal conditions for conception and providing care in early pregnancy, which might have attracted women who had previously experienced problems during pregnancy. Thus, the majority of supplemented women were at high risk of an adverse pregnancy outcome, whereas most unsupplemented women could be considered to be at low risk.

The CCT confirmed the protective effect of folic acid-containing multivitamin supplementation and its role in reducing the incidence of NTDs. We found one NTD among the informative offspring in the supplemented group and nine NTDs among informative offspring in the unsupplemented cohort (Table 2). However, 34 informative offspring in the supplemented cohort had 36 previous siblings with NTD (two had two siblings with NTD). In addition, six mothers and two fathers had NTDs themselves (including three mothers and two fathers who had the mild form of NTD, the so-called spinal dysraphism). There was no recurrent NTD in our supplemented cohort. In the unsupplemented cohort, three women with previous offspring with NTD had informative offspring, and one of these had a recurrence of NTD.

Table 3 shows the incidence of other CAs in the supplemented and unsupplemented groups. Cardiovascular CAs are heterogeneous in their origin and manifestation, and have different critical periods, but their total occurrence (31 vs. 50) was again significantly reduced in the

Figure 1. From left to right: János Rácz (Secretary of the Hungarian RCT), Prof. R.W. Smithells (SMAC), Dr. A. Hanck (scientist with Hoffmann-La Roche), Mr. Árpád Goncz (the President of Hungary), Dr. A. E. Czeizel, Dr. G. Kunovits (scientist with Hoffmann-La Roche), Dr. T. C. Chalmers (SMAC), Dr. J. D. Erickson (SMAC), SMAC, member of the Scientific Advisory Committee.
supplemented cohort. This can be explained mainly by the reduction in the number of ventricular septal defects (5 vs. 19) (OR, 0.26; 95% CI, 0.09–0.72) in the supplemented cohort. Urinary tract CAs are also heterogeneous in their origin and manifestation, but there was no significant difference in their occurrence between the supplemented and unsupplemented cohorts (14 vs. 19 cases). However, within the subgroup of obstructive CAs (10 vs. 19), stenosis of the pelvico ureteric junction (2 vs. 13) showed a significant reduction in the supplemented cohort (OR, 0.19; 95% CI, 0.04–0.86). The causes and manifestations of limb reduction defects are many and heterogeneous, and there was again a trend toward reduction in incidence in the supplemented cohort (1 vs. 3); it is perhaps worth mentioning that all children in the unsupplemented cohort had unimelic terminal transverse type defects. Congenital pyloric stenosis was diagnosed in two infants of the unsupplemented cohort, but was not found in the supplemented cohort. There was no reduction in the incidence of cleft lip with or without palate or cleft palate in the supplemented group.

Finally, two “syndromic” groups with multiple CAs were evaluated. There was no difference in the rate of Down syndrome between the supplemented and unsupplemented cohorts. We did not detect any change in the rate of unclassified multiple CAs following periconceptional supplementation.

The results of the Hungarian CCT were thus in agreement with the findings of the previous RCT, showing that periconceptional multivitamin supplementation protects against some CAs of the cardiovascular system, principally ventricular septal defects, and obstructive CAs of the urinary tract, particularly stenosis of the pelvico ureteric junction. These preventive effects were clearly evident despite the fact that the supplemented pregnant women represented a cohort at high risk, because of a higher rate of maternal morbidity and a greater number of unsuccessful previous pregnancies.

Prevention of Congenital Abnormalities Other Than NTD by Supplementation with Folic Acid–Containing Multivitamins

The efficacy of folic acid–containing multivitamin supplementation in preventing cardiovascular CAs—mainly conotruncal defects (e.g., common truncus, transposition of the great vessels, tetralogy of Fallot) and certain types of ventricular septal defects)—was also demonstrated in two U.S. studies (Botto et al., 1996, 2000). Their results, together with our results from the RCT and CCT trials, suggest that periconceptional multivitamin supplementation was associated with an approximately 40% reduction in risk for cardiovascular CAs. The effect of early postconceptional supplementation with a pharmacologic dose (6 mg) of folic acid alone in protecting against cardiovascular CAs was also discernible in the data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (Czeizel et al., 1996). Recently, two groups reported raised plasma homocysteine levels and methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms in association with cardiovascular CA (Kapusta et al., 1999, van Beynum et al., 2006). However, three other U.S. studies (Shaw et al., 1995, Werler et al., 1999, Scanlon et al., 1998) failed to demonstrate a significant protective effect of periconceptional multivitamin supplementation for cardiovascular outflow tract defects, though the reduction was close to significance (RR, 0.7; 95% CI, 0.5–1.1) in the study of Shaw et al. (1995). Incidentally, cardiovascular CAs were induced by pteroylglutamic acid deficiency during gestation in rat fetuses (Baird et al., 1954; Monie and Nelson, 1963).

In both the RCT and CCT, the incidence of obstructive CAs of the urinary tract (more precisely, stenosis of the pelvico ureteric junction) was reduced in infants born to mothers who had received multivitamin supplementation (Table 3). In the 1950s, Monie and Nelson (1957) had been able to produce CAs of the urinary tract in folic acid–deficient rat embryos, whereas Li et al. (1995) and Werler et al. (1999) also observed a significant reduction in the rate of human urinary tract CAs following multivitamin supplementation in the first trimester of pregnancy.

One U.S. study showed a significant reduction in congenital limb deficiencies following multivitamin supplementation (Yang et al., 1997). Two other studies (Shaw et al., 1999; Werler et al., 1999) also found reductions in incidence (RR, 0.50, 0.64), but these differences were not significant, as the confidence intervals were too wide. In human embryos, the teratogenic effects of folate deficiency caused by folic acid antagonists were associated with limb deficiencies, among other CAs (Warkany et al., 1959; Hernandez-Diaz et al., 2000).

The combined incidence of pyloric stenosis in the Hungarian RCT and CCT showed a significant reduction after periconceptional multivitamin supplementation. However, this finding was not confirmed in a U.S. study (Werler et al., 1999).

In the China/U.S. Collaborative Project for Neural Tube Defect Prevention (Berry et al., 1999), a somewhat lower occurrence of rectal atresia/stenosis was found following periconceptional folic acid supplementation (Myers et al., 2001). The Hungarian RCT and CCT showed a similar trend (1 vs. 5) (Table 3).

Tolarova (1982) reported that periconceptional supplementation with a multivitamin and a high-dose folic acid (10 mg) formulation was effective in reducing the recurrence rate of cleft lip. However, the Hungarian RCT and CCT failed to show a reduction in the birth prevalence of cleft palate and cleft lip with or without cleft palate following supplementation with a multivitamin preparation containing a low dose (0.8 mg) of folic acid (Table 3). Alternatively, a significant reduction was observed in the data set from the HCCSCA (Czeizel et al., 1999) following a high dose (usually 6 mg) of folic acid alone. Thus, a dose-dependent preventive role for folic acid in the prevention of orofacial clefting cannot be excluded. Other studies yielded controversial results, varying according to dosage, population genetic background, and the socioeconomic status and lifestyle, particularly the diet, of the women studied (Czeizel, 2002; Botto et al., 2004).

Botto et al. (2002b) found a lower rate of omphalocele in newborn infants born to mothers following periconceptional multivitamin supplementation (RR, 0.4; 95% CI, 0.2–1.0). The supplemented and unsupplemented groups of the Hungarian RCT and CCT contained 1:1 and 3:1 infants with omphalocele, respectively.

Recent publications had suggested an association between polymorphisms in genes involved in folate metabolism and maternal risk of Down syndrome (James et al., 1999, Hobbins et al., 2000, Barkai et al., 2003, Gueant et al., 2003). We therefore sought to explore this putative...
association in the HCCSCA, which indicated that supplementation with a high dose (usually 6 mg) of folic acid and iron had some impact (adjusted OR, 0.41; 95% CI, 0.2–0.7) in preventing Down syndrome (Czeizel and Puho, 2005).

We did not find any difference in the incidence of cases with unclassified multiple CA in the RCT and CCT following multivitamin supplementation during the periconceptional period (Czeizel and Medveczky, 2003) (Table 3). However, the birth defect registries of Shaw et al. (2000) and Yuskin et al. (2005) reported a higher occurrence of multiple CAs following periconceptional multivitamin supplementation. We therefore sought to evaluate this in the data set of the HCCSCA. However, our data showed that periconceptional folic acid/multivitamin supplementation did not reduce the incidence of multiple unclassified CAs, nor did supplementation cause an increase in the number of cases (Czeizel et al., 2006).

The total reduction in CAs was 20.0/1000 (40.6–20.6/1000) in the Hungarian RCT. The rate of NTD was 2.5/1000 in the trace element group, and this figure was near the previously determined prevalence at birth of NTD (2.8/1000) in Hungary (Czeizel and Révész, 1970). Thus, the total reduction of CAs without NTD was 17.5/1000 in the multivitamin group, which is approximately 6.3 to 7.0 times greater than the incidence of NTD in Hungary, indicating the importance of folic acid–containing multivitamins in the reduction in risk for CAs other than NTD. This reduction is principally due to a reduction of cardiovascular CAs, because the birth prevalence of cardiovascular CAs was 10.2/1000 in Hungary (Meszaros et al., 1975), which is 3.6 times greater than the total (birth + fetal) prevalence of NTD. Thus, the role of this new primary preventive measure in preventing other CAs is at least as important, from a public health point of view, as its role in preventing NTDs. In light of this finding, it is strange that the value of folic acid/multivitamin supplementation for prevention of NTD was accepted with enthusiasm by the international scientific community in the early 1990s and prompted fresh recommendations for practical implementation, yet these novel data have been received with reservations and have failed to stimulate any further recommendations for exploiting their protective effect against other CAs. Alternatively, these reservations are understandable because different CAs have different origins, making it difficult to believe that an intervention as simple as multivitamin supplementation can reduce the incidence of CAs of distinctly different origins. However, several studies (Bottis et al., 2004) have confirmed its role in preventing or reducing the incidence of CAs other than NTDs. It is clearly necessary, therefore, to identify and clarify the mechanism by which periconceptional folic acid and folic acid–containing multivitamin supplementation acts to reduce the incidence of specific CAs.

The HCCSCA data set showed that folic acid–containing multivitamin supplementation can reduce or protect against the teratogenic effects of high fever (e.g., influenza) (Acs et al., 2005), and we were thus able to confirm the previous findings of Botto et al. (2002a).

Currently, 20% to 25% of infant mortality in industrialized countries can be attributed to CAs, which are among the leading causes of death (Czeizel and Sankaranarayanan, 1984). An important point to note is that CAs represent a defect condition, and complete recovery from a CA, although the most desirable outcome, is therefore difficult to achieve. For this reason, prevention is considered the best option, and often the only feasible option, in the medical care of cases affected with CA.

In conclusion, folic acid or folic acid–containing multivitamin supplementation offers a breakthrough in the primary prevention of NTD and some other CAs, because of its ability to reduce the incidence of CAs by about one third (Tarusco, 2004). It constitutes a better alternative than so-called secondary prevention (i.e., termination of a pregnancy following diagnosis of severe fetal defect).

Folic Acid Alone or Multivitamins? What Is the Optimal Dose of Folic Acid?

The use of a multivitamin containing folic acid and other B vitamins in the studies of Smithells et al. (1990, 1989), and in the Hungarian RCT (Czeizel and Dudas, 1992) and CCT (Czeizel et al., 2004), indicates a higher degree of efficacy (approximately 90%) in the reduction of NTD than in the MRC Vitamin Study (1991), which employed a high dose of folic acid alone (71%), and in the Chinese/U.S. study (Berry et al., 1999), which used a low dose of folic acid (41%–79%). The usual argument against the use of vitamins other than folic acid is that the group, supplemented with “other vitamins” in the MRC Vitamin Study, did not exhibit a significant reduction in NTD recurrence rates. However, it is worth mentioning that supplementation with other vitamins without folic acid resulted in a 40% reduction (2.6% vs. 4.3%) in the recurrence rate of NTDs, a finding that approaches significance.

Another argument is that folic acid–containing multivitamin supplements seem to be effective in reducing the incidence of cardiovascular, urinary tract, and limb reduction CAs. However, there are limited data concerning a similar effect of folic acid alone in reducing the incidence of these CAs.

Finally, hyperhomocysteinemia plays a role in the causation of at least some NTDs, and vitamins B12, B2, and B6 are important cofactors in folate-homocysteine metabolism. Supplementation with folic acid alone is much cheaper than multivitamin supplementation. Some countries reimburse the major part of the cost of multivitamin supplementation (e.g. Turkey), or the full cost of folic acid supplementation (e.g. Italy) during the periconceptional period. To my knowledge, there is no multivitamin product containing “only” folic acid or vitamins B12, B6, and B2 currently available that could be used for the prevention of NTD and some other CAs.

The second question concerns the optimal dose of folic acid. Currently, there is no unequivocal evidence for, or consensus regarding, the optimal dose of folic acid. Folic acid has two forms (known as vitamin B11 in the Netherlands and vitamin B8 in France): dietary polyglutamate folate and synthetic monoglutamate folic acid. These two forms have different modes (active and passive) of absorption from the gastrointestinal tract, and their levels have to be combined when calculating the dose of folic acid. The Institute of Medicine, of the U.S. National Academy (1998), and the European Commission Scientific Committee on Food (1998) all recommend 1 mg folate/
folic acid as the highest amount suitable for ingestion by healthy individuals, including pregnant women. It is important, therefore, to make a distinction between a physiologic dose of folic acid (<1 mg daily), being taken by healthy individuals for preventive purposes, and a pharmacologic dose (>1 mg daily) being used to treat patients. Currently, it is not possible to exclude the possibility of adverse effects following administration of high doses of folic acid (Butterworth and Tamura, 1989). However, Wald et al. (2001) calculated a dose-effect relation for folic acid in the reduction of hyperhomocysteinemia and those NTDs that are preventable; on this basis they suggested a daily dose of 5.0 mg of folic acid for women seeking to become pregnant. The United States recommended the daily consumption of 0.4 mg of folic acid per day by all women who were capable of becoming pregnant, to prevent NTD. The Chinese/U.S. study (Berry et al., 1999) later confirmed the efficacy of this estimation and delivered another important message: that the efficacy of prevention by folic acid supplementation is dependent on the incidence of NTD. Periconceptional multivitamin supplementation with 0.8 mg of folic acid in the Hungarian intervention trials resulted in a drastic reduction (approximately 90%) in the occurrence of primary NTD. However, the study by McPartlin et al. (1993) suggested that the optimal daily intake of folate/folic acid in the preconceptional and postconceptional period is 0.66 mg per day, and on the basis of this the Food Safety Authority of Ireland (2006) recommended that 0.7 mg folate/folic acid be taken by all sexually active women of childbearing age (180 mg for women of childbearing age). This recommended dose is much higher than the recent RDA, because folate requirements in pregnant women are greater because of decreased absorption, accelerated breakdown of folate to p-aminobenzoyl-glutamate and its acetylated derivative p-acetamidobenzoyl-glutamate, increased urinary loss, and fetal transfer. The calculated total fetal and placental content of tetrahydrofolate (the parent compound of all biologically active folates) is 0.8 mg/100 g at term (Iyengar and Apte, 1972); thus, fetal blood contains higher levels of tetrahydrofolate than maternal blood, which is indicative of active placental transfer (Streling, 1976).

Following the study of Daly et al. (1997), which showed that there was no obvious increase in reduction of NTD following supplementation with higher doses of folic acid, the current consensus recommendation is that all pregnant women, or those who may become pregnant, require 0.7 mg of folate/folic acid daily. Dietary folate accounts for 0.2 to 0.4 mg of this recommendation, requiring supplementation with an additional 0.3 to 0.5 mg folic acid to attain the recommended daily dose.

The topics of folate-rich and other vitamin-rich diets, and of food fortification with folic acid and possibly vitamin B12, are not discussed here. I have focused on periconceptional multivitamin supplementation with folic acid-containing multivitamins, mainly on the basis of the Hungarian intervention trials. To increase public awareness of the value of preconceptional folic acid–containing multivitamin supplementation, and uptake, requires a strong and widespread educational campaign to stress the importance of commencing folic acid or multivitamin supplementation immediately after the discontinuation of oral or other methods of contraception, when couples wish to have a baby. Unfortunately, such educational campaigns have enjoyed only limited success (Botto et al., 2005).

Periconceptional care, in addition to its other benefits, is the optimal time at which to introduce periconceptional folic acid–containing multivitamin supplementation, and our Hungarian experiences have shown that it is possible to do so in a way that ensures a good cost-benefit balance (Czeizel et al., 2005). Lastly, I am convinced that proper preparation for conception is the earliest and most effective method of preventing birth defects.

Epilogue

On May 17, 2000, I received a letter from the United States, signed by Eunice Kennedy Shriver, which commenced: “Dear Dr. Czeizel, I am extremely pleased to notify you that you have been selected, with your colleagues, Dr. Smithells and Dr. Wald, to share the prestigious Joseph P. Kennedy, Jr. Foundation International Award for Scientific Research for your research proving that B-vitamin folic acid can prevent serious birth defects.”

This recognition of our work, and that of others, in the field of CA prevention was a wonderful accolade. Dr. Dick Smithells, who was a fantastic medical doctor, a great scientist, and a true gentleman, was of enormous help and encouragement in facilitating these achievements, and his friendship was one of the greatest gifts of my life.

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References

References


