Original Research

Improper Supplementation Habits of Folic Acid Intake by Hungarian Pregnant Women: Improper Recommendations

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Background: Neural tube defects (NTDs) are some of the most common congenital anomalies. Proper folic acid supplementation is a dominant risk factor, which has been shown to decrease the incidence of NTDs. In Canada, the incidence of neuroblastoma has presented a considerable decrease of 60% as a result of enrichment cereal grain flours with synthetic folic acid. The aim of this study was to investigate the effect of folic acid intake by pregnant women on the incidence of NTDs and neuroblastoma.

Methods: Regular folic acid intake has been recommended to pregnant women in Hungary since the eighties of the last century by health visitors eventually raking effect as an official protocol which had been released in 1997. During 2001, 2002 and 2003, folic acid intake habits of pregnant women were evaluated by health visitors, proving to be successful in collecting data from 95.06% of the pregnant women. The incidence of NTDs has been registered by the Hungarian National Centre of Epidemiology, Department of Human Genetics and Teratology. The Pediatric Cancer Registry provided the incidence of neuroblastoma in children.

Results: Consistent findings revealed a regular intake of supplementary folic acid products by 68.71% of the pregnant women. Out of these, 93.13% of pregnant women who were taking folic acid, started the supplementation after their 7 weeks of pregnancies, a time designated as the completion period of the development of the neural tube. The dose of folic acid supplementation was evaluated as less than 5 mg/day in 84.75% of the pregnant women. In Hungary, the incidence of NTDs has remained constant, while the incidence of neuroblastoma has shown constant slight increase in spite of the introduction of folic acid supplementation in 1997.

Conclusions: Based on our experience, folic acid supplementation was initiated after the recognition of pregnancy and its application in a dose of lower than 5 mg/day neither decreased the incidence of NTDs nor did it have an effect on the neuroblastoma incidence. It is implicated that proper folic acid supplementation, which is started from the conception, can be achieved only with the enrichment of cereal grain flours.

INTRODUCTION

The effect of folic acid on the development of congenital anomalies was first described by Smithills and Hibbard in 1965 [1]. Since then, several studies have confirmed that depending on the dose, folic acid administration started before the pregnancy moderates the occurrence of neural tube anomalies [2–7]. In Hungary, Czeizel et al. proved in a double-blind randomised study that folic acid supplementation in a dose of 0.8 mg/day started before the pregnancy can prevent the development of neural tube defects (NTDs) [8]. Neuroblastoma is a malignant disorder of the primitive sympathetic neural system. In 2003, a Canadian study described that since the introduction of folic acid fortificated flour, the occurrence of neuroblastoma has shown a considerable decrease by 60% [9].

The benefits of medicine and/or medical nutriment use

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Contributers: M. Bognár and M. Garami coordinated the study and were involved in the study design, analysis, and interpretation of results and writing of the report. A. Ponyi and P. Hauser interpreted the results. Zs. Jakab and J. Müller contributed to the data collection and performed the statistical analysis. T. Constantin helped the design and initiated the study. D Schuler formed the hypothesis and guided the study.

during pregnancy are not restricted to the recovery of maternal health but also result in some advantages for the fetus as well, because the maternal well-being is important for the optimal development of the fetus. The low number of the planed pregnancies in Hungary is one of the major causes of the improper use of folic acid.

Our aim was to study whether folic acid supplementation that started after the recognition of pregnancy and given in a dose of 0.8 mg daily according to the official recommendation in Hungary, can decrease the frequency of NTDs and whether any relations between the administration of folic acid during the pregnancy and the occurrence of neuroblastoma can be found.

METHODS

Participants and Study Design

A retrospective, cross-sectional, nationwide study was designed to investigate the folic acid administration habits of Hungarian pregnant women. The frequency of NTDs and neuroblastomas were also studied. During 2001, 2002 and 2003, analyses were conducted resulting in the collection of a considerable amount of data in these three years. The folic acid intake habits were observed and recorded in written forms during the pregnancies. The survey was conducted, based on a questionnaire-based personal data collection by health visitors, which was governed by the delivery of 4,630 forms to the country's 20 welfare centres. The questionnaire form was constructed to obtain a clear picture of folic acid intake routine among pregnant women. The answers to the following questions were sought through this questionnaire: (i) During your pregnancy, have you taken any folic acid medication? If so, regularly or sometimes only?; (ii) From which week of the pregnancy did you begin to take the folic acid?; (iii) Which product did you take?; and (iv) Please quote the number of tablets per day? Moreover, we separately specified the time when women did not take any folic acid products, or there were no available data about the given pregnant woman. Gathering information about the factory product and the daily quantity, the daily dose was calculated.

Between 2001 and 2003, 285,884 children were born in Hungary, according to the data of the Hungarian National Statistical Office. The completed questionnaires covered the data of 271,748 pregnant women, which accounted for 95.06% of the pregnant women from 2001 till 2003.

All pediatric cancer patients in Hungary are now registered and followed in the Hungarian Pediatric Cancer Registry. Our registry contains patient identification information, date of diagnosis, histological findings (and in solid tumors, stage and primary site of the tumor), treatment and outcome of the oncology treatment (relapses, survival rates) [10].

Written informed consent was obtained for participation in all cases. The study conformed to ethical standards currently applied in Hungary. Data are collected regularly from the pregnant women by health visitors regarding the condition of the conceptions and the pregnancies. These data collection procedure have the Medical Scientific Board approval. Our data cover a part of the above mentioned data collection procedure. This study does not require any additional ethical approval.

Statistical Analysis

The obtained data were entered into SPSS for Windows 10.0 statistics software (SPSS Inc., Chicago, IL, USA). Almost, one and a half million data were processed into computer for statistical analysis. Breakdown analysis and regression calculation were performed.

RESULTS

As Fig. 1 illustrates, 186,713 (68.71%) of the pregnant women took folic acid containing products regularly, 22,179 (8.16%) had a frequent intake and 41,993 (15.45%) never took them at all. However, the data concerning 20,863 (7.68%) of the pregnant women were missing. The regular intake of folic acid varied in different countries of Hungary ranging between 61–80%; however, there was no relation between the frequency of the regular intake and the geographical location of the countries.

During the analyzed years, 95,783 (45.85%) of the pregnant women started taking folic acid in the first, 87,075 (41.68%) in the second and 26,034 (12.46%) in the third trimester, respectively. Week-based breakdown of starting the folic acid intake

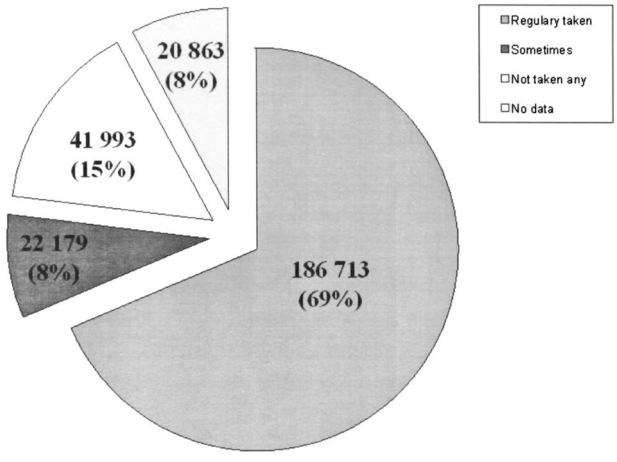

Fig. 1. Fashion of folic acid intake of Hungarian pregnant women during three years (2001–2003). Based on the data, it can be stated that 186,713 (68.71%) of pregnant women were consuming drugs containing folic acid regularly, 22,179 (8.16%) less frequently and 41,993 of them did not consume it (15.45%) at all. There were no available data about 20,863 (7.68%) of pregnant women.

is shown on Fig. 2. Majority of the pregnant women started the supplementation in weeks 7–12. Thus, a high percentage of the pregnant women started the intake of the various folic acid containing drugs after the closure of the neural tube. Between weeks 0 and 6, 14,353 (6.87%) of the pregnant women started the intake of folic acid. We suppose that these were planned pregnancies. A significant majority of the regular consumers (84.75%) took a daily dose of less than 5 mg [11–13].

Based on the data of the National Centre for Epidemiology, Department of Human Genetics and Teratology, since 1997, the number of NTDs has been almost constant in Hungary: in the year 1997, it was estimated as 0.5/1000 whereas in 2002, it was 0.6/1000 children. As presented in Fig 3, the incidence of neuroblastoma has varied since 1975 in Hungary, but it shows a slightly increasing trend according to the National Pediatric Cancer Registry. During 2001–2003, 45% of children with neuroblastoma were less than 1 year old, another 45% were between 1–5 years of age, 6% were between 5–10 years and 4% were between 10–14 years. It was evident that 90% of the patients with neuroblastoma were younger than 5 years, which was a rate being higher as compared with international data (66%) [14].

DISCUSSION

Several international and Hungarian studies proved that the incidence of neural tube anomalies can be decreased by folic acid administration during pregnancy. Five of six studies published about a decrease of about 40 to 100% in the frequency of NTDs in cases where folic acid was consumed on a daily basis [3,4,8,15–17]. In these studies, the daily dose of folic acid alone or part of a multivitamin substance, varied between 0.4 mg and 5 mg, and its intake was started at least one month before conception and continued during the first trimester. According to some publications, folic acid moderates the occurrence of NTDs depending on the dose: increasing the daily dose with 0.4 mg means a decrease of 36%, while at 5 mg, the decrease is 85% [11–13,18,19]. However, as regards the optimal dose, there is yet no international agreement.

Hungarian and foreign recommendations differ in terms of the daily folic acid quantity. United States Public Health Service recommends that "all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina

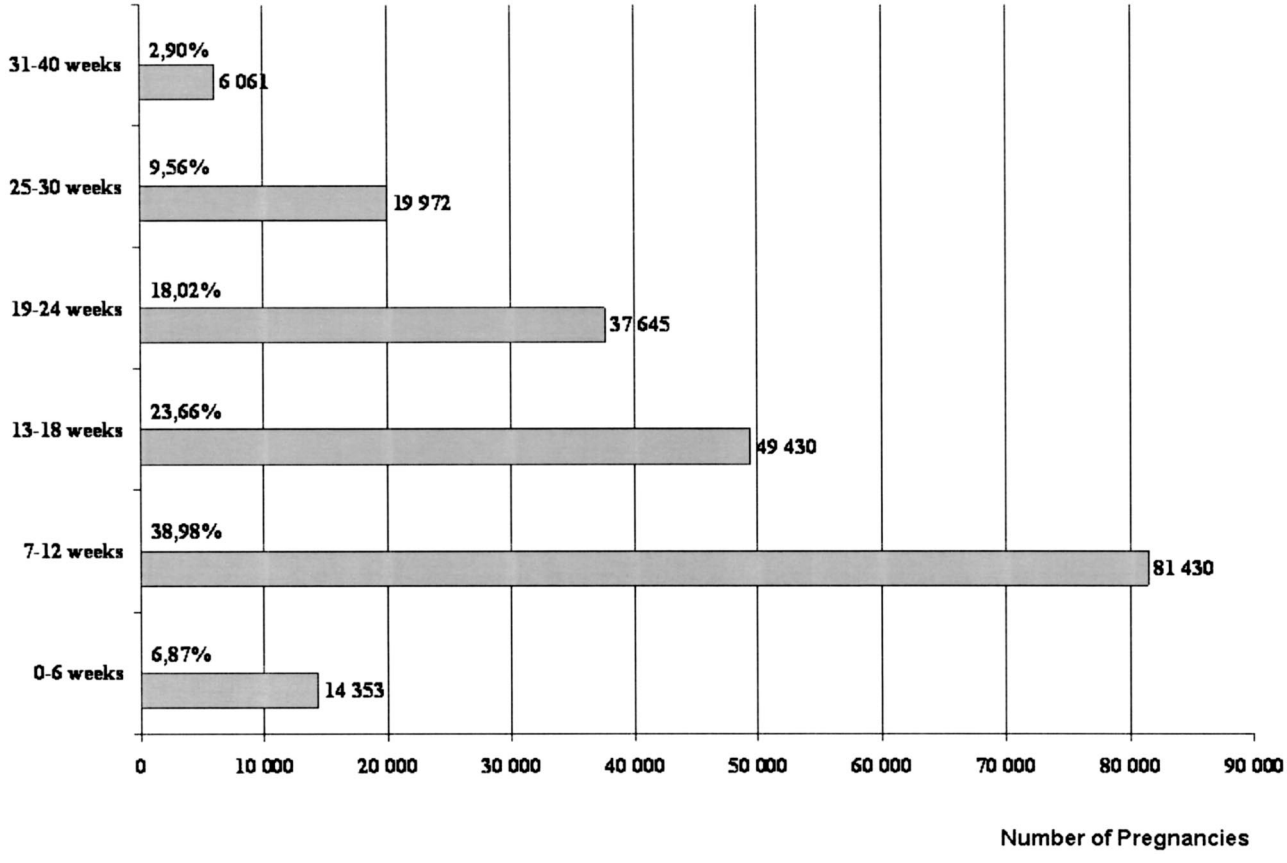

Fig. 2. Week-based breakdown of starting folic acid intake. The majority of pregnant women started the supplementation in weeks 7–12. Thus, a high percentage of pregnant women started the intake of the various folic acid containing drugs after the closure of the neural tube. Between weeks 0 and 6, only 6.87% of pregnant women started the intake of folic acid.

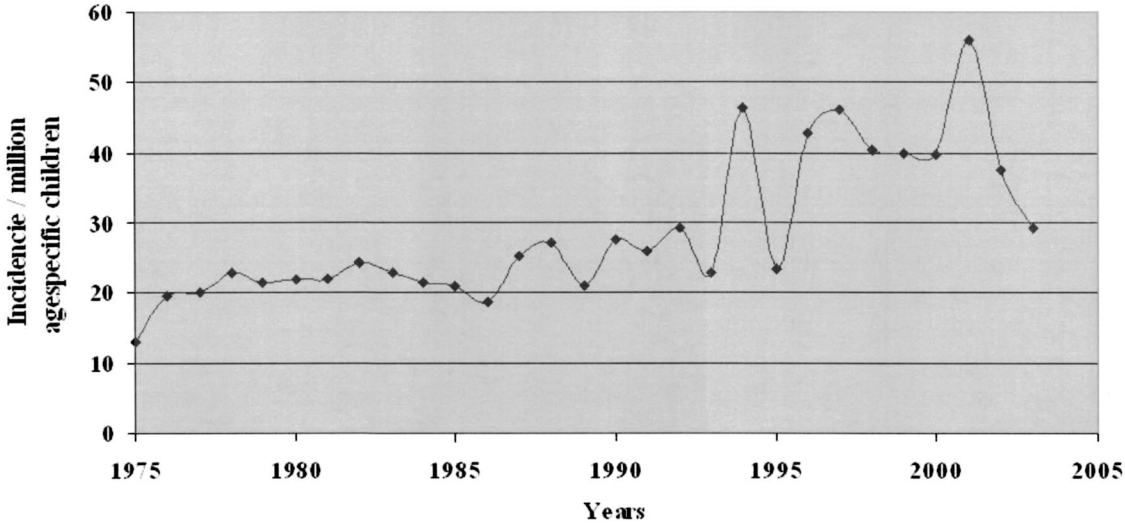

Fig. 3. Incidence of neuroblastoma in Hungary between 1975 and 2003; age: 0–4 years. According to The National Paediatric Cancer Registry, the incidence of neuroblastoma has varied in Hungary since 1975, but has shown a slightly increasing trend.

bifida or other NTDs" (Centres for Disease Control and Prevention, 1992) [7]. In 1998, the US National Academy of Sciences' Institute of Medicine recommended that all women of childbearing age should consume 0.4 mg of synthetic folic acid per day from fortified foods and/or supplements in addition to folate from a varied diet. The Institute of Medicine specified the preference for synthetic folic acid because of its greater bioavailability than food folate. In England, based on the British Medical Research Council Medical Study recommendation, the suggested quantity is 4 mg for the women who already had a child with neural tube anomaly [6]. Wald et al. recommended that the daily folic acid dose should be raised to 5 mg/day for every fertile woman [11]. Kierke et al. stressed that the daily folic acid intake should not exceed 1 mg unless the substance is prescribed by a professional doctor in certain cases, because it may cover-up the symptoms of B12- deficiency [20]. However, there are other publications which did not confirm this observation [21].

In Hungary, health visitors have recommended folic acid intake to pregnant women since the eighties of the last century. The official recommendation of the Obstetric and Gynaecological Professional Board was published in 1997, which states that all fertile women should daily take 0.4 mg folic acid while those who are at risk with NTDs should take 0.8 mg daily. The starting day of folic acid consumption has a paramount importance: the fetal nervous system develops most dynamically during the first trimester, and the neural tube closes between the days 24–30 (in average on the 28th day) which is often before the recognition of the pregnancy. There are no available data whether the supplementation of folic acid started later has any effect on the already established developmental anomalies. The optimal prevention consists of administration of folic acid in an optimal daily dose for every fertile woman. Enrichment of flour with folic acid for the prevention of neural tube anomalies started in 1997 in Canada and in 1998 in the USA [22,23]. Addition of 0.14 and 0.15 mg folic acid to 100 gram flour resulted in a 31% and 16% decrease of the incidence of spina bifida and anencephaly, respectively [24–26].

In the current study, we performed a nation-wide survey collecting data about folic acid intake habits of pregnant women through questionnaires circulated during 2001, 2002 and 2003 in Hungary. Data of 271,748 young mothers were collected and more than 1 million data were obtained. According to our results, 68.1% of the pregnant women presented a regular consumption of some folic acid containing substance. Despite the regular folic acid intake, the frequency of NTDs did not show a decreasing tendency. However, it could be a bias that only 68.1% of the pregnant women took folic acid. It was not possible to identify the number of children born from mothers' on a regular consumption-, frequent consumption and no consumption of any folic acid supplementation. Hence, we compared the number of children born from all the three groups with historical control. It may be a further bias that the registry of developmental anomalies is not of proper accuracy in Hungary. The suggested average reporting ratio of the past years was 40%. Czeizel E. et al made a nationwide data collection to analyze the NTDs frequencies in Hungary between 1963–1967 [27]. They concluded that the frequency of NTDs was 2.95/1000 newborn babies in Hungary. This investigation had been reconfirmed in 1992, 1994 and 2004 by these authors [8,28,29]. These studies underline the fact, that the reported NTDs from Hungarian National Centre of Epidemiology, Department of Human Genetics and Teratology are representing an insufficient number of NTDs. This is supported by the fact that in other countries, the frequency of these developmental anomalies is much higher. The number of reported cases in Hungary is 0.5–0.6/1000, while it is 2.4–3.7/1000 in England and Ireland, 1.6–2.0/1000 in Australia, and 1–2/1000 in the USA

[30,31]. However, the incomplete reporting of the developmental anomalies itself does not explain the fact that after introducing the folic acid prophylaxis, the number of NTDs did not decrease. Based on our experience, the prophylactic supplementation of folic acid begins in Hungary later than the date of neural tube closure in more than 90% of the pregnant women. A further observation was that the daily dose of folic acid was less than that recommended by Wald et al. in 85% of the pregnant women [11]. Thus, we can conclude that the currently applied folic acid supplementation method is not a proper prophylaxis in Hungary despite the hard work of health visitors and good compliance of the pregnant women. The increasing number of planned pregnancies would enable to start the intake of substances containing folic acid earlier by pregnant women. General practitioners and gynaecologists should provide available information and should recommend folic acid intake to women in their fertility period. Social campaigns, posters and brochures could help in drawing attention to the benevolent effect of folic acid. However, this study also proves that the whole targeted population can be reached only if the folic acid is mixed with everyday food, e.g. flour.

A further surprising observation according to a Canadian survey performed in 2003, is that the mixing of folic acid into the flour decreased the incidence of neuroblastoma by 60% [9]. Based on the data provided by The National Pediatric Cancer Registry, the incidence of neuroblastoma has varied since 1975, showing a slightly increasing tendency in Hungary. The incidence did not reveal any significant change in 68.7% of pregnant women, after the folic acid prophylaxis was started. Our study showed that increased maternal folic acid intake during the pregnancy does not decrease the risk of neuroblastoma. However, the folic acid intake began during the first trimester of pregnancy in 45.85%, during the second trimester in 41.68% and during the third trimester in 12.46%, respectively. It is possible that the decreased incidence of neuroblastoma observed in Canada after the introduction of the enrichment of flour by folic acid was due to an increased folic acid intake initiated already before the conception and continued even after delivery or it was due to other environmental factors besides the increased folic acid intake.

In each year approximately 5,000 pregnancies are affected by NTDs in the European Union (EU). Most of the EU countries have a public health strategy similar to the one followed in Hungary, regarding the primary prevention of NTDs [32]. However, the Canadian experience and our current study proved that public education campaigns would not be effective alone in achieving optimal preconceptional folic acid intake for the majority of women [33]. The "Canadian like" public health strategy, based on food fortification with folic acid, defined that all women in their childbearing age who increased their dietary intake of folic acid effectively, consequently decreased the frequency of NTDs [18,19,32–34]. Based on a more than five year long experience, it is worth considering changing not only the Hungarian, but the EU public health strategy about folic acid intake by pregnant woman to prevent and/or reduce the number of NTDs.

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