

FOLIC ACID SUPPLEMENTATION PRACTICE IN EUROPE – PLENARY LECTURE

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There are sparse data on supplementation practice related to folic acid (FAS). The prevalence of FAS usage in different European countries/areas varied from 10% to 43% among women before pregnancy, from 9% to 80% during pregnancy and from 0% to 53% in other population groups. With respect to public health, the results of this study indicate that there is a need to consider which strategy of increasing folates intake could be effective in demographic, cultural, economic *etc.* situation in each country. Because of the increased intake of folic acid there is a need for monitoring supplements and fortified food as the sources of this nutrient to determine exposure at the individual and population levels as well as some measurable health outcomes. It was found that a high intake of folic acid resulted in an increased level of this unmetabolized form in plasma, hence the use of [6S-]-5-methyltetrahydrofolic acid, the natural circulating folate form, should be considered as a supplement and fortificant.

INTRODUCTION

Many studies on the metabolic function of folate have recently established potential benefit to health that may occur from the daily intake of 400 µg of this nutrient. It is difficult to supply such an amount from natural products only, thus different strategies for increasing the folates intake are applied. In many countries taking folate supplements is recommended, especially for women in childbearing age to prevent neural tube defects [Czernichow *et al.*, 2005] as well as for elderly to prevent cardiovascular diseases [Stanger *et al.*, 2003], even though recent studies have questioned the benefits for middle-aged and older adults from lowering homocysteine level in plasma for cardiovascular protection [Carlsson, 2006].

Moreover the availability of the supplements on the market is growing and consumption of dietary supplements has considerably increased in the past decade not only in the US but also in Europe [Messerer *et al.*, 2001; Pietruszka & Brzozowska, 1999]. Hence, the usage of supplements may contribute substantially to the average population nutrient intake.

Also fortification of food products with folic acid becomes more and more popular. The results of surveys carried out in the US, where fortification of flour is obligatory, indicated that there is a risk of folic acid overdose because some people combine supplements and fortified products [Troen *et al.*, 2006].

The inclusion of dietary supplements and fortified products into quantitative estimation of nutrient intake becomes necessary in the studies of relationship between intake, folate status and disease risk. It is also important to know the effect of educational campaigns directed to some population groups, like young women. Moreover there are questions important for policy makers, *i.e.* what is the population group at risk of in-

adequate consumption ignored folic acid supplements and, on the other hand, what is the daily folate intake from additional sources like supplements and fortified products together, because of possible adverse effect of high doses of folic acid.

The aim of the study was to collect and compare data on folate supplement usage among Europeans.

MATERIALS AND METHODS

Data on folic acid supplement usage in different European countries were gathered through searching literature as well as personal or e-mail contacts. The original assumptions were to include surveys published in the last 5 years, but because of scanty amount of suitable data it was decided to extend the period of search. Data gathered are presented separately for women before and during pregnancy (17 papers from the years 1994-2003), women in childbearing age (5 papers from the years 1999-2001), elderly (8 papers from the years 1991-2004) and adolescents/adults/whole population (8 papers from the years 1998-2004) from Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland and UK.

The following data are presented: country/area, year of survey, population under study (number, gender, and age) and prevalence of folic acid supplement use. Only data related to surveys among healthy people were included.

RESULTS AND DISCUSSION

Most data are related to folic acid supplement (FAS) usage among women before and during pregnancy (Table 1). The prevalence of FAS usage before pregnancy varied between

TABLE 1. Folic acid supplements usage among women before and during pregnancy in different European countries.

Country Town/area/ year of the study	Population under study	Folate supplement use (% of total population)	Reference
Hungary, Budapest (1980-1991)	105 women Center of FamilyPlaning case control study	6.7% periconceptual 30.0- 63.1% pregnancy	[Czeizel & Susánszky, 1994]
UK, Glasgow	487 who deliver normal baby	21% before conception 57% during pregnancy	[McGovern <i>et al.</i> , 1997]
Germany, Munich	921 women PEGASUS study	<10% periconceptual 50% during pregnancy	[Irl <i>et al.</i> 1997]
Finland, Oulu (1995/96)	118 women in third trimester of pregnancy	27.1%	[Erkkola <i>et al.</i> , 1998]
UK, South West England (1991/92)	11923 pregnant women	9% before 18 weeks gestation 18% at 32 weeks gestation	[Rogers & Emmett, 1998]
Italy, eastern Sicily	987 pregnant women	0.5% periconceptual 4.1% before pregnancy 12.3% two first months of pregnancy	[Pepe <i>et al.</i> , 1999]
The Netherlands Nijmegen	575 pregnant women	70% daily, 52% periconceptual	[Bekkers & Eskes, 1999]
The Netherland, Rotterdam (1994/97)	881 periconceptual period	18% 1994 60% 1997	[Brandenburg <i>et al.</i> , 1999]
Ireland Dublin (1997)	300 women antenatal clinic	16% before pregnancy 51% during pregnancy	[McDonnell <i>et al.</i> , 1999]
Ireland	80 women, representative sample 18-50 y.	26%	[Kiely <i>et al.</i> , 2001]
The Netherlands northern part (1995)	352 pregnant women	4% periconceptual 7.1% before pregnancy	[De Walle <i>et al.</i> , 1998]
after campaign (1998)	453 pregnant women	35.5% periconceptual 42.6%before pregnancy	[De Walle <i>et al.</i> , 1999]
UK Northampton, (2001)	301 antenatal clinic, 16-42 years old	43% before pregnancy 67% first trimester	[Langley-Evans & Langley-Evans, 2002]
Ireland, Dublin (2000)	300 women antenatal clinic	18% before pregnancy	[Oleary <i>et al.</i> , 2002]
Poland, Warsaw	90 pregnant women	24% before pregnancy 76.7% during pregnancy	[Hamułka <i>et al.</i> , 2003]
Spain	general population of pregnant women	9% before pregnancy 80% first trimester	[Martinez-Frias <i>et al.</i> 2003]
The Netherlands (1996)	1555 pregnant women	56% non-western women 69% western women	[Bakker <i>et al.</i> , 2003]

studies and was lower than 10% in the Eastern part of Sicily, Italy [Pepe *et al.*, 1999], in Norway [Vollset & Lande, 2000], in Spain [Martinez-Frias *et al.*, 2003] and in the Netherlands in 1995 [De Walle *et al.*, 1998]. The highest prevalence, *i.e.* 43%, was observed in Northampton, UK [Langley-Evans & Langley-Evans, 2002]. Other results were in the range of 16-24% of populations under study.

The percentage of women taking FAS during pregnancy was in the range of 9% to 80%. The lowest percentages were observed in the studies carried out approx. 10 years ago in the United Kingdom and in such areas like Eastern Sicily [Pepe *et al.*, 1999], and the highest, up to 80%, in first trimester of pregnancy in Spain [Martinez-Frias *et al.*, 2003], and in Poland [Hamułka *et al.*, 2003]. The percentage of women taking FAS during pregnancy was usually much higher than that before pregnancy and most investigations reported the

use of FAS by 50-70% of pregnant women.

The most important is to take FAS during entire periconceptual period. Such data are less available but it is interesting to compare the results from the Netherlands. In this country mass media campaign to reduce the risk of fetal neural-tube defects was held in 1995 and the awareness about folic acid as well as FAS usage increased significantly from 4.8% in 1995 to 35.5% in 1998 [De Walle *et al.*, 1998, 1999].

FAS use by childbearing age women is presented in Table 2. In Poland the supplements of this nutrient were less popular (13 and 18%) than in Ireland (26%), Denmark (26%) and Norway (53%) at almost the same years of studies.

Data on FAS use by elderly (Table 3) are available from SENECA project and from the United Kingdom, Denmark and Poland. SENECA results indicated vast differences be-

TABLE 2. Folic acid supplements usage among women in childbearing age in different European countries.

Country Town/area/ year of the study	Population under study	Folate supplement use (% of total population)	Reference
Poland, Warsaw (1999)	400 women aged 15-50	13% of multivitamins containing folic acid	[Szumska & Mazur, 1999]
Poland, Warsaw(1999)	78 women aged 18-35 y	18%	[Rogalska-Niedzwiedz <i>et al.</i> , 2000]
Norway (1998)	1146 women aged 18-45	0.9% current use 2.4% before and in the last pregnancy 10.3% during pregnancy within last year (53.3% multivitamins)	[Vollset & Lande, 2000]
Denmark, Kopenhagen Aalborg (1998)	290 women aged 25-30 y	36.2%	[Rasmussen <i>et al.</i> , 2000]
Ireland	80 women, representative sample 18-50 y	26%	[Kiely <i>et al.</i> , 2001]

TABLE 3. Folate supplement usage among the elderly.

Country Town/area / year of the study	Population under study	Folate supplement use (% of total population)	Reference
18 small towns of 12 European countries (1989)	1217 men 1241 women born between 1913-1918 SENECA	0-3% France, Belgium, Grece, Italy, Portugal, Spain, the Netherlands, Poland Switzerland,, 39% Denmark, 12% Norway	[Amorim Cruz <i>et al.</i> , 1991]
12 European small towns (1993)	658 men 731 women born between 1913-1918 SENECA	1 – 5% Belgium, France, Italy, the Netherlands, Portugal, Spain, Poland Switzerland, 10% UK, 12% Norway 53% Denmark	[Amorim Cruz <i>et al.</i> , 1996]
12 European small towns (as above) (1993 and 1999)	621 persons born between 1913-1918	men: 1993 – 4.8%, 1999 – 5.2% women: 1993 – 11.8%, 1999 – 12.6%	[Brzozowska <i>et al.</i> , 2002]
Poland, Marki (1993)	130 individuals aged 75-80	3.8%	[Pietruszka & Brzozowska, 1995]
UK, Nottingham area	809 persons aged 65+	multivitamins: 8% urban area 10.8% rural area	[Johnson <i>et al.</i> , 2000]
Denmark, Kopenhagen Aalborg (1998)	288 women 60-65 y	44.2%	[Rasmussen <i>et al.</i> , 2000]
UK (1994/95)	852 individuals aged 65+	3.8% 2.5% North, 4.7% South	[Bates <i>et al.</i> , 2001]
Poland, Warsaw (1996-2002)	126 women 60 y 168 men 70 y	13% women 14% men	[Charzewska <i>et al.</i> , 2004]

tween countries (prevalence range in 1993 was 0-53%) with overall tendency to increase during time, especially in Denmark, Portugal, Spain and Switzerland. In Warsaw the percentage of elderly taking FAS was higher (13-14%) than in small Polish town Marki (3.8%), but the differences in the age of subgroups and year of the study could also be the reason of differences observed.

Other data on FAS usage are presented in Table 4. It is difficult to compare them because they varied in terms of the age of population under study and the year of the study as

well as the period captured by investigation.

Technical and methodological difficulties are inherent in collecting detailed information on supplement usage. Especially information about prevalence and trends in consumption, based on nationally representative data, is lacking in most European countries [Messerer *et al.*, 2001]. The additional problem is that the papers on supplement usage are published in domestic journals which are not easily available. It is also difficult to compare data on dietary supplement usage between countries and studies because of different defi-

TABLE 4. Folate intake among other age groups.

Country Town/area/ year of the study	Population under study	Folate supplement use (% of total population)	Reference
Germany, Augsburg (1994/95)	4856 individuals aged 25-74 years	Folate users: 3.2% of women 2.0% of men Folate regular users: 2.1% of women 1.4% of men	[Schellhorn <i>et al.</i> , 1998]
Poland central and eastern area (1994)	594 women 425 men aged 18+	14.4%	[Pietruszka & Brzozowska, 1999]
Poland, Warsaw (1994, 1999)	in 1994 n=396 in 1999 n=312 aged 18+	in 1994 – 8.8% in 1999 – 33.0%	[Pietruszka & Brzozowska, 2000]
The Netherlands (1992)	6218 aged 1-92 years (Dutch National Food Consumption Survey)	1.7% (108 persons among them: 58% of women, 80% aged above 16 y.	[Konings <i>et al.</i> , 2001]
Finland, Helsinki area (1997)		15%	[Alfthan <i>et al.</i> , 2003]
Warsaw, Poland (2002)	290 women, 159 men aged 18 and over	30.0% women 24.5% men	[Pietruszka & Brzozowska, 2004]
The Netherlands (1997/98)	6250 1-96 years old	6.5%	[Konings, 2004]
Poland, Warsaw (1999/2000)	543 girls, 593 boys 11-15 y old	12% girls 13% boys	[Chwojnowska <i>et al.</i> , 2004]

nitions of these preparations as well as set of information gathered during survey and reported in the papers (usage of preparations like multivitamins, intake of folic acid from different preparations, the amount of folate intake from all the sources together *etc.*). Moreover different descriptions of supplement users as: regular, on daily basis, irregular, occasional, rare, heavy user are applied. Also the periods of measures varies between studies from one day (the day of the study) to any use in the last year.

Only a few investigations were dedicated to the method of collecting supplement intake data [Satia-Abouta *et al.*, 2003]. In comparison with three 24-hour recalls, a brief questionnaire accurately and reproducibly captured data on supplement use for frequently consumed products like multivitamins. Probably it may perform less well for products used less often or more intermittently. Single supplements of folic acid were not included in that comparison [Murphy *et al.*, 2002]. Future studies need to be standardised to enable comparison between different survey populations [Messerer *et al.*, 2001].

Information on supplement usage are gained usually by using self administered questionnaires or by oral interviews (personal or telephone). Burton *et al.* [2001] studied relation between reported use of folic acid supplements and blood folate levels. They found that self reporting by questionnaire provided a valid method of assessing folic acid supplementation and they suggested that it is suitable for assessing the effectiveness of public health intervention strategies within the population of pregnant women.

There are sparse data on demographic, health, diet as well as cultural factors related to folic acid supplement usage. Based on the characteristics of supplement (total) users who have been profiled in numerous surveys [Jasti *et al.*, 2003],

including our own, we can conclude that supplement users are more likely to be older women, with education beyond high school and higher income. They are also more likely to be physically active, nonsmokers, with lower body mass index and a higher intake of nutrients from food [Pietruszka & Brzozowska, 2004]. Understanding these determinants of supplement use is crucial for the success of encouraging such a practice in subgroups that can benefit most. These data should be used to target health education and behaviour modification effort in regard to the use of supplements. Concerning folic acid, greater emphasis on periconceptional use focusing also on less affluent people from small towns and villages is also important.

With respect to public health, the results of this study indicate that there is a need to consider which strategy of increasing folates intake could be effective in demographic, cultural, economic *etc.* situation in each country. In situation when supplements are used by a substantial part of the population at risk of folate deficiency, for example of young women or elderly, or when the preventive/nutrition education programs or periconceptional care exist and reach the target groups such a practice is a good approach. However data on the prevalence of folic acid supplement use indicate that in many situations (countries, area of living, education level or economic situation) people at risk ignore supplements, probably from many reasons, like lack of knowledge about the role of folic acid in human body, believes that their nutritional habits are good, economic difficulties *etc.* Fortification of staple food in such situation would be the better choice.

Many European countries have postponed a decision to introduce mandatory fortification because of concerns about a possible adverse effect of high doses of folic acid (a syn-

thetic form of folates) not only in older people among whom B₁₂ deficiency is common. In German DONALD study [Sichert-Hellert *et al.*, 2006], it was found that the intake of folic acid from supplements and fortified foods exceeded the tolerable upper level in many age groups (the highest prevalence 13% of children aged 2-3 y). There was not a case among adults from Warsaw [Pietruszka & Brzozowska, 2006]. Moreover, a high intake of folic acid resulted in an increased level of this unmetabolized form in plasma. Such a situation was observed among 78% of plasma samples from fasting postmenopausal women by Troen *et al.* [2006]. They found an inverse relation between the presence of unmetabolized folic acid in plasma and natural killer cell cytotoxicity. Other discussed concerns are related to promoting cancer [Kim, 2004; Charles *et al.*, 2004] and mutation of MTHFR gene [Lucock & Yates, 2005].

Because of the increased intake of folic acid in many countries there is a need for continuous monitoring of these sources of nutrients to determine temporary patterns of intake and exposure at the individual and population levels and ultimately to some measurable health outcomes. Moreover the use of [6S]-5-methyltetrahydrofolic acid, the natural circulating folate form, should be considered as an equivalent fortificant.

CONCLUSIONS

Because of increasing tendency of supplement usage in some subpopulation and broadening market of supplements and fortified products and at the same time a large part of population with too low intake there is a need to assess prevalence and doses of folate supplements intake as well as determinants of supplement use in European countries. It is important to create suitable policy for strategies of increasing folate intake at the population level as well as to carry out effective nutrition education taking into account also the possibility of an adverse effect of high folic acid intake.

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STOSOWANIE SUPLEMENTÓW KWASU FOLIOWEGO W EUROPIE – WYKŁAD PLENARNY

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W dostępnej literaturze istnieje niewiele danych dotyczących rozpowszechnienia stosowania suplementów kwasu foliowego. Częstość ich stosowania wahała się w różnych krajach (obszarach) Europy od 10% to 43% wśród kobiet przed zajściem w ciążę, od 9% to 80% w czasie ciąży (tab. 1) i od 0% to 53% w innych grupach populacyjnych (tab. 2, 3 i 4). Biorąc pod uwagę zdrowie publiczne należy zastanowić się, która strategia zwiększania spożycia folianów może być efektywna w sytuacji demograficznej, ekonomicznej, kulturowej w każdym kraju. Ze względu na wzrost spożycia kwasu foliowego w postaci suplementów oraz w postaci produktów wzbogacanych istnieje potrzeba monitorowania jego spożycia z tych źródeł, zarówno na poziomie indywidualnym, jak i populacyjnym, jak również monitorowanie efektów zdrowotnych. Ponieważ nadmierne spożycie może prowadzić do pojawiania się niezmetabolizowanego kwasu foliowego w osoczu należałoby rozważyć użycie kwasu [6S-]-5-metyltetrahydrofoliowego, formy naturalnie występującej we krwi, jako składnika suplementów i dodatku do produktów spożywczych.