CONCORDANCE BETWEEN PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION AND CANADIAN CLINICAL GUIDELINES

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ABSTRACT

Background
In 2007, the Society of Obstetricians and Gynaecologists of Canada (SOGC) introduced new guidelines on periconceptional folic acid supplementation.

Objectives
To evaluate the concordance between the SOGC guidelines and actual vitamin/folic acid supplementation, and to identify maternal determinants of concordant folic acid use.

Methods
From May to July 2010, pregnant women attending the outpatient clinic at CHU Ste-Justine in Montreal were surveyed to assess use of folic acid. Data on socio-demographic factors, lifestyles, family and personal medical history, and periconceptional folic acid supplementation were collected using a self-administrated questionnaire. Concordance between maternal reported intake of folic acid and SOGC guidelines was estimated accounting for pregnancy history, comorbidities, and lifestyles.

Results
A total of 361 eligible women gave informed consent; of these, 97 (27%) had periconceptional folic acid supplementation intake that was concordant with guidelines. Women with no personal history of neural tube defects (NTDs) were the most concordant with guidelines (36%), followed by women with a previous child with NTD (26%), and women with health risk factors for NTDs (18%). Women who smoked and drank alcohol had the lowest concordance with guidelines (4%). Women with planned pregnancies and higher income were more likely to be concordant with guidelines; whereas, smokers, alcohol and recreational drug user and women with health risk for NTDs were less likely to be concordant.

Conclusions
Concordance with clinical guidelines was low, even for women with a history of NTDs. Our findings highlight the need for public health programs to inform women to consume folic acid every day before and during pregnancy.

Key Words: *Folic acid; neural tube defects; practice guidelines; guideline adherence; pregnancy; vitamins*

Neural tube defects (NTDs), including spina bifida and anencephaly, are congenital malformations of the central nervous system resulting from the lack of closure of the neural tube. In the United-States of America (USA) and Canada, they are respectively the second and third cause of infant mortality, among birth defects.[1,2] The development of the neural tube is usually

completed by the 28th day after conception, at a time when many women may not be aware that they are pregnant.[3] Infants with anencephaly are stillborn or die shortly after birth;[4] whereas, many infants born with spina bifida are now surviving due to extensive medical and surgical care.[3] The etiology of NTDs remains unknown; but, epidemiologic studies suggest that these malformations result from a combination of environmental factors and genetic predispositions.

Folic acid, a water-soluble B vitamin also known as folate or pteorylglutamic acid,[5] is an essential nutrient and a component of DNA and RNA synthesis;[5] it helps produce and maintain new cells during times of rapid growth and cell division, such as pregnancy.[6] Folate deficiency during embryogenesis is the predominant environmental factor that has been associated with NTDs. Randomised clinical trials[7-10] have shown that women who take folic acid supplements daily during the periconceptional period have a 72% reduced risk of having an affected foetus (relative risk [RR]= 0.28 [95% confidence interval (CI) 0.13-0.58]).[11] In order to reduce the incidence of NTDs, in 1993 the Canadian health authorities recommended that women of childbearing age should be advised about the benefits of folic acid and should take a multivitamin containing 0.4 mg to 1.0 mg of folic acid daily[12,13] before conception and during the first trimester of pregnancy. Moreover, fortification of a large variety of flour, pasta and cereal products with folic acid became mandatory in 1998.[14] Food fortification was followed by a 46% reduction in the birth prevalence of NTDs.[15]

Previous studies show that although the percentage of women reporting having heard or read about folic acid increased from 52% in 1995 to 84% in 2005, only a small proportion is aware that folic acid prevents birth defects (19%) and should be taken before pregnancy (7%).[16] Knowledge and awareness of folic acid benefits vary greatly among women; for example, it has been shown that non-Caucasian women, between the ages of 18 and 24 years, less educated and with a lower overall socio-economic status were less likely to know about folic acid.[16,17]

In 2007, the Society of Obstetricians and Gynaecologists of Canada (SOGC) with the Motherisk program proposed new practice clinical guidelines[18] on the use of preconceptional vitamin/folic acid supplementation for the prevention of NTDs, with specific recommendations to prevent recurrences and occurrences among women with intermediate to high health risk factors or risky lifestyles. This guideline has not been evaluated at present. Therefore, the objectives of this study were to evaluate the concordance between the new guidelines and folic acid use in real life according to maternal risk factors identified by the SOGC-Motherisk recommendations, and to identify predictors associated with a recommended folic acid supplementation in women of childbearing age.

METHODS

Study Population

A cross-sectional study of pregnant women attending the Obstetric or the High-Risk Pregnancy clinic of the Centre Hospitalier Universitaire Ste-Justine (CHU Ste-Justine), affiliated with the University of Montreal, Quebec, Canada, was conducted from May 2010 to July 2010. Ethics approval for this study was obtained from the CHU Ste-Justine's ethics committee (#2922). Women were asked to participate during one of their follow-up visits and were eligible if they were: (1) at least 18 years of age, (2) in their second or third trimester of pregnancy, (3) able to read and understand French or English, and (4) willing to give written informed consent.

Data Collection

Women who accepted to participate were asked to fill out a self-administered questionnaire comprised of up to 28 questions. Specifically, they were asked whether they had used any folic acid, multivitamin supplements or both, before and/or during pregnancy. Folic acid/multivitamin users were also asked to report in detail the dosage of their periconceptional folic acid supplementation and duration of use (months) prior to and during pregnancy. Data on demographic and socioeconomics variables (age, weight, height, education level, annual familial income, marital status, ethnic group and country of birth), lifestyle (caffeine and alcohol intake, and tobacco, and recreational drug use), comorbidities (type 1 and 2 diabetes, epilepsy,

and others), prescribed and over-the-counter medication use, personal and familial history of congenital malformations and pregnancy history (gestational age, pregnancy planning, parity and use of fertility treatment) were also collected.

Concordance between SOGC-Motherisk clinical guideline and maternal folic acid supplementation

We first classified women in 4 groups according to the SOGC-Motherisk risk factor definitions and then assessed concordance status dichotomously (yes/no). Women included in the 1st group (*option A*) had no personal health risks. They had a concordant status if they had a daily supplementation of 0.4-1.0 mg folic acid at least two to three months before conception and during the first trimester of pregnancy. The 2nd group (*option B*) was composed of women with intermediate to high health risks, including epilepsy, obesity (body mass index (BMI) > 35kg/m^2), pre-existing diabetes, belonging to a high risk ethnic group (Sikh, Celtics and women from northern China) and with a family history of NTDs. The 3rd group (*option C*) included women who had risky lifestyles and possible teratogenic substance use (alcohol (> 9 glasses per week),[19] tobacco and recreational drug use). Finally, the 4th group (*recurrence group*) was composed of women with a previous child or foetus with a NTD or another congenital anomaly, excluding chromosomal anomalies. Women in options B, C and in the recurrence group were considered concordant if they had a supplementation of 5 mg of folic acid for at least three months before conception and during the first 12 weeks post-conception. Although the guideline stated that supplementation should be achieved with multivitamins with folic acid, we considered supplementation in the form of supplements of folic acid alone and from multivitamins containing folic acid. In Quebec, one brand of multivitamin containing 5 mg of folic acid is available when prescribed, but it is not reimbursed by the public drug plan. However, prescribed supplements of 5 mg of folic acid alone are covered, and they can be used in combination with over the counter multivitamin tablets.

Statistical Analyses

Descriptive statistics were used to estimate maternal characteristics and folic acid supplementation in the study population, and to compare women according to their folic acid concordance status. Student T-tests and Chi-square tests were used to assess differences between the concordant and discordant groups, when appropriate. Predictors of concordant folic acid supplementation prior to and during pregnancy were calculated using univariate and multivariate logistic regression models. All sociodemographic variables and variables selected on the basis of the published literature on folic acid supplementation were included in the multivariate model, except ''marital status'' and ''country of birth''. Results were expressed in odds ratio (OR) and 95% confidence interval (CI). All tests were bilateral and a p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.2 (SAS Institute, NC, USA).

RESULTS

A total of 361 women completed the questionnaire and were considered for analyses. Maternal characteristics of the study population, and according to clinical guideline concordance status, are presented in Table 1. Mean maternal age was 30.9 (standard deviation [SD] = 5.3 years). More than half of participants had a high annual family income (>60,000 CAD$), 76% had a post-secondary education, 91% were in a stable relationship (living with spouse or common-law partner), and more than 80% were Caucasians; 29% were primiparous and 73% reported having planned their pregnancy.

TABLE 1 Maternal characteristics of the study population, and according to the concordance status of folic acid supplementation

VARIABLES		n (%)	Folic acid supplementation status: Concordant (n=97) n (%)	Folic acid supplementation status: Non-concordant (n=264) n (%)	*p*-value
Prevention Strategies					
Option A		223 (61.8)	80 (35.9)	143 (64.1)	**< 0.0001***
Option B		45 (12.5)	8 (17.8)	37 (82.2)	
Option C		70 (19.4)	3 (4.3)	67 (95.7)	
Recurrence group		23 (6.4)	6 (26.1)	17 (73.9)	
Maternal Characteristics					
Age [years] (mean ± SD)	(n=361)	(30.9 ± 5.3)	(31.4 ± 4.4)	(30.7 ± 5.6)	0.29 †
< 20 years old		10 (2.8)	1 (10.0)	9 (90.0)	0.09*
20-35 years old		281 (77.8)	83 (29.5)	198 (70.5)	
> 35 years old		70 (19.4)	13 (18.6)	57 (81.4)	
Country of birth	(n=353)				
Canada		259 (73.4)	70 (27.0)	189 (73.0)	0.94*
Others		94 (26.6)	25 (26.6)	69 (73.4)	
Ethnicity	(n=348)				
Caucasian		287 (82.5)	79 (27.5)	208 (72.5)	0.84*
Others		61 (17.5)	16 (26.2)	45 (73.8)	
Education level	(n=358)				
Pre-Secondary		86 (24.0)	13 (15.1)	73 (84.9)	**0.0050***
Post-Secondary		272 (75.9)	83 (30.5)	189 (69.5)	
Marital status	(n=358)				
Stable relationship		327 (91.3)	95 (29.1)	232 (71.0)	**0.0019***
Non-stable relationship		31 (8.7)	1 (3.2)	30 (96.8)	
Annual familial income [CAD$]	(n=349)				
19,999 or less		49 (14.0)	4 (8.2)	45 (91.8)	**0.0002***
20,000 - 59,999		112 (32.1)	24 (21.4)	88 (78.6)	
60,000 or more		188 (53.9)	66 (35.1)	122 (64.9)	
Pregnancy History					
Pregnancy planning	(n=357)				
Intended		260 (72.8)	85 (32.7)	175 (67.3)	**<0.0001***
Unintended		97 (27.2)	9 (9.3)	88 (90.7)	
Parity	(n=360)				
Primipare		103 (28.6)	33 (32.0)	70 (68.0)	0.14*
Multipare		257 (71.4)	63 (24.5)	194 (75.5)	
Fertility treatment	(n=361)				
Yes		21 (5.8)	9 (42.9)	12 (57.1)	0.09*
No		340 (94.2)	88 (25.9)	252 (74.1)	

* Chi-Square test, †Student T-test, SD = Standard deviation, CAD$= Canadian dollars

Among our study population, 97 women (27%) used folic acid before and during the first trimester of pregnancy in concordance with the SOGC-Motherisk practice clinical guidelines. A total of 223 women (62%) had no personal health risk and were thus included in the *option A* group, 45 women (13%) were in the intermediate to high risk group (*option B*), 70 women (19%) were considered to have risky lifestyles (*option C*), and 23 women (6%) had a previous child or foetus with a NTD or another congenital anomaly (*recurrence group*). Concordance with the SOGC-Motherisk clinical guidelines for periconceptional folic acid supplementation were 36%, 18%, 4%, and 26%, for those in Option A, B, C, and recurrence groups, respectively. A total of 155 women did not have a folic acid supplementation before pregnancy and 109 women had a non-concordant folic acid use. These women either had a higher or a lower folic acid dosage intake than what is recommended by the clinical guideline (72 women) or a supplementation for less than the recommended two to three months pre-pregnancy (58 women) (categories were not mutually exclusives) (Table 2). Overall, 206 women (57%) had folic acid supplementation at some point before pregnancy (concordant or not), and 293 women (81%) had folic acid supplementation (concordant or not) during first trimester of pregnancy.

Predictors of concordance between SOGC-Motherisk guideline on periconceptional folic acid supplementation and actual folic acid use

Predictors of folic acid supplementation concordant with the SOGC-Motherisk clinical guideline are presented in Table 3. Predictors increasing the likelihood of folic acid concordance between clinical guideline and actual use before and during the first trimester of pregnancy were having an annual family income above 60,000 CAD$ (OR=2.01 [95%CI: 1.06-4.07]), and a planned pregnancy (OR=4.47 [95%CI: 1.86-10.74]). Characteristics decreasing the probability of having folic acid concordance between clinical guideline and actual use before and during the first trimester of pregnancy were having risky lifestyles or using potentially teratogenic substances (OR=0.10 [95%CI: 0.03-0.35]) and having intermediate to high personal health risk factors for NTDs (OR=0.22 [95%CI: 0.07-0.66]). Having a previous child or a foetus affected with a NTD or another congenital anomaly did not increase the likelihood of being concordant (OR=0.83 [95%CI: 0.29-2.42]).

TABLE 2 Reasons for a non-concordant periconceptional folic acid supplementation

Supplementation Status	N (%)
Absence of supplementation before Pregnancy	155 (42.9)
Concordant periconceptional Supplementation	97 (26.9)
Non-concordant periconceptional Supplementation	**109(30.2)**
Right Dosage <2-3 months	37 (33.9)
Wrong Dosage ≥ 2-3 months	51 (46.8)
Wrong Dosage <2-3 months	21 (19.3)

TABLE 3 Predictors of a concordant periconceptional folic acid supplementation among the 333 women with complete data

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)*
Prevention Strategies		
Option A	1.00 (Ref)	1.00 (Ref)
Option B	0.39 (0.17-0.87)	**0.22 (0.07-0.66)**
Option C	0.08 (0.02-0.26)	**0.10 (0.03-0.35)**
Recurrence group	0.63 (0.24-1.66)	0.83 (0.29-2.42)
Maternal Characteristics		
Age [years]	1.02 (0.98-1.07)	0.98 (0.92-1.04)
Ethnicity (Caucasian vs. others)	1.07 (0.57-1.99)	0.73 (0.33-1.60)
Education level (Post vs. Pre-secondary)	2.47 (1.30-4.70)	1.06 (0.43-2.62)
Annual familial income [CAD$]		
19,999 or less	0.33 (0.11-1.00)	0.72 (0.21-2.47)
20,000 – 59,999	1.00 (Ref)	1.00 (Ref)
60,000 or more	1.98 (1.15-3.41)	**2.01 (1.06-4.07)**
Pregnancy History		
Pregnancy planning (Intended vs. Unintended)	4.75 (2.28-9.89)	**4.47 (1.86-10.74)**
Parity (Primipare vs. Multipare)	1.45 (0.88-2.40)	1.21 (0.65-2.25)
Fertility treatment (yes/no)	2.15 (0.88-5.27)	1.11 (0.39-3.14)

* Adjusted for all variables presented in the table, OR= odds ratio, CI = confidence interval, CAD$= Canadian dollars

DISCUSSION

In order to prevent NTDs, folic acid should be started before conception[8,9] since the neural tube forms within the first 28 days of pregnancy, at a time when many women may not be aware that they are pregnant.[20] The primary objective of this study was to evaluate the concordance between the SOGC-Motherisk's clinical guidelines and the actual intake of folic acid by pregnant women.

We did not study whether this guideline was adequate or valid for NTDs prevention. Consequently, we assessed concordance based on the guideline recommendations only. In the present study of pregnant women attending obstetric clinics in a tertiary care center, only 27% had folic acid/multivitamins supplementation use concordant with the SOGC-Motherisk clinical

guideline recommendations.[18] According to this guideline, low dosage (0.4 – 1.0 mg) of folic acid for at least 2 to 3 months pre-pregnancy is recommended for women with no personal health-risk for NTDs (*option A*), whereas high dosage (5 mg) for at least 3 months before conception is recommended for women with intermediate to high health risk for NTDs (*option B*), women with risky lifestyles and possible use of teratogenic substances (*option C*) and women with a previous child or foetus affected with a NTD or another congenital anomaly (*recurrence group*). For each of the studied groups, concordance was respectively seen in 36%, 18%, 4% and 26% of women.

In our study population, 206 women (57%) reported taking a folic acid supplementation anytime before pregnancy, but less than half of them (97 women) had a concordant use according to guideline definitions. We also found that close to 81% of the women were using folic acid supplements during the first trimester. This shows that many women use folic acid associated with their pregnancy, but the dosage was below or above levels that are recommended, and/or the initiation of the supplementation was too late for appropriate NTDs prevention. In Quebec, 5 mg of folic acid (in a multivitamin or alone) is a prescribed medication, making it difficult for women who did not meet their physician before their pregnancy to have the recommended dosage. The 0.4-1.0 mg dosage of folic acid is however readily available in over the counter prenatal vitamins or multivitamins formulations, and is less expensive. This could explain why, although many women started supplementation before conception, concordance was still low. Although the SOGC recommends 5 mg of folic acid for women at higher risk for NTDs, literature on the efficacy of this dosage, for a greater reduction of the risk compared to 1 mg, is not available. Moreover, clinical studies showed prevention of recurrences with a dose of 4 mg of folic acid daily.[8] There may also have been mixed messages within the country since 4 mg of folic acid is only recommended to prevent recurrences of NTDs and for women using anti-epileptics (carbamazepine and valproic acid) by Health Canada.[21] Health care providers and medical organizations may have been less likely to endorse this guideline, partly explaining the low concordance. Folic acid supplementation guidelines vary across countries. In the United States (US) and in some European countries, high doses of folic acid (4 mg) is only recommended to prevent recurrences, for women taking antiepileptic drugs[20,22] or for women with a personal or family history of NTDs.[23] A survey conducted in the US between 2005 and 2008 reported that 51% of the contacted pregnant women took folic acid supplementation before pregnancy (any dosage).[24] In Canada, analyses of the 2005 version of the cyclic Canadian Community Health Survey (CCHS) showed that 58% of women reported a supplementation before they found out they were pregnant.[25] Our results on use of folic acid at any dosage and any time before pregnancy are similar to the Canadian results (both around 57%) and slightly higher than the prevalence reported in the US.

Our results regarding the differences in maternal characteristics between concordant and non-concordant periconceptional folic acid supplementation were consistent with other reports on folic acid use.[17,26,27] However, our study showed that only planned pregnancy and higher annual familial income were predictors of concordant folic acid supplementation and women with risky lifestyles and possible teratogenic substances use (*option C*) were less likely to have a concordant SOGC-Motherisk supplementation. More than 70% of the women reported that they had planned their pregnancies, but amongst them, only 33% had concordant folic acid supplementation. As discussed above, 5 mg of folic acid is more expensive than 1 mg, which would explain why familial income is a determinant of a recommended use. Among women who had a previous pregnancy affected with congenital anomalies, only 26% had concordant folic acid supplementation. Even in the highly motivated group of women who had used fertility treatment, only 43% had a concordant folic acid supplementation.

Promoting folic acid supplementation before pregnancy, especially among women that are less educated, have lower income, have risk factors for NTDs (obesity, epilepsy, pre-existing diabetes, women from high risk ethnic group, and women with familial history of NTDs) and have risky lifestyles (tobacco, alcohol and recreational drug use) is essential to increase the number of childbearing age women taking preconceptional

folic acid and to further decrease the prevalence of NTDs. Despite the health care providers' concerns on the scientific basis for some recommendations, it appears that this message is not clearly perceived by women of reproductive age. Women who need a prescribed dose of folic acid (5 mg) do not necessarily see their physician before their pregnancy and women who do not plan their pregnancies might not start folic acid before conception. Thus, they are less likely to be concordant. This may suggest that education on folic acid intake may also be provided in other settings such as pharmacies (i.e. stickers could be placed on oral contraceptives packages) as practised in the Netherlands.[28] An oral contraceptive containing 0.4 mg of folic acid is also available in the US.[29]

To our knowledge, this is the first study to evaluate the concordance between folic acid use among Canadian pregnant women and the most recent SOGC-Motherisk clinical practice guidelines including dosage recommendations according to maternal risk factors. Strengths of this study include detailed information on vitamin and supplement intake (dosage and duration in months before and during pregnancy). Furthermore, questions were asked while women were pregnant, reducing the potential for recall bias. The findings from this study are subject to some limitations. As the use of folic acid may be considered a socially desirable behaviour, our study may be limited by the maternal self-report of periconceptional folic acid/vitamins supplementation. In fact, women may have over-reported the dosage, timing, and frequency of supplementation use; however, self-report is a valid method for assessing folic acid supplementation[30] and given our low folic acid intake reported by mothers, the potential misclassification was probably low. Women under the age of 18 were not included in the study. Given that this age group might be even less likely to be aware of the benefits of preconceptional folic acid use[16,17], concordance could be even lower than what we are reporting in the general population of pregnant women. Nevertheless, births from mothers under 19 years of age account for only 4.2% of live births in Canada[31], decreasing the impact on external validity. Women were recruited in a tertiary mother-child hospital that serves a multicultural local population as well as a wider high-risk population. This may explain why our study population has a higher proportion of comorbidities and this could hence impact generalizability. Finally, a comparison between our study population education level and that reported in the national survey for 2010 indicated that women with a higher education level (post-secondary) may be overrepresented in our study (75% in our cohort as compared with 51% in Quebec and 50% in Canada).[32] Since level of education is usually associated with use of folic acid, concordance in the general population could actually be even lower than what we observed. These limitations may have very little impact on internal validity but could partly affect generalizability.

CONCLUSION

Concordance between actual periconceptional folic acid intake and the SOGC-Motherisk clinical guidelines among women in this study was low, even for those with a history of major congenital malformations including NTDs. Our findings suggest the need for more public health programs to inform and encourage women to consume the recommended amounts of folic acid through a folate-rich diet and vitamins or supplements containing folic acid. In addition, high dose folic acid should be available to women without cost obstacles, especially for women with lower income.

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