Changes in Frequencies of Select Congenital Anomalies since the Onset of Folic Acid Fortification in a Canadian Birth Defect Registry

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ABSTRACT

Objectives: Fortification of grain products with folic acid has been shown to significantly reduce the occurrence of neural tube defects (NTDs) in Canada and elsewhere. However, the impact on non-NTD anomalies has not been well studied.

Methods: Using the Alberta Congenital Anomalies Surveillance System (ACASS), we examined changes in occurrence of select congenital anomalies where folic acid supplementation with multivitamins had previously been suggested to have an effect. Anomalies documented in the ACASS 1992-1996 (pre-fortification) were compared to 1999-2003 (post-fortification).

Results: A significant decrease in spina bifida (OR 0.51, 95% CI 0.36-0.73) and ostium secundum atrial septal defects (OR 0.80, 95% CI 0.69-0.93) was evident, but there was a significant increase in obstructive defects of the renal pelvis and ureter (OR 1.45, 95% CI 1.24-1.70), abdominal wall defects (OR 1.40, 95% CI 1.04-1.88) and pyloric stenosis (OR 1.49, 95% CI 1.18-1.89).

Conclusions: Consistent with other studies, a 50% reduction in spina bifida was associated with the post-fortification time period. Supporting the possibility that folic acid fortification may play a role in preventing other birth defects, a 20% reduction in atrial septal defects was also associated. The increase in abdominal wall defects, most notably gastroschisis, is likely related to pre-existing increasing trends documented in several regions around the world. The increase in pyloric stenosis and obstructive urinary tract defects was not expected and any causal relationship with folic acid fortification remains unclear. Similar studies by other birth defects surveillance systems in Canada and elsewhere are needed to confirm these trends.

Key words: Folic acid; heart septal defects, atrial; congenital abnormalities; pyloric stenosis; gastroschisis

La traduction du résumé se trouve à la fin de l'article.

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Acknowledgements: The authors thank Dr. Clarke Fraser, who provided helpful suggestions on an earlier version of the manuscript. Sarah McIntosh, MSc, assisted in editing and formatting the final manuscript. Laura Arbour is a Michael Smith Foundation for Health Research Scholar in Population Health.

Congenital anomalies are a major cause of morbidity, disability and mortality among children, contributing significantly to health care costs.¹⁻³ The discovery of folic acid as a simple and economical way to prevent at least neural tube defects (NTDs) was therefore an important public health success. Indeed, here in Canada, a recent multicentre study has confirmed an associated 46% reduction of NTDs since the onset of folic acid fortification of grain, supporting the effectiveness of the public health initiative.⁴ There is now interest in whether folic acid will reduce rates of other birth defects.⁵⁻⁷

It has been long established that periconceptional use of vitamin supplements containing folic acid reduces the risk of neural tube defects (NTDs).^{8,9} This information led to recommendations of periconceptional folic acid supplementation of 0.4 mg/day for all women of childbearing age and an increased amount (0.8-5 mg daily) for higher risk women (those with diabetes, taking anti-epileptic drugs, or previous NTD-affected pregnancies).^{10,11} Fortification of grain products with folic acid was implemented to ensure that the majority of women have the benefit of at least some folic acid intake during the periconceptional time frame.¹² In December 1996, Canada, along with the US, allowed the addition of folic acid to white flour, enriched pasta and cornmeal.¹² Mandated in Canada by November 1998, the level of fortification was estimated to increase the average daily intake of folic acid in women of childbearing age by about 0.1 mg.¹³

Evaluation of the fortification program has been largely focused on significant reductions in NTDs and has been declared successful in the US and Canada.^{4,14-17} The significant decline temporally associated with fortification provides convincing evidence that folic acid is the nutrient responsible.

For non-neural tube birth defects, there is evidence that periconceptional use of multivitamin supplements containing folic acid and other vitamins is associated with decreased occurrence of some anomalies including: orofacial clefts,^{6,18-23} limb reduction defects,^{6,20,24,25} urinary tract defects,^{6,20,26,27} omphalocele,²⁸ conotruncal and septal heart defects,^{6,24,29,30} and pyloric stenosis.³¹ However, decreases may not be due to

TABLE I

Congenital Anomalies Pre- and Post-folic Acid Fortification According to ICD-9 Codes

Defect (ICD-9 Code)	Pre-fortification (1992-1996) [Total live/stillbirths = 198,321]		Post-fortification (1999-2003) [Total live/stillbirths = 191,028]				
	N	Rate*	N	Rate*	OR†	95% CI	P value
Anencephaly (7400)	38	0.19	27	0.14	0.74	0.45-1.21	0.2759
Spina Bifida (741)	97	0.49	48	0.25	0.51	0.36-0.73	0.0002
Cleft Palate (7490)	146	0.74	159	0.83	1.12	0.90-1.42	0.3102
Cleft Lip (7491)	84	0.42	75	0.39	0.93	0.68-1.27	0.6924
Cleft Palate + Cleft Lip (7492)	155	0.78	140	0.73	0.94	0.75-1.18	0.6215
Obstructive Defects of the Renal Pelvis and Ureter (7532)	267	1.35	373	1.95	1.45	1.24-1.70	<0.0001
Reduction Deformities of the Upper Limb (7552)	121	0.61	127	0.66	1.10	0.85-1.40	0.5400
Reduction Deformities of the Lower Limb (7553)	63	0.32	72	0.38	1.19	0.85-1.64	0.3647
Bulbus Cordis Anomalies + Anomalies of Cardiac Septal Closure (745)	1183	6.0	1107	5.8	0.97	0.89-1.06	0.5009
Common Truncus (7450)	14	0.07	10	0.05	0.74	0.33-1.67	0.6026
Transposition of Great Vessels (7451)	64	0.32	72	0.38	1.17	0.83-1.64	0.4128
Tetralogy of Fallot (7452)	63	0.32	56	0.29	0.92	0.64-1.32	0.7295
Ventricular Septal Defect (7454)	536	2.7	528	2.76	1.02	0.91-1.15	0.7372
Ostium Secundum Type Atrial Septal Defect (7455)	412	2.1	319	1.7	0.80	0.69-0.93	0.0037
Anomalies of the Abdominal Wall (7567)	77	0.39	104	0.54	1.40	1.04-1.88	0.0289
Omphalocele	30	0.15	43	0.23	1.49	0.93-2.37	0.1176
Gastroschisis	38	0.19	70	0.37	1.91	1.29-2.84	0.0015
Hypertrophic Pyloric Stenosis (7505)	119	0.60	171	0.90	1.49	1.18-1.89	0.0009
Total	3507	18/1000	3501	18/1000	1.02	0.99-1.0	0.13

* Rate = # cases (N) per 1000 live/stillbirths

† OR = Odds Ratio – A bold number designates statistical significance of 95% Confidence Interval Bonferroni correction for multiple testing $p < 0.003$ depicts statistical significance

folic acid alone since multivitamin preparations contain other nutrients such as other B vitamins and vitamin A, that are also important in development.^{32,33}

Supportive of folic acid being a protective nutrient, Simmons et al. reported reductions in birth defects in the Arkansas Reproductive Health Monitoring System between two time periods, 1993 and 2000.³⁴ Although rates decreased post-fortification for spina bifida, orofacial clefts, limb reduction defects and omphalocele, only the decrease in spina bifida was statistically significant. However, a multi-state population study found modest yet statistically significant decreases for transposition of the great arteries, cleft palate (without cleft lip), pyloric stenosis, upper limb reductions and omphalocele post-fortification. Interestingly, modest yet significant *increases* in the prevalence of obstructive urinary tract defects were also observed.³¹

We used the Canadian-based Alberta Congenital Anomalies Surveillance System (ACASS) to examine changes in birth prevalence of select structural congenital anomalies between two time periods, 1992-1996 (pre-fortification) and 1999-2003 (post-fortification) to determine whether there was a change in frequencies of birth prevalence of select congenital anomalies thought to be amenable to the benefits of folic acid.

METHODS

Birth defect selection

Specific birth defects to be evaluated were selected on the basis of previous reports of potential folic acid benefit: anencephaly and spina bifida, orofacial clefts, specific heart defects (conotruncal and septal defects), urinary tract anomalies, reduction limb defects, abdominal wall defects and pyloric stenosis.

Database

The ACASS was chosen for this assessment as one of the few comprehensive Canadian population-based sources of birth defects.³⁵⁻³⁷ ACASS obtains information on infants with congenital anomalies up to 1 year of age from numerous sources. All acute-care hospitals in the province notify Alberta Vital Statistics of the live birth, stillbirth, admission or hospital death of an infant less than one year of age who has a congenital anomaly. A notification form called the Congenital Anomaly(ies) Reporting Form (CARF) is completed by the hospital health records personnel following the birth or admission of an affected child. This form serves as the most important source of case ascertainment. In addition, outpatient information (such as that from medical genetics and other specialties) is also obtained. When multiple congenital anomalies occur in a single

infant, each birth defect is categorized separately. Trained personnel within the registry, consistent medical oversight, and clarification from treating physicians when needed ensure appropriate classification. All infants are included, even if they have an identifiable genetic syndrome. The ACASS has only ascertained terminations of pregnancies affected with congenital anomalies since 1997.

Years of analysis

Exposure to folic acid fortification was classified by year of birth. Birth years 1992-1996 were classified as pre-fortification and 1999-2003 as post-fortification. 1999 was chosen as the first year of full fortification exposure based on the plateau of serum folate evident in population-based studies by the first third of 1998.³⁸ Since voluntary folic acid fortification commenced in 1996, with mandatory folic acid fortification starting in 1998, we excluded data from delivery years 1997 and 1998 to enhance the analytic contrasts, as has been done in similar studies.³¹ Since elective abortions for congenital anomalies were only ascertained since 1997, we excluded abortion data from our analysis.

Analysis of data

The birth prevalence of select congenital anomalies using the number of live births and stillbirths for the appropriate period as

the denominator was calculated. Two-way contingency table analysis was performed using Graphpad Instat version 3.02 to generate odds ratios with 95% confidence intervals using the chi square approximation.³⁹ The Bonferroni correction was also used, suggesting a *p* value of <0.003 was highly supportive of statistical significance taking into account multiple testing.

RESULTS

There were 198,321 live births and stillbirths in the pre-fortification time period, and 191,028 post-fortification. Table 1 summarizes the number of anomalies and rates per 1000 live births and stillbirths for each ICD-9 coded congenital anomaly by time period, including odds ratios with 95% confidence interval. Significant decreases in the birth prevalence of spina bifida [odds ratio (OR) 0.51, 95% confidence interval (CI) 0.36-0.73] and ostium secundum type atrial septal defects (OR 0.80, 95% CI 0.69-0.93) were evident in the post-fortification period. Birth prevalence also decreased for anencephaly, cleft lip, cleft lip and palate, bulbus cordis anomalies and anomalies of cardiac septal closure, common truncus and tetralogy of fallot, but these differences were not statistically significant.

Statistically significant *increases* in prevalence were observed for three congenital anomalies in the post-fortification period: obstructive defects of the renal pelvis and ureter (OR 1.45, 95% CI 1.24-1.70), anomalies of the abdominal wall (OR 1.40, 95% CI 1.04-1.88) especially gastroschisis (OR 1.91, 95% CI 1.29-2.84), and hypertrophic pyloric stenosis (OR 1.49, 95% CI 1.18-1.89). Non-significant increases were observed for cleft palate, reduction limb deformities, transposition of the great vessels and omphalocele (Table I).

DISCUSSION

This provincial registry-based analysis comparing congenital anomalies before and after folic acid fortification supports previously recognized reductions in spina bifida attributable to folic acid fortification.^{4,14-17,40} Anencephaly was also reduced by a third, consistent with the recent Canadian multicentre study,⁴ but small

numbers (likely secondary to pregnancy terminations in both time periods) precluded statistical significance.

Although other jurisdictions have reported increasing trends in septal heart defects possibly secondary to improved ascertainment of cases,⁴¹ no change in the rate of ventricular septal defects was seen in our study. The fact that there was no overall increase in septal defects, and that a significant reduction in atrial septal defects (ASDs) was observed, may support the hypothesis that folic acid is at least one of the critical nutrients responsible for the reduction in heart defects associated with multivitamin use.^{5,24,27,29,30} Although Bonferroni correction for multiple testing revealed borderline significance with a *p* value of 0.0037 (significance considered <0.003), this test is considered highly conservative. The reduction of ASDs was well supported by 95% CI 0.69-0.93. However, further studies with longer-term evaluation are needed to corroborate this finding.

The increase in obstructive defects of the renal pelvis and ureter was also significant (OR 1.45, 95% CI 1.24-1.70). Since prenatal ultrasound information is not collected in this registry, the soft-marker 'pyelectasis' was not a determinant of the results. However, increased vigilance to more advanced prenatally-detected urinary tract dilatation, followed by confirmatory postnatal ultrasounds could account for the increase. It is interesting, however, that Canfield et al. also found a significant increase in obstructive urinary tract defects after fortification in the United States.³¹ Furthermore, Yuskiv et al. found that the only congenital anomaly that occurred more frequently than expected among infants with multiple congenital anomalies exposed to periconceptional multivitamin use was urinary obstructive defects.⁴² Yuskiv's study was one of two registry-based studies that demonstrated an increased risk of multiple congenital anomalies with the periconceptional use of multivitamins. No particular organ system was overrepresented in the other study by Shaw et al.⁴³

Although the reason is unclear, it has been widely recognized that gastroschisis, a birth defect presumed to be caused by vascular disruption, is increasing, especially in younger women.^{44,45} The increasing rate of

gastroschisis seemed to pre-date folic acid fortification, and likely reflects a pre-existing trend unrelated to fortification.

The increase in birth prevalence of hypertrophic pyloric stenosis was unexpected since several studies suggested a decrease with the use of multivitamins, and recently with fortification.³¹ Although the underlying etiology of hypertrophic pyloric stenosis remains unclear,⁴⁶ an Ontario study suggests the rate in that province is increasing.⁴⁷ Our data support this observation in another population, however more study is needed to determine if this trend is occurring elsewhere.

Even after numerous folic acid awareness campaigns, fewer than 50% of women appear to take multivitamins with folic acid periconceptionally.^{48,49} Thus, it seems fortified grain products remain an important source of folic acid for the majority of women. However, there have been few population studies in Canada evaluating whether fortification is achieving blood folate levels sufficiently protective for birth defects.^{49,50}

Although the current study is helpful as a first Canadian evaluation of the birth prevalence of select non-NTD birth defects pre- and post-folic acid fortification, a registry analysis such as this can only reveal associations between the timing of fortification and trends in birth defect rate. Our study was further limited because elective abortion data were not collected in the first time period, and therefore were not used from the second. A higher rate of terminations in the second time period could give a false impression of a beneficial effect of fortification. However, for this study it is reassuring that the recent multi-centred study on the effects of folic acid fortification on NTD rates did collect elective abortion data, and the difference in rates were similar to that observed in our study.⁴ Furthermore, on review of the elective abortion data available, there were no documented ASDs.

For those birth defects that were increased in the post-fortification period, other changing demographics (such as increasing obesity rates) were not assessed. Further study to explore the increases more comprehensively is needed. Furthermore, because of the relative rarity of many birth defects, numerical power in any one jurisdiction may be insufficient to provide the

information needed to assess public health efforts in a timely manner. In Canada, there are few provincial registries that are capable of providing the information needed to make a confident assessment of changes in rates of birth defects.³⁵ Ideally, registries in every jurisdiction in the country should be available with the ability to link to prenatal risk factors and to each other to produce more meaningful results.

In summary, following folic acid fortification, Albertan women were less likely to have an infant with spina bifida or an ASD but more likely to have an infant with an obstructive urinary tract defect, pyloric stenosis, or gastroschisis. Apart from spina bifida, the relation of these trends to folic acid fortification needs to be clarified. Assessments of blood levels of folate and corroborating assessments of birth defect rates in other Canadian jurisdictions are needed to determine if the public health efforts implemented in 1998 are having an impact on rates of non-NTD congenital anomalies.

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Received: August 1, 2007

Accepted: February 19, 2008

RÉSUMÉ

Objectifs : Il est prouvé que l'enrichissement en acide folique des produits céréaliers réduit la fréquence des anomalies du tube neural (ATN) au Canada et ailleurs dans le monde. Cependant, l'impact d'un apport supplémentaire en acide folique sur les autres anomalies congénitales n'a pas été suffisamment étudié.

Méthode : À l'aide du système de surveillance des anomalies congénitales de l'Alberta (ACASS), nous avons examiné les variations dans la fréquence de certaines anomalies congénitales pour lesquelles on pense qu'une supplémentation multivitaminique contenant de l'acide folique aurait un effet. Les anomalies répertoriées dans l'ACASS de 1992 à 1996 (avant l'enrichissement) ont été comparées aux données de 1999-2003 (après l'enrichissement).

Résultats : Des baisses significatives du spina bifida (RC=0,51, IC de 95 % = 0,36-0,73) et de la persistance de l'ostium secundum [variété la plus fréquente de communication interauriculaire] (RC=0,80, IC de 95 % = 0,69-0,93) ont été observées, avec par contre des augmentations significatives des malformations obstructives du bassinet du rein et de l'uretère (RC=1,45, IC de 95 % = 1,24-1,70), des malformations de la paroi abdominale (RC=1,40, IC de 95 % = 1,04-1,88) et de la sténose du pylore (RC=1,49, IC de 95 % = 1,18-1,89).

Conclusion : Conformément aux résultats d'autres études, une diminution de 50 % dans la fréquence du spina bifida était associée à la période suivant l'enrichissement en acide folique. Un tel enrichissement pourrait jouer un rôle dans la prévention d'autres anomalies congénitales, comme en témoigne la baisse de 20 % dans la fréquence de la communication interauriculaire. L'augmentation des malformations de la paroi abdominale, en particulier du laparoschisis, est probablement liée à des tendances haussières préexistantes signalées dans plusieurs régions du monde. Les augmentations de la sténose du pylore et des malformations obstructives du tractus urinaire n'étaient pas prévues, mais une relation causale entre ces anomalies et l'enrichissement en acide folique n'est pas encore établie. Il faudrait mener des études semblables à partir d'autres systèmes de surveillance des anomalies congénitales au Canada et ailleurs dans le monde pour confirmer ou infirmer ces tendances.

Mots clés : acide folique; communication interauriculaire; anomalies congénitales; sténose du pylore; laparoschisis

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2. **Maintenez une vie sociale active.**
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