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Red blood cell folate levels in pregnant women with a history of mood disorders: a case series

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Abstract

Objective—Maternal folate supplementation reduces offspring risk for neural tube defects (NTDs) and other congenital abnormalities. Maternal red blood cell (RBC) folate concentrations of >906nmol/L have been associated with the lowest risk of having an NTD affected pregnancy. Mood disorders (e.g. depression, bipolar disorder) are common among women and can be associated with folate deficiency. Thus, pregnant women with histories of mood disorders may be prone to RBC folate levels insufficient to provide optimal protection against NTDs. While previous studies have assessed RBC folate concentrations in pregnant women from the general population, none have looked specifically at a group of pregnant women who have a history of a mood disorder.

Methods—We collected data about RBC folate concentrations and folic acid supplement intake during early pregnancy (<161days gestation) from n=24 women with histories of mood disorders. We also collected information about offspring congenital abnormalities and birthweight.

Results—Among women with histories of mood disorders, the mean RBC folate concentration was 674 nmol/L (range: 362 –1105nmol/L). Only 12.5% (n=3) of the women had an RBC folate concentrations >906nmol/L, despite all participants reporting current daily use of folic acid supplements. Data regarding offspring were available for 22 women: birthweights ranged from 2296g to 4819g, and congenital abnormalities were identified in two (hypoplastic left heart, annular pancreas).

Conclusion—Data from this exploratory case series suggest a need for future larger scale controlled studies investigating RBC folate concentrations in early pregnancy and offspring outcomes among women with and without histories of mood disorders.

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Keywords

folic acid; folate; pregnancy; mood disorders; depression; birth defects; congenital abnormalities

Introduction

Neural tube defects (NTDs) and related congenital abnormalities are among the leading causes of infant mortality and disability (Carmona, 2005). Folate is essential during the early stages of pregnancy, and there is a well-documented link between suboptimal maternal folate status and the incidence of NTDs and other congenital anomalies (Goh et al., 2006). Recognition of this precipitated the mandatory fortification of wheat flour and other grains with folic acid in many countries including Canada, where fortification began in 1998 (Ray, 2004). Fortification resulted in increased blood folate concentrations and has been linked to a sizable reduction (46%) in the prevalence of NTDs (Shakur et al., 2010).

Despite food fortification, there is evidence that women may not meet the recommendation of a daily folic acid intake of 4003g from fortified foods during the periconceptional period (Shuaibi et al., 2008). Therefore, current guidelines recommend that women capable of becoming pregnant should consume 0.4 mg of folic acid per day from supplements and fortified foods, in addition to dietary folate (Health Canada, 2009),and that women considered to have increased risk of having an NTD affected pregnancy (e.g. those who have a family history of NTDs or take folic acid antagonist medications) should take a 5mg folic acid vitamin beginning at least three months before conception (Wilson, 2007).

An Irish study observed that women with red blood cell (RBC) folate concentrations >906nmol/L have the lowest risk of an NTD affected pregnancy (Daly et al., 1995). In recent Canadian studies, 40% and 86% of women of childbearing age in Ontario and Manitoba, respectively, were shown to have RBC folate concentrations <906nmol/L, and thus below the optimum for protection against NTDs in their offspring (Shuaibi et al., 2008, Bar-Oz et al., 2008). National data from the Canadian Health Measures Survey showed that a smaller, but still sizeable proportion of Canadian women (22%) had RBC folate concentrations of <906nmol/L (Colapinto et al, 2011). To date, only one Canadian study has looked at RBC folate concentrations among *pregnant* women – and found that 36% of women in Ontario had concentrations insufficient to provide optimum protection against NTDs in offspring (Bar-Oz et al., 2008).

Mood disorders are common – particularly in women (Marcus, 2009), and are associated with several nutrient inadequacies, including folate deficiency (Davison & Kaplan, 2011). This suggests that pregnant women with a history of mood disorders may be at increased risk for NTDs in offspring as a result of suboptimal folate status.

Further, in terms of evaluating folate status in pregnant women with respect to NTDs, the most clinically meaningful approach is to look at RBC folate concentrations during early gestation. Specifically, RBC folate concentrations measured before 161 days gestation offer some insight into circulating folate concentrations prior to completion of neural tube closure (the neural tube completes closure after 28 days (Nakatsu & Uwabe, 2000) of embryonic

development, which corresponds to 42 days gestation, and RBC folate concentrations reflect long-term folate status because folate is only taken up by RBCs during erythropoiesis, and RBCs have a half-life of 120 days) (Herbert, 1989), and are therefore more clinically meaningful from the perspective of assessing protection against NTDs by adequate folic acid intake.

Methods

We recruited pregnant women (<161 days gestation, as calculated from date of last menstrual period or by information from detailed ultrasound if available) with a history of a mood disorder (bipolar disorder or depression) from the Greater Vancouver area via posters in clinics, Internet advertisements, community events for pregnant women, and the Provincial Reproductive Mental Health Program. The study was approved by the University of British Columbia Clinical Research Ethics Board (UBC CREB, H06-70145).

For all participants, lifetime psychiatric diagnosis was confirmed by Structured Clinical Interview for DSM-IV (SCID) administered by a trained healthcare professional (First et al., 1997). Questionnaires were administered to collect data on use of cigarettes, psychotropic medications and folic acid supplements (including timing of initiation in relation to conception, as well as current dose and frequency). Further, the Edinburgh Postnatal Depression Scale (EPDS) a 10-item, self-administered, Likert scale-based questionnaire (each item is rated by selecting from 4 options, scored from 0 to 3) that has been validated for prenatal use(Murray & Cox, 1990) was used to assess level of depression. An EPDS score of ≥15 during pregnancy has a sensitivity of 100% and a positive predictive value of 60% (Murray & Cox, 1990) for major depression (with a false positive rate of 4%) (Murray & Cox, 1990). With participants consent, we also obtained information about offspring birthweight and congenital anomalies from hospital records.

To measure RBC folate, 3ml of blood was drawn into an EDTA-treated vacutainer and immediately transported the lab for analysis. Hematocrit was measured on whole blood at room temperature. Plasma and whole blood folate were each quantified using an Abbott AxSYM autoanalyzer (folate was measured directly in untreated plasma after separation from blood cells by centrifugation, whole blood was immediately treated with ascorbic acid, then frozen at −80 until analysis) (Innis et al., 2003). RBC folate values were calculated using standard corrections for hematocrit and plasma folate according to the manufacturer's instructions (AXSYM Abbott laboratories, Abbott park, IL), specifically:

$$\text{RBC folate nmol/L} = \frac{(\text{whole blood folate} \times 22) - \text{serum folate}\,(1 - \text{hematocrit}/100)}{\text{hematocrit}/100}$$

We provide descriptive statistics for all data.

Results

Demographic description of participants

Within our group of 24 participants, the mean age was 32 years (range 25–40 years), and mean gestational age was 129.5 days (range 77–154 days). Two (8%) of participants were Hispanic, one (4%) was Filipino, and 18 (75%) were Caucasian, and ethnicity data for three (13%) participants was unavailable. Seven participants (29%) had SCID confirmed lifetime diagnoses of Bipolar Disorder, and 17 (71%) had Major Depressive disorders. At the time of the study visit and blood draw, all participants reported taking folic acid supplements, five (21%) were currently depressed (as defined by EPDS≥15), and 19 (79%) were not currently depressed. Nine women (38%) were currently taking psychotropic medications, and one participant reported smoking (10–20 cigarettes) daily (detailed information about these factors can be found in Table 1).

Maternal RBC Folate concentrations

Participants' RBC folate values are shown in Table 1 (range: 362nmol/L-1105nmol/L, mean 674nmol/L); although none had RBC folate concentrations indicating clinical deficiency (<305nmol/L) (24), only three (12.5%) had RBC folate concentrations >906nmol/L.

Although statistical comparisons between groups were neither appropriate nor possible because of the exploratory case series study design and small group sizes, the mean RBC folate concentration for those currently depressed (EPDS ≥15, n=5) was 707nmol/L, and for those not currently depressed (EPDS <15, n=19) was 666nmol/L. Of those currently depressed, 60% (3/5) were currently taking psychotropic medications, as compared to 32% (6/19) of those not currently depressed. The mean RBC folate concentration for those currently taking psychotropic medications (n=9) was 595nmol/L and 721nmol/L for those not currently taking psychotropic medications (n=15).

Offspring outcomes

Records regarding offspring deliveries were unavailable for two participants. Among the 23 offspring (including one set of twins) for whom data were available, birthweights ranged from 2296g to 4819g (mean: 3531g), with 3/23 (13%) being of low birthweight (<2500g). Two participants' offspring were diagnosed with congenital anomalies: one (maternal RBC folate = 668nmol/L) had hypoplastic left heart syndrome, the other (maternal RBC folate = 1105nmol/L) had an annular pancreas. Neither of these participants took psychotropic medications during their pregnancies or had congenital anomalies in their family histories.

Discussion

In this exploratory descriptive case series, most (21/24, 87.5%) pregnant women with a lifetime diagnosis of a mood disorder in our study had RBC folate concentrations that were insufficient to provide optimum protection against NTDs in their offspring, despite the fact that all women reported taking folic acid supplements of at least 1mg daily. The only other Canadian study to look at RBC folate concentrations in pregnant women (unselected for history of psychiatric illness or gestational age) found that only 36% had insufficient

concentrations of RBC folate to provide optimal protection against NTDs in offspring (Bar-Oz et al., 2008).

There are a number of possible explanations (beyond the possibility of chance finding arising from small sample size) for why such a large proportion of women in the current study had RBC folate concentrations <906nmol/L that are sufficiently potentially important that they may warrant further investigation. First, pregnancy increases demands for folate by up to 70% (Bodnar & Wisner, 2005); and it is possible that in response to the physiological challenge of pregnancy RBC folate concentrations drop substantively in the first trimester in *all* women. Importantly, the only study documenting naturalistic concentrations of RBC folate through pregnancy that we could identify does not support this possibility. Second, perhaps women who have a history of mood disorders do not regularly take their folic acid supplements – however, women in the current study reported taking supplements daily, and previous work has shown that self-report about supplement use is reliable(Burton et al., 2001). Third, it is possible that there is something inherent to, or associated with, having a history of a mood disorder that results in lower concentrations of RBC folate, for example, genetic variations that influence both vulnerability to mood disorder and how folate is metabolized (Joober et al., 2000). Alternatively, perhaps our findings are stochastic and related to some other factor (such as weight, eating disorder, or food insecurity (Davison & Kaplan, 2011).

While we were able to find no data reporting a direct link between maternal depression and offspring NTDs or other congenital anomalies, increased risk of NTDs has been associated with the use of some psychotropic medications (Allison, 2004). The low RBC folate concentrations we identified during early pregnancy among women with psychiatric disorders who were *not* taking these medications, supports the theoretical possibility that this increased rate of NTDs could be attributable to low folate concentrations associated with the underlying condition rather than the medication used to treat it (Davalos et al., 2012). This could be an important topic for future investigation, particularly in light of the evidence from studies comparing offspring of non-depressed and depressed mothers that there are negative consequences of *in utero* exposure to depression (Grote et al., 2010, Marcus, 2009).

It is important to remember that this was an exploratory descriptive case series designed to generate hypotheses rather than test them, and thus we did not conduct statistical analyses to investigate relationships between RBC folate concentrations and factors such as presence/absence of current depression or psychotropic medication use, so conclusions cannot be meaningfully drawn from descriptive observations of these issues. However, it is important to note that none of the medications that the participants were taking is known to affect folate metabolism, and therefore there are no recommendations that women on any of these medications take higher amounts of folic acid supplements.

While there were no NTDs among the offspring of participants in this study, two did present with other congenital abnormalities, annular pancreas and hypoplastic left heart syndrome. Hypoplastic left heart syndrome occurs at a rate of 2.2/10,000 live births (Public Health Agency of Canada, 2002) and has been associated with low concentrations of folate (Botto et al., 2000), indeed this case was associated with low maternal RBC folate. Annular

pancreas has not previously been reported to be associated with low folate concentrations and did not seem to be associated with low folate in this case.

We suggest that data from this exploratory, descriptive case series provide a rationale for further research in a number of areas. First, it is important to determine how RBC folate concentrations vary naturalistically over time during pregnancy. Second, a larger, controlled study to compare the proportions of pregnant women with and without a history of mood disorders who are not reaching an RBC folate concentration of 906nmol/L may be warranted. Third, it may be interesting to use a controlled study design to compare the rates of NTDs and other birth defects between large groups of women with and without histories of mood disorders.

The question remains as to whether the current folic acid supplementation and fortification guidelines are sufficient for all women to achieve the maximum reductions in the incidence of NTDs that are folate preventable. Additionally, numerous other factors may be contributing to low RBC folate concentrations in each individual. Ongoing examination of RBC folate concentrations, supplementation practices, current depression, and nutritional and genetic factors of pregnant women with a history of mood disorders will be critical to understand which factors are contributing to sub-optimum folate concentrations and what additional factors may promote optimum folate concentrations.

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References

1. Allison SK. Psychotropic Medication in Pregnancy. Ethical Aspects and Clinical Management. J Perinat Neonat Nurs. 2004; 18:194–205.
2. Bar-Oz B, Koren G, Nguyen P, Kapur BM. Folate fortification and supplementation-Are we there yet? Reprod Toxicol. 2008; 25:408–412. [PubMed: 18550330]
3. Bodnar LM, Wisner KL. Nutrition and depression: Implications for improving mental health among childbearing-aged women. Biol Psychiatry. 2005; 58:679–85. [PubMed: 16040007]
4. Botto LD, Mulinare J, Erickson JD. Occurrence of congenital heart defects in relation to maternal mulitivitamin use. Am J Epidemiol. 2000; 151:878–884. [PubMed: 10791560]
5. Burton A, Wilson S, Gillies AJ. Folic acid: Is self reported use of supplements accurate? J Epidemiol Community Health. 2001; 55:841–842. [PubMed: 11604442]
6. Colapinto CK, O'Connor DL, Tremblay MS. Folate status of the population in the Canadian Health Measures Survey. CMAJ. 2011; 182:100–106.
7. Carmona RH. The global challenges of birth defects and disabilities. Lancet. 2005; 366:1142–44. [PubMed: 16198750]
8. Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects: implications for prevention. JAMA. 1995; 274:1698–1702. [PubMed: 7474275]
9. Davalos DB, Yadon CA, Tregallas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. Arch Women's Ment Health. 2012; 15:1–14. [PubMed: 22215285]

10. Davison KM, Kaplan BJ. Vitamin and mineral intakes in adults with mood disorders: comparisons to nutrition standards and associations with sociodemographic and clinical variables. J Am Coll Nutr. 2011; 6:547–58.
11. First, MB., Spitzer, RL., Gibbon, M., Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). Washington DC: American Psychiatric Press; 1997.
12. Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: A meta-anlysis. J Obstet Gynaecol Can. 2006; 28:680–89. [PubMed: 17022907]
13. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon W. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010; 67:1012–1024. [PubMed: 20921117]
14. Health Canada. Prenatal Nutrition Guidelines for Health Professionals. 2009. p. 1-8.
15. Herbert, V. Development of human folate deficiency. In: Picciano, MF.Stokstad, ELR., Gregory, JF., II, editors. Folic acid metabolism in health and disease. New York: Wiley Liss; 1989. p. 195-200.
16. Innis SM, Davidson AGF, Chen A, Dyer, Melnyk S, James SJ. Increased plasma homocysteine and S-adenosylhomocysteine and decreased methionine is associated with altered phosphatidylcholine and phosphatidylethanolamine in cystic fibrosis. Journal of Pediatrics. 2003; 143:351–356. [PubMed: 14517519]
17. Joober R, Benkelfat C, Lal S, Bloom D, Labelle A, Lalonde P, et al. Association between the methylenetetrahydrofolate reductase 677T>C missense mutation and schizophrenia. Mol Psychiatry. 2000; 5:323–326. [PubMed: 10889537]
18. Marcus SM. Depression during pregnancy: rates, risks and consequences--Motherisk Update 2008. Can J Clin Pharmacol. 2009; 16:15–22.
19. Murray D, Cox JL. Screening for depression during pregnancy with the Edinburgh Depression Scale (EPDS). J Reprod Infant Psychol. 1990; 8:99–107.
20. Nakatsu T, Uwabe C. Neural tube closure in humans initiates at multiple sites: evidence from human embryos and implications for the parthogenesis of neural tube defects. Anat Embryol. 2000; 201:455–466. [PubMed: 10909899]
21. Public Health Agency of Canada. Congenital Anomalies in Canada: A Perinatal Health Report. 2002. p. 1-87.
22. Ray JG. Folic acid food fortification in Canada. Nutr Rev. 2004; 2:S35–S39.
23. Shakur AY, Garriguet D, Corey P, O'Connor D. Folic acid fortification above mandated levels results in a low prevalence of folate inadequacy among Canadians. Am J Clin Nutr. 2010; 92:818–25. [PubMed: 20739423]
24. Shuaibi AM, House JD, Sevenhuysen GP. Folate status of young Canadian women after folic acid fortification of grain products. J Am Diet Assoc. 2008; 108:2090–2093. [PubMed: 19027414]
25. Wilson DR. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007; 29:1003–26. [PubMed: 18053387]

Table 1

Red blood cell (RBC) folate concentrations, Psychotropic Medication Use, and folic acid (FA) supplementation (start, dose, self-reported frequency), EPDS scores, and SCID Diagnosis.

Participant ID	RBC Folate (nmol/L)	Psychotropic Medications	Start of FA Supplementation (Days)	Dose of FA (mg)	Self Reported Frequency of FA (per day)	EPDS Score	SCID Diagnosis
1	1105	n/a	30 Pre-Conception	1 or 2	1x or 2x	7	Bipolar Disorder
2	489	lorazepam	30 Gestational Age	1.8	1x	20	Bipolar Disorder
3	566	n/a	30 Gestational Age	1	1x	3	Major Depressive Disorder
4	630	n/a	730 Pre-Conception	1	1x	8	Bipolar Disorder
5	600	sertraline	60 Pre-Conception	1	1x	6	Major Depressive Disorder
6	945	quetiapine	49 Gestational Age Red blood cell folate levels in pregnancy	1	1x	19	Recurrent Major Depressive Disorder
7	1046	n/a	1460 Pre-Conception	6	1x	7	Major Depressive Disorder
8	676	n/a	365 Pre-Conception	1	1x	7	Recurrent Major Depressive Disorder
9	677	n/a	90 Pre-Conception	1	1x	6	Major Depressive Disorder
10	804	n/a	365 Pre-Conception	4	1x	16	Recurrent Major Depressive Disorder
11	435	n/a	365 Pre-Conception	1	1x	2	Recurrent Major Depressive Disorder
12	508	n/a	420 Pre-Conception	1	1x	5	Recurrent Major Depressive Disorder
13	440	fluoxetine	56 Gestational Age	1.4	2x	18	Major Depressive Disorder
14	489	citalopram	150 Pre-Conception	1	1x	1	Bipolar Disorder
15	661	n/a	120 Pre-Conception	1	1x	5	Major Depressive Disorder
16	362	sertraline	30 Pre-Conception	1	1x	14	Major Depressive Disorder
17	668	n/a	210 Pre-Conception	1	1x	11	Major Depressive Disorder
18	663	bupropion	30 Gestational Age	1	1x	0	Major Depressive Disorder
19	805	n/a	730 Pre-Conception	1	1x	1	Bipolar Disorder
20	773	n/a	45 Pre-Conception	1	1x	10	Major Depressive Disorder
21	746	fluoxetine	150 Pre-Conception	1	1x	7	Bipolar Disorder

Participant ID	RBC Folate (nmol/L)	Psychotropic Medications	Start of FA Supplementation (Days)	Dose of FA (mg)	Self Reported Frequency of FA (per day)	EPDS Score	SCID Diagnosis
22	613	n/a	28 Gestational Age	1	1x	9	Bipolar Disorder
23	854	n/a	365 Pre-Conception	1	1x	21	Major Depressive Disorder