

Maternal ethnicity and risk of neural tube defects: a population-based study

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Abstract

Background: Maternal body mass and the presence of diabetes mellitus are probable risk factors for neural tube defects (NTDs). The association between maternal ethnicity and the risk of NTDs remains poorly understood, however.

Methods: We performed a retrospective population-based study and included all women in Ontario who underwent antenatal maternal screening (MSS) at 15 to 20 weeks' gestation between 1994 and late 2000. Self-declared maternal date of birth, ethnicity and weight and the presence of pregestational diabetes mellitus were recorded in a standardized fashion on the MSS requisition sheet. NTDs were detected antenatally by ultrasonography or fetal autopsy and postnatally by considering all live and stillborn affected infants beyond 20 weeks' gestation. The risk of open NTD was evaluated across the 5 broad ethnic groups used for MSS, with white ethnicity as the referent.

Results: Compared with white women ($n = 290\,799$), women of First Nations origin ($n = 1551$) were at increased associated risk of an NTD-affected pregnancy (adjusted odds ratio [OR] 5.2, 95% confidence interval [CI] 2.1–12.9). Women of other ethnic origins were not at increased associated risk compared with white women (women of Asian origin [$n = 75\,590$]: adjusted OR 0.9, 95% CI 0.6–1.3; black women [$n = 25\,966$]: adjusted OR 0.6, 95% CI 0.3–1.1; women of "other" ethnic origin [$n = 10\,009$]: adjusted OR 0.1, 95% CI 0.02–0.9).

Interpretation: The associated risk of NTD-affected pregnancies was higher among women of First Nations origin than among women of other ethnic origins. The mechanisms for this discrepancy should be explored.

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The risk of neural tube defects (NTDs) can be reduced by periconceptional folic acid supplementation.¹ In previous US studies, the NTD rate varied with ethnicity,^{2,3} but potential confounders, including maternal weight⁴ and the presence of diabetes mellitus,⁵ were not controlled for. Because no data exist on the relationship between ethnicity and the occurrence of NTDs in pregnancies in Canada, including pregnancies of women of First Nations origin, we initiated the following study.

Methods

We performed a retrospective population-based study and included all women in Ontario who underwent antenatal maternal

serum screening (MSS) between 1994 and late 2000. Since 1993, standardized MSS has been accessible to all women at 15 to 20 weeks' gestation through any physician or midwife, with a mean rate of uptake of more than 70%.⁶ Self-declared maternal date of birth, ethnicity and weight and the presence of pregestational diabetes mellitus are recorded in a standardized fashion on the MSS requisition sheet, which is completed at the time of screening.

Women with a positive MSS are referred for counselling at 1 of 17 genetics centres in Ontario. Each centre contributes follow-up data to the Ontario MSS Database, which is funded by the Ontario Ministry of Health and Long-term Care. Anomalies were detected antenatally by ultrasonography or fetal autopsy and postnatally by considering all live and stillborn affected infants after 20 weeks' gestation.⁶ The latter were identified by data linkage of the mother's Ontario health insurance number with her infant's number assigned during the delivery hospital admission through the Canadian Institute for Health Information Discharge Abstract Database.

The risk of open NTDs was evaluated across the 5 broad ethnic groups used for MSS, with white ethnicity as the referent. Crude and multivariate odds ratios (ORs), along with 95% confidence intervals (CIs), were derived using unconditional logistic regression analysis. We adjusted for maternal age (1-year increments), weight at the time of MSS (1-kg increments),⁴ presence of pregestational diabetes⁵ and year of screening, each of which may influence either the uptake of MSS or the risk of NTDs. All variables were included in the model a priori. Participant identifiers were removed from the data set before analysis.

Permission to conduct this study was obtained through a research protocol approved by the Ontario Ministry of Health and Long-term Care and by the Research Ethics Board of St. Michael's Hospital.

Results

The characteristics of all 403 915 women who underwent MSS are given in Table 1. Women of First Nations origin were younger, weighed more and had at least 3 times the rate of self-declared diabetes mellitus compared with women of other origins. Of all 276 NTDs reported, 202 (73.2%) were identified antenatally (Table 1).

Compared with white women, the associated risk of NTD-affected pregnancies was highest among women of First Nations origin (adjusted OR 5.2, 95% CI 2.1–12.9) (Table 2). The lower associated risk of NTD-affected pregnancies among Asian women was no longer apparent after adjusting for potential confounders (adjusted OR 0.9, 95% CI 0.6–1.3). There was little difference in the risk of

NTD-affected pregnancies between white women and black women (adjusted OR 0.6, 95% CI 0.3–1.1). Women of “other” ethnicity appeared to be at lower risk of NTDs (adjusted OR 0.1, 95% CI 0.02–0.91), and only 1 NTD-affected pregnancy occurred in this group.

Interpretation

We observed a higher associated risk of NTD-affected pregnancies among Ontario women of First Nations origin who underwent MSS, something not seen in other ethnic groups. Because of the low event rates, the OR observed herein can be approximated by a relative risk estimate. Accordingly, the adjusted risk of NTD-affected pregnancy appears to be about 5 times higher among women of First Nations origin than among white women.

A relatively small number of First Nations women underwent MSS over the 7-year period of this study, such that these data may not be applicable across all ethnogenetic groups of First Nations peoples. The broad ethnic categories were generated for use within the MSS program and were not intended to mirror known ethnic stratifications sometimes used by population geneticists. They cannot account for the diversity within each group, nor do they identify birth origin or other factors such as socioeconomic status. Accordingly, we do not believe that maternal ethnicity should be used to modify the pretest probability of having an NTD-affected pregnancy. Some study participants may have had unrecognized type 2 diabetes, a risk factor for NTDs,⁵ but adjusting for maternal weight likely controlled for at least some of the potential confounding effect.⁷ Finally, by considering both antenatally and postnatally detected NTDs, we missed probably only a few events, even for pregnancies that resulted in a termination.

We did not determine who in our study was taking folic acid supplements. Unfortunately, there is a paucity of data about ethnic differences in folic acid intake among Canadian women and about differences in their nutritional status, especially among women belonging to the First Nations. In a study conducted in the Eastern James Bay region, mean erythrocyte folate concentrations were

significantly lower among Cree women who had previously experienced an NTD-affected pregnancy than among unaffected Cree or white control subjects.⁸ Moreover, maternal case subjects had a lower estimated daily intake of foods containing folic acid, an observation that has been made elsewhere.⁹

If the risk of NTD-affected pregnancies is truly higher among women of First Nations origin than among women of other origins, then the mechanisms for this discrepancy should be elucidated. This might entail determining the rates of smoking and pregnancy planning, including screening for prepregnancy diabetes in high-risk groups. Canadian initiatives, including the First Nations Chiefs' Health Committee Pre-Natal Nutrition Program (www.fnchc.ca/CPNP.html), should continue to emphasize the importance of planned conception and higher dietary and supplemental folic acid intake periconceptionally. Assurance is also needed that all flour supplied to Canadians is fortified with folic acid, in accordance with federal law.⁶

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Table 2: Risk of pregnancy affected by open neural tube defects by ethnicity

Ethnicity	Neural tube defects*		
	No. (rate per 1000)	Crude OR (95% CI)	Adjusted OR† (95% CI)
White	221 (0.8)	1.0	1.0
Asian	38 (0.5)	0.6 (0.5–0.9)	0.9 (0.6–1.3)
Black	11 (0.4)	0.6 (0.3–1.0)	0.6 (0.3–1.1)
Other	1 (0.1)	0.1 (0.02–0.9)	0.1 (0.02–0.9)
First Nations	5 (3.2)	4.2 (1.8–10.3)	5.2 (2.1–12.9)

Note: OR = odds ratio, CI = confidence interval.

*Isolated anencephalus, spina bifida with hydrocephalus and isolated spina bifida (International Classification of Diseases, 9th revision, diagnostic codes 740.0, 741.0 and 741.9).

†Adjusted for maternal age (1-year increments), weight (1-kg increments), presence of pregestational diabetes mellitus and year of screening.

Table 1: Characteristics of women in Ontario who underwent antenatal maternal serum screening between 1994 and late 2000, by ethnicity

Characteristic	Ethnicity				
	White <i>n</i> = 290 799	Asian <i>n</i> = 75 590	Black <i>n</i> = 25 966	Other <i>n</i> = 10 009*	First Nations <i>n</i> = 1551
Age, mean (SD), yr	30.1 (5.0)	30.5 (4.8)	29.2 (5.7)	29.8 (5.5)	26.5 (6.3)
Weight, mean (SD), kg	68.9 (14.4)	58.1 (10.3)	70.4 (15.3)	64.5 (13.7)	74.9 (14.2)
Prevalence of pregestational diabetes mellitus, %	0.53	0.33	0.54	0.69	2.0
% (no.) of neural tube defects detected antenatally	74.2 (164/221)	65.8 (25/38)	63.6 (7/11)	100.0 (1/1)	100.0 (5/5)

*Includes 1324 women of Hispanic ethnicity.

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Competing interests: None declared.

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