Population-Wide Folic Acid Fortification and Preterm Birth: Testing the Folate Depletion Hypothesis

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Objectives. We assess whether population-wide folic acid fortification policies were followed by a reduction of preterm and early-term birth rates in Québec among women with short and optimal interpregnancy intervals.

Methods. We extracted birth certificate data for 1.3 million births between 1981 and 2010 to compute age-adjusted preterm and early-term birth rates stratified by short and optimal interpregnancy intervals. We used Joinpoint regression to detect changes in the preterm and early term birth rates and assess whether these changes coincide with the implementation of population-wide folic acid fortification.

Results. A change in the preterm birth rate occurred in 2000 among women with short (95% confidence interval [CI] = 1994, 2005) and optimal (95% CI = 1995, 2008) interpregnancy intervals. Changes in early term birth rates did not coincide with the implementation of folic acid fortification.

Conclusions. Our results do not indicate a link between folic acid fortification and early term birth but suggest an improvement in preterm birth rates after implementation of a nationwide folic acid fortification program. (*Am J Public Health.* 2015;105: 793–795. doi:10.2105/AJPH.2014.302377)

Preterm and early term birth are linked with a higher risk of infant mortality and morbidity,[1,2] and evidence suggests that rates of early delivery are increasing in many countries.[3] Short interpregnancy intervals, or the elapsed duration between a woman's previous pregnancy and her next conception, are a well-known risk factor for preterm birth, and potentially early term birth.[4] Folate depletion from the previous pregnancy is hypothesized to underlie the relation between short interpregnancy intervals and preterm birth.[5] Research suggests that up to 20% of women are folate deficient at 6 months postpartum, the cutoff for short interpregnancy intervals.[6]

In Canada, all grain products sold in the country were fortified with folic acid beginning in December 1998 because of overwhelming evidence that periconceptional folic acid prevents neural tube defects.[7] However, evidence conflicts on the role of periconceptional folic acid intake on preterm birth.[8] Moreover, recent research has suggested possible tumor-promoting effects of folic acid,[9] fueling controversy on whether mandatory fortification is a useful public health policy.[10,11]

To contribute to this debate, we assessed whether Canada's folic acid fortification program was related to lower rates of preterm and early term birth among women with short and optimal interpregnancy intervals after 1998. If folate depletion indeed causes early delivery, preterm and early term birth rates should decrease following folic acid fortification, and the magnitude of this decrease should be greater in women with short interpregnancy intervals.

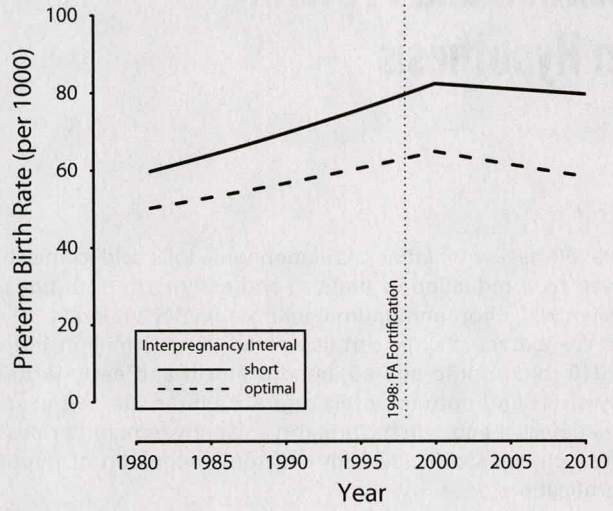
METHODS

We extracted 1 340 130 preterm, early term, and full-term live singleton births from multiparous women by year for 2 categories of interpregnancy interval: less than 6 months (short) and 6 months or longer (optimal) from the Québec birth registry, which contains information on all live born infants between 1981 and 2010. Gestational age in weeks was based on first- or second-trimester ultrasound measurements and used to define preterm (< 37 weeks gestation) and early term birth (37 and 38 weeks gestation). We used a pre–post quasi-experimental design[12] to assess whether changes in preterm and early term birth rates coincided with the implementation of the national folic acid fortification policy. We calculated annual age-adjusted preterm and early term birth rates, and used Joinpoint regression[13] to assess whether and when rates changed between 1981 and 2010.

RESULTS

Between 1981 and 2010, the proportion of mothers with short interpregnancy intervals was steady at 3.0%. The lowest and highest preterm birth rates were 54.1 and 66.3 per 1000 pregnancies in 1987 and 2004, respectively. Similarly, the lowest and highest early term birth rates were 21.0 and 28.3 per 1000 pregnancies in 1987 and 2004, respectively. Overall, 64.9%, 24.3%, and 10.8% of pregnancies in the cohort were from mothers with only 1 prior birth, only 2 prior births, and 3 or more prior births, respectively.

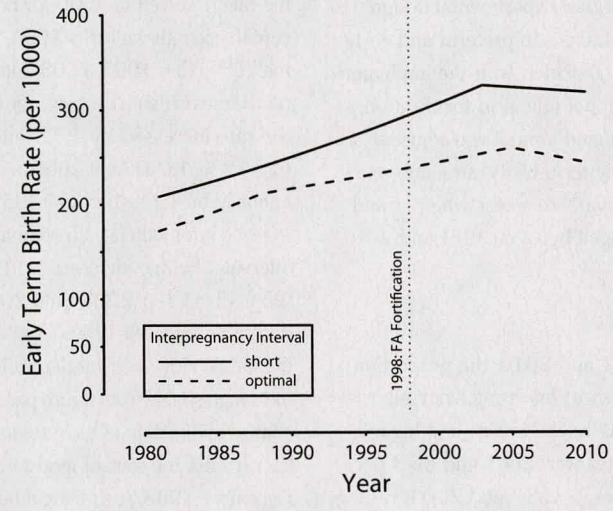
Figure 1 shows that preterm birth rates changed over time for short and optimal interpregnancy intervals. A change in direction of the rate occurred in 2000 for both short (95% confidence interval [CI] = 1994, 2005) and optimal (95% CI = 1995, 2008) intervals. For mothers with short interpregnancy intervals, the rate increased by 1.3% annually (95% CI = 1.1%, 1.6%) until 2000, and decreased annually by 1.1% thereafter (95% CI = −1.7%, −0.4%). For mothers with optimal interpregnancy intervals, the rate increased by 1.7% annually (95% CI = 1.1%, 2.3%) until 2000, and then decreased by 0.3% (95% CI = −2.0%, 1.4%) thereafter. However, this decrease was statistically indistinguishable from a zero percent change. The change in direction of the rates in 2000 occurred shortly after the start of food fortification in December 1998, suggesting a beneficial impact of fortification for both short and optimal interpregnancy intervals. Furthermore, this beneficial impact was greater among women with short versus optimal interpregnancy intervals.



Note. FA = folic acid.

FIGURE 1—Joinpoint analysis of preterm birth rate for short and optimal interpregnancy intervals for 1.3 million live births in Quèbec between 1981 and 2010.

Figure 2 shows rates for early term birth. For optimal interpregnancy intervals, Joinpoint analysis indicated that the rate of early term delivery changed twice, first in 1988 (95% CI = 1983, 1993), and then in 2005 (95% CI = 2002, 2005)—neither change occurred in the immediate period after 1998. The rate increased by 3.0% annually (95% CI = 1.7%, 4.2%) until 1988, and afterward increased by 1.2% annually (95% CI = 1.0%, 1.4%). In 2005, the rate began decreasing by 1.2% annually (95% CI = −2.3%, −0.1%). For short interpregnancy intervals, the rate of early term delivery changed only once in 2003 (95% CI = 1995, 2005). The rate increased by 2.0% annually (95% CI = 1.7%, 2.4%) until 2003 and then stabilized (annual decrease of 0.3%; 95% CI = −1.6%, 1.0%).



Note. FA = folic acid.

FIGURE 2—Joinpoint analysis of early term birth for short and optimal interpregnancy intervals for 1.3 million live births in Quèbec between 1981 and 2010.

DISCUSSION

Population-wide folic acid fortification has a number of beneficial reproductive effects, including reduced neural tube[14] and congenital heart defects.[15] Our results suggest that folic acid fortification might have lowered preterm birth rates in Quèbec after 1998, in women with both short and long interpregnancy intervals. The evidence was less clear for early term birth, and suggestive of no impact. One possible explanation might be that congenital anomalies account for a larger proportion of preterm than early term births.[16] Thus, folic acid fortification would have a stronger impact on preterm birth rates because of its protective effects on congenital malformations.[17]

Evidence on different possible effects of folic acid fortification has been found in the literature, including an increase in serum and erythrocyte blood folate concentrations in the United States,[18,19] and a reduction of neural tube[14] and congenital heart defects[15] in Canada. One previous study[20] found that folic acid fortification was related to a small reduction in preterm birth rates among 5 million singleton births between 1990 and 2000 in California. In that study, Shaw et al. used adjusted Poisson regression models to compare the rate of preterm birth prior to and following fortification. In contrast to this previous study, the years in which preterm birth rates changed in our study were estimated using a nonparametric permutation technique[13] that was not influenced by knowledge of when folic acid fortification was implemented.

The results of this study should be considered in light of certain limitations. We used an ecological design, which provides valid individual-level estimates under strict assumptions that were not met in this study.[21] However, our interest was at the ecologic level. Furthermore, we were unable to account for the clustering of different pregnancies from the same woman. Yet over 65% of the 1.3 million pregnancies in our cohort were not clustered, and restricting our analysis to these 869 302 women did not materially change the results. Finally, to attribute post-1998 changes entirely to population-wide folic acid fortification, we must also assume that risk factors for preterm and early term birth (e.g., elective induction,

tocolytic therapy, tobacco consumption, folate supplementation) did not change around 1998. Though it was not possible to verify that all risk factors for preterm and early term birth remained constant during our study period, we were able to rule out changes in several demographic risk factors (maternal or paternal age, maternal education, maternal, paternal, or infant place of birth, and marital status) as an alternative explanation for our results.

In spite of its reproductive benefits, folate might have tumor-promoting properties in neoplastic and preneoplastic cells.[9] Evidence that folic acid fortification might have spurred an increase in colorectal cancer rates in Canada and the United States[22] has led some to call for a cessation of fortification.[10,11] More research is needed on the benefits and risks of population-wide folic acid fortification on a range of health outcomes. Although our results do not show that folic acid fortification improves early term birth rates, they are consonant with an improvement in preterm birth rates after implementation of a nationwide folic acid fortification program. ■

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Contributors

A. I. Naimi conceptualized the study and its design and contributed to data analysis and manuscript preparation. N. Auger contributed to data analysis and manuscript preparation.

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Human Participant Protection

Data were de-identified and conformed to standards for ethical conduct of research involving humans in Canada.

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