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TYPE 1 DIABETES: PATHOPHYSIOLOGY AND PREVENTION

Investigating the association between prenatal exposure to folic acid and risk of neonatal diabetes/hyperglycemia and type 1 diabetes: A Norwegian register-based study

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Abstract

Background: Experimental animal studies suggest a novel role for the folate receptor 1 in β-cell differentiation in the pancreas, with potential implications for glycemic control. We tested the hypothesis of a protective association between prenatal folic acid use and neonatal diabetes or hyperglycemia and type 1 diabetes in an observational cohort study using data from the national population health registers in Norway.

Methods: All singleton pregnancies resulting in live births from 2005 to 2018 were identified. Prenatal exposure to folic acid was determined based on maternal report at antenatal care in early pregnancy. Diagnoses of neonatal diabetes, hyperglycemia, and type 1 diabetes for the children were identified. Associations were estimated with logistic regression or Cox proportional hazard model and included crude and adjusted estimates.

Results: Among 781,567 children, 69% had prenatal exposure to folic acid, 264 were diagnosed with neonatal diabetes or hyperglycemia, and 1390 with type 1 diabetes. Compared to children with no prenatal exposure to folic acid, children with prenatal exposure to folic acid had similar odds of having a neonatal diabetes or hyperglycemia diagnosis (adjusted odds ratio 0.95, 95% confidence interval [CI] 0.72, 1.25) and similar risk of being diagnosed with type 1 diabetes (adjusted hazard ratio 1.05, 95% CI 0.93, 1.18).

Conclusions: No association between prenatal folic acid exposure and neonatal diabetes/hyperglycemia or type 1 diabetes was found. These findings do not rule out a translational effect of the experimental results and future studies with longer follow-up and more precise information on the window of prenatal exposure are needed.

KEYWORDS
folic acid, neonatal diabetes, pharmacoepidemiology, pregnancy, type 1 diabetes

1 | INTRODUCTION

Recent findings from experimental animal studies suggest that folic acid treatment and reinforcing one-carbon metabolism can induce β-cell differentiation in the zebrafish and neonatal pig islets.[1] As diabetes can be caused by an insufficient β-cell mass, prenatal folic acid exposure may have potential implications for glycemic control or onset of type 1 diabetes early in life.

Folic acid is widely taken by women prior to conception and during the first trimester of pregnancy. Since the late 1990s, women in Norway have been advised to take 0.4 mg of folic acid daily from 1 month pre-pregnancy through to the end of the first trimester, which is available for over-the-counter purchase alone or as part of a multivitamin.[2] This study aimed to examine if there is evidence of a protective association between prenatal folic acid use and neonatal diabetes or hyperglycemia and type 1 diabetes in a cohort of Norwegian children.

2 | METHODS

2.1 | Data sources

This is a cohort study with data from the national population registers in Norway. A unique personal identity number issued to all residents of Norway upon birth or immigration was used to link patient-level data from the population registers, including Norwegian Medical Birth Register (NMBR), the Norwegian Prescription Drug Register (NorPD), the Norwegian Patient Register, the Cause of Death Register, the National Education Database, and the National Population Register containing information on migration.[3]

2.2 | Study population and exposure definition

All singleton pregnancies resulting in live births between January 1, 2005 and December 31, 2018 ($n = 800{,}009$) were identified. Pregnancies were excluded if the mother had a diagnosis of diabetes prior to the start of pregnancy ($n = 7519$), had an antidiabetic medication prescription filled before the start of pregnancy ($n = 781$), except for metformin since it is also used as a fertility-enhancing drug, or children died before the end of the study period ($n = 2089$). Furthermore, pregnancies with filled prescriptions of a higher dose of folic acid in the 90 days before the start of pregnancy and during pregnancy were removed ($n = 8053$). This dosage of folic acid is recommended for women taking certain types of antiepileptic medications and for women taking low dose methotrexate to treat rheumatoid arthritis and psoriasis, which may impair folate activity. The final study population consisted of 781,567 children.

At the first antenatal care visit at approximately 10–16 weeks gestation, pregnant women were specifically asked about the use of folic acid before and during pregnancy, which was recorded in checked boxes (yes/no) in the patient chart and then included in the NMBR. This information was used to categorize the children into those with prenatal exposure to folic acid and those with no prenatal exposure to folic acid.

2.3 | Outcome definition and covariates

Diagnoses of neonatal diabetes, neonatal hyperglycemia, and type 1 diabetes were identified in by ICD-10 codes P70.2, P70.8, and E10, respectively. As hyperglycemia can occur as a result of early parenteral nutrition in extremely-low-birth-weight (ELBW) infants,[4] only children with a birth weight greater than 1000 grams were classified as having neonatal diabetes or hyperglycemia. Maternal characteristics were described (Table 1).

2.4 | Statistical analysis

To estimate the association between prenatal folic acid exposure and neonatal diabetes or hyperglycemia logistic regression models using generalized estimating equations (GEE) were used, with robust standard errors to account for dependency in the data, since multiple children could have the same mother. Cox proportional hazard regression analysis was used to estimate the association between prenatal folic acid exposure and type 1 diabetes to account for the length of follow-up of the children. The time to event was defined as time to a type 1 diabetes diagnosis, migration, or administrative end of data (December 31, 2018).

For both analyses, crude and adjusted estimates were generated. Covariates included in the adjusted model are listed in Table 1, except for early pregnancy BMI. Due to the large proportion of missing early pregnancy BMI values and a potential mediating role of this covariate, BMI was not adjusted for in the main analysis. A complete case analysis was conducted on the subset of the population with complete information on maternal BMI. Analyses were conducted in R.[5]

3 | RESULTS

In this Norwegian cohort of 781,567 children, 68.7% ($n = 537{,}121$) had prenatal exposure to folic acid, with exposure increasing over time from 45.0% in 2005 to 81.9% in 2018. Mothers self-reporting folic acid use in early pregnancy were more often born in a Nordic country, more likely to be cohabiting with a partner, had higher levels of education, and had lower parity. Among mothers with data on smoking and BMI, those with self-reported folic acid use were less likely to smoke in early pregnancy, and had a lower BMI than women who did not report folic acid use. Additionally, mothers with and without folic acid use had similar rates of diagnoses of hypertension, epilepsy, and psychiatric disorders and the use of antiepileptic and antipsychotic medications (Table 1).

In total, 264 children had a diagnosis of neonatal diabetes or neonatal hyperglycemia, and 1390 had a diagnosis of type 1 diabetes. For children with prenatal exposure to folic acid, the odds of having a

TABLE 1 Maternal characteristics of children prenatally exposed and unexposed to folic acid born in Norway between 2005 and 2018

		No prenatal folic acid exposure		Prenatal folic acid exposure	
	Total = 781,567	*n* 244,446	% 31.3[a]	*n* 537,121	% 68.7[a]
Age at delivery, years	<20	7238	3.0	6208	1.2
	20–24	40,474	16.6	64,381	12.0
	25–29	74,440	30.4	175,090	32.6
	30–34	75,464	30.9	188,153	35.0
	35–39	38,243	15.6	87,182	16.2
	40–44	8114	3.3	15,408	2.9
	≥45	473	0.2	699	0.1
	Missing	0	0	0	0
Parity	0	92,653	37.9	238,298	44.4
	1+	151,793	62.1	298,823	55.6
	Missing	0	0	0	0
Body mass index (kg/m^2), early pregnancy	0 to <18	2546	1.0	7034	1.3
	18 to <25	47,908	19.6	200,766	37.4
	25 to <30	18,935	7.7	67,232	12.5
	30 to <35	7446	3.1	24,372	4.5
	35-high	3450	1.4	10,784	2.0
	Missing	164,161	67.2	226,933	42.3
Smoking, early pregnancy	No	156,101	63.9	451,585	84.1
	Yes	26,601	10.9	38,198	7.1
	Missing	61,744	25.3	47,338	8.8
Cohabitation	Not cohabiting	22,523	9.2	26,298	4.9
	Cohabiting	219,318	89.7	506,829	94.4
	Missing	2605	1.1	3994	0.7
Highest achieved maternal education in year of delivery	Compulsory	60,526	24.8	71,006	13.2
	Secondary	65,082	26.6	139,035	25.9
	Postsecondary	67,398	27.6	218,107	40.6
	Postgraduate	23,307	9.5	849,76	15.8
	Missing	28,133	11.5	23,997	4.5
Maternal country of birth	Nordic	160,407	65.6	443,281	82.5
	Non-Nordic	81,086	33.2	89,642	16.7
	Missing	2953	1.2	4198	0.8
Comorbidity and medication use[b]	Epilepsy	1152	0.5	3251	0.6
	Hypertension	1185	0.5	2957	0.6
	Psychiatric Disorder	12,748	5.2	32,098	6.0
	Antiepileptics	1148	0.5	3388	0.6
	Antipsychotics	13,148	5.4	31,061	5.8

[a]Percentage of the total number of children in the study population. All other values in these columns are percentages of the total number of children in each exposure group.

[b]Diagnoses of epilepsy (ICD10 G03), hypertension (ICD-10 O10, O11, I10–I15), and psychiatric disorders (ICD10 F10–99) received in the year before the start of pregnancy and prescription of antiepileptics (ATC N03A) or antipsychotics (ATC N05, N06) in the 6 months before or during pregnancy were identified.

neonatal diabetes or hyperglycemia diagnosis were similar to children not exposed to folic acid (adjusted odds ratio 0.95, 95% confidence interval [CI] 0.72, 1.25; Table 2). Similarly, children with prenatal exposure to folic acid had a similar risk of being diagnosed with type 1 diabetes compared to children without prenatal exposure to folic acid (adjusted HR 1.05, 95% CI 0.93, 1.18; Table 2).

TABLE 2 Crude and adjusted estimates for the association between prenatal folic acid exposure and neonatal diabetes/hyperglycemia or type 1 diabetes diagnoses compared to no prenatal folic acid exposure

	No prenatal folic acid exposure n (%)	Prenatal folic acid exposure n (%)	Unadjusted model	Adjusted model 1
All children $n = 781{,}567$	244,446 (31.3[a])	537,121 (68.7[a])		
Neonatal diabetes or hyperglycemia $n = 264$ (0.034%[a])	87 (0.036)	177 (0.033)	OR (95% CI) 0.93 (0.72, 1.20)	OR (95% CI) 0.95 (0.72, 1.25)
Type 1 diabetes $n = 1390$ (0.178%[a])	505 (0.207)	885 (0.165)	HR (95% CI)[b] 1.05 (0.94, 1.18)	HR (95% CI)[b] 1.05 (0.93, 1.18)

Note: Model 1 adjusted for maternal age, cohabitation, smoking, education, country of birth, epilepsy, hypertension, psychiatric diagnoses, antiepileptic medication, and antipsychotic medication.

Abbreviations: CI, confidence intervals; HR, hazard ratio; OR, odds ratio.

[a]Percentage of the total number of children in the study population. All other percentages in the table are percentages of the total number of children in each exposure group.

[b]The time to event is time to type 1 diabetes diagnosis, migration, or administrative end of data.

In the complete case analysis conducted in the subset of the study population with BMI data, adjusting for early pregnancy BMI produced similar estimates to the main analysis albeit with wider confidence intervals due to the lower numbers, demonstrating that BMI does not have a large influence on the associations reported (results not shown).

4 | DISCUSSION

In this population-based Norwegian cohort study, children who had prenatal exposure to folic acid supplements did not have a reduced risk of being diagnosed with either neonatal diabetes or hyperglycemia, nor type 1 diabetes. Based on recent findings from experimental animal studies showing a previously unknown role of the folate receptor 1 and one-carbon metabolism in the generation of beta-cells,[1] and the hypothesis for this study was that prenatal folic acid exposure could have potential implications for glycemic control early in life, resulting in a protective association between prenatal folic acid exposure and neonatal diabetes or hyperglycemia and type 1 diabetes. Specifically, beta-cell mass is set during development and folic acid exposure leading to a larger beta cell pool at birth could potentially protect against the development of neonatal diabetes and/or delay the onset of type I diabetes. However, these null results do not rule out a potential translational effect.

Neonatal diabetes is rare, occurring in approximately 3 in 100,000 live births in Norway.[6] Neonatal hyperglycemia is relatively more common, with some evidence of insufficient pancreatic insulin secretion as one potential cause.[7] Due to diagnosis coding discrepancies, we could not distinguish between neonatal diabetes diagnoses and neonatal hyperglycemia diagnoses, and therefore, the analysis could not be performed separately for these two distinct conditions. Hence, additional studies with larger study populations should explore this potential association.

Additionally, the children in this cohort were born between 2005 and 2018, with the oldest children being 13 years of age at the end of follow-up. Longer follow-up of this cohort may show a different association between prenatal folic acid exposure and type 1 diabetes diagnoses since type 1 diabetes onset is typically between ages 10 and 14 years and can be first diagnosed in adulthood as well.[8]

The recommended folic acid supplementation period for pregnant women is 1 month pre-pregnancy to the end of the first trimester. This does not overlap with the development of pancreatic ducts in humans, which is the suggestive source of the new beta-cells according to the experimental animal data. Human beta-cells start to form from week 8 of embryonic development, but ductal structures in the pancreas made up of ductal cells only appear at gestational week 24.[9] This may be another reason why we do not find an association in this study.

Folic acid use in the mothers was based on self-reported information provided at antenatal appointments, and does not include the dose, frequency, and duration of use in pregnancy. However, while information on maternal folic acid levels was not available, reported folic acid use has been shown to correspond well with plasma folate levels in a sample of pregnant women in Norway.[10] Moreover, a systematic review of studies that have explored the association between maternal folate status during pregnancy and the development of insulin resistance/obesity in the offspring showed contradictory results.[11] This further corroborates our hypothesis that the window of the folic acid uptake during pregnancy is critical to observe an improved metabolic health in the offspring.

Given that folic acid is safe and widely used, it is an appealing supplement to be further studied with regards to its influence on β-cell development and diabetes etiology. Future epidemiological studies should attempt to capture details on the exact timing and dose of prenatal exposure to folic acid. Additional experimental animal studies should focus on elucidating the appropriate dose and mechanisms in which prenatal folic acid exposure could influence the development of diabetes. Alternatively, a randomized control study with folic acid supplementation in different windows of embryo development could give a more conclusive answer on the influence of folic acid on neonatal diabetes/hyperglycemia and type 1 diabetes risk.

CONFLICT OF INTEREST

Carolyn E. Cesta and Laura Pazzagli are employees at the Centre for Pharmacoepidemiology, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for conducting drug safety and drug utilization studies that are unrelated to this work.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. *Analysis*: Laura Pazzagli. *Writing—original draft preparation*: Carolyn E. Cesta and Christos Karampelias. *Writing—review and editing*: all authors. *Approval of final version for submission*: all authors.

ETHICAL APPROVAL

The study was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research of South-East Norway.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13263.

DATA AVAILABILITY STATEMENT

For the Norwegian register-based cohort, original data are held by the Norwegian Institute of Public Health and due to data privacy laws, the data cannot be made publicly available. Researchers can access the data by obtaining an ethical approval from a regional ethical review board and the Norwegian Data Inspectorate, and thereafter request the original data from the Norwegian Institute of Public Health. Aggregated data used in the analysis of this study are available from the authors upon reasonable request and with approved data sharing and data processing agreements in line with the General Data Protection Regulations. Further use of these data must be authorized by the local ethical committee.

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