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Folic acid supplements in pregnancy and early childhood respiratory health

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Abstract

Background—Folate supplementation is recommended for pregnant women to reduce the risk of congenital malformations. Maternal intake of folate supplements during pregnancy might also influence childhood immune phenotypes via epigenetic mechanisms.

Objective—To investigate the relationship between folate supplements in pregnancy and risk of lower respiratory tract infections and wheeze in children through 18 months of age.

Methods—In the Norwegian Mother and Child Cohort Study, questionnaire data collected at several time points in pregnancy and after birth, from 32,077 children born between 2000 and 2005, were used to assess effects of folate supplements during pregnancy on respiratory outcomes up to 18 months of age, accounting for other supplements in pregnancy and supplementation in infancy.

Results—Folate supplements in the first trimester were associated with increased risk of wheeze and respiratory tract infections up to 18 months of age. Adjusting for exposure later in pregnancy and in infancy, the relative risk of wheeze for children exposed to folic acid supplements in the first trimester was 1.06 (95% confidence interval: 1.03, 1.10), for lower respiratory tract infections the relative risk was 1.09 (95% confidence interval: 1.02, 1.15), and for hospitalizations for lower respiratory tract infections the relative risk was 1.24 (95% confidence interval: 1.09, 1.41).

Conclusions—Folic acid supplements in pregnancy were associated with a slightly increased risk of wheeze and lower respiratory tract infections up to 18 months of age. Results support possible epigenetic influences of methyl donors in maternal diet during pregnancy on respiratory health in children.

Keywords

Dietary Supplements; Folic acid; Pregnancy; Respiratory Tract Infections; Wheezing

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INTRODUCTION

Folic acid supplementation in pregnancy has repeatedly been shown to reduce the risk of neural tube defects and other congenital malformations.[1, 2] This has lead to public health campaigns to increase folic acid supplementation both in women in the first trimester of pregnancy and in women of childbearing potential. Several countries, including the United States, fortify flour with folic acid to help ensure adequate blood levels in the first weeks of pregnancy. In Norway, pregnant women are recommended to take 400μg of folic acid daily as supplements before and in the first 3 months of pregnancy,[3] but food is not fortified with folic acid. This makes the assessment of folic acid by questionnaire somewhat simpler in Norway compared to countries with fortification of food.

Norwegian women are also recommended to take 5 ml cod liver oil daily throughout pregnancy, and cod liver oil is publicly recommended for children from 4 weeks of age.[4] Other prenatal vitamin supplements are not included in the public recommendations, but are commonly used.[5, 6] Not all women follow the recommendations for supplements use, which makes the Norwegian population during the early 2000s suitable for research in effects of folic acid during pregnancy.

There are various mechanisms whereby folate supplements in pregnancy and early life could influence the maturing immune system. Folate and other vitamins serve as methyl donors and may affect the offspring by epigenetic mechanisms. In mouse models, intake of methyl donor micronutrients during pregnancy can alter methylation levels in the offspring, and thereby influence gene expression and disease phenotypes.[7, 8] Although the impact of methylation in immune and respiratory diseases has not been well studied, recent evidence implicates methylation as crucial in the development and function of T regulatory cells, and could influence early childhood airway inflammation by this and other mechanisms.[9] In mice, high intake of folic acid and other methyl donors in pregnancy led to increased global methylation and development of allergic asthma phenotypes in the offspring.[10] There are few data on humans on possible effects of folate supplementation in pregnancy on the respiratory or atopy related phenotypes in children, and results are conflicting.[11, 12]

The Norwegian Mother and Child Study (MoBa) is a large population based study with information on supplement use from several time points in pregnancy. We used data on the first 32,077 children in MoBa to investigate if folic acid supplements during pregnancy were associated with lower respiratory tract infections and wheeze up to 18 months of age.

METHODS

Study population

Data collection was conducted as part of the Norwegian Mother and Child Cohort Study (MoBa) [13] at the Norwegian Institute of Public Health. MoBa is a cohort including 100,000 pregnancies enrolled through 2008, and described elsewhere.[13] The study population for the current analyses included all children, born between 2000 and 2005, who had reached 18 months, and for whom the 17-week and the 30-week questionnaires in pregnancy, the 6-month and the18-month questionnaires were processed as of April 2007 (further details in the online supplement). The questionnaires are available at the MoBa website.[14]

Definition of wheeze and lower respiratory tract infections

Respiratory outcomes were wheeze and lower respiratory tract infections (LRTIs) up to 18 months of age. Wheeze was defined as chest congestion/tightness or whistling/wheezing in the chest between 6 and 18 months of age. Episodes of wheeze before 6 months of age were not queried. Mothers were also asked at which age (in three-month intervals) wheezing occurred, but not asked number of episodes. In addition to assessing reports of any wheeze, we compared children with recurrent wheeze to non-wheezers. LRTIs included maternal reports of respiratory syncytial-virus, bronchiolitis, bronchitis and pneumonia. Children with reports of hospitalizations for any of these conditions were classified as "hospitalized for LRTI". LRTIs, with or without hospitalization, were compared to no episode of LRTI.

Exposure to folic acid supplements in pregnancy

The main exposure was maternal intake of folic acid supplements in pregnancy, assessed from week 0 – 30 in pregnancy. The pregnant women marked in which four-week period they used different supplements, according to the label on their supplement container. Exposure to folic acid in any four-week-period during week 0 – 12 in pregnancy was defined as exposure in the first trimester, and any use after week 12 as exposure after the first trimester.

Covariates

Covariates included other supplements in pregnancy (cod liver oil and other vitamins). Intakes of vitamin B2, B6, B12 and vitamins A, C, D, and E in pregnancy were highly correlated (correlation coefficient 0.7 – 1.0) and were included in a compound variable. Other covariates included were sex, birthweight, month of birth, and maternal atopy, maternal educational level, parity, maternal smoking in pregnancy, type of daycare, parental smoking first three months after birth, breastfeeding at six months, and exposure to vitamin supplements or cod liver oil at 6 months of age.

Statistical analyses

Data were analyzed using Stata 9.2 (Stata Corporation, College Station, Texas). For regression analyses, we used the binreg command with the relative risk option. This is a generalized linear model with a log-link for binary data which gives relative risks as association measures. First, models included an exposure variable with four mutually excluding categories: no exposure, exposure in first trimester, after first trimester or both time periods. We also used models which included variables for folate exposure in first trimester and after first trimester simultaneously, obtaining adjusted effects for each time period.

For LRTIs first 6 months of life, we adjusted for other supplements in pregnancy. For outcomes at 6 – 18 months we additionally controlled for supplements at age six months. In Norway, kindergarten usually starts around age one, and type of daycare were included in analyses for respiratory outcomes between 6 – 18 months. We ran models including adjustment for factors that might be associated with higher risk of health problems and supplement use, such as maternal atopy, previous stillbirths and spontaneous abortions, and models excluding low birthweight children, and multiple births.

To obtain correlation coefficients we used the phi correlation. Children without information on respiratory outcomes were not included in analyses (2.1% for wheeze, and 4.3% for LRTIs 0 – 6 months, and 2.3% for LRTIs 6 – 18 months).

The MoBa study has been approved by the Regional Committee for Ethics in medical research, the Norwegian Data Inspectorate and the Institution Review Board of the National Institute of Environment Health Sciences, USA.

RESULTS

Folic acid supplements in pregnancy were related to higher maternal education, higher maternal age, longer duration of breast feeding, and lower smoking among parents (table 1). Being a first born child and daycare outside the home was slightly more common among those exposed to folic acid supplements. Folic acid supplements were also slightly more common among atopic mothers. Overall, 79.3% of women took folate supplements at some point during pregnancy, 22.3% used folate supplements in the first trimester only, 13.8% used supplements only after the first trimester, and 42.6% used supplements in both periods. Cod liver oil was taken by 40.2% in pregnancy, and given to 54.6% of the children at six months. Aside from cod liver oil, vitamins other than folic acid were taken by 55.3% in pregnancy and vitamin supplements were given to 37.0% of the children at six months. The correlation was 0.17 between folic acid and cod liver oil use in pregnancy, and 0.37 between folic acid supplements and other vitamin supplements in pregnancy.

We classified children into mutually exclusive categories for folate exposure in the first trimester and later to compare associations between exposure at different time points in pregnancy and respiratory disease susceptibility (table 2). Relative to children not exposed at any point in pregnancy, respiratory infections and wheeze were most strongly associated with folic acid supplementation in the first trimester of pregnancy, significantly for those exposed only in the first trimester. The risks were significantly different for exposure in the first trimester only compared to exposure exclusively after the first trimester, for wheeze: $p = 0.03$, for LRTIs: $p = 0.02$, and for hospitalizations for LRTIs: $p = 0.004$.

We adjusted the effects of exposure to folate supplements in the first trimester to exposure both later in pregnancy and infancy, and associations with exposure in first trimester remained significant (table 3). We also analyzed LRTIs before six months and from six to 18 months separately, adjusting the later outcomes for infant supplement use up to six months and kindergarten attendance. Folic acid supplements in the first trimester of pregnancy remained associated with LRTIs at both 0 – 6 months and 6 – 18 months (table 4).

In addition, we did analyses with recurrent wheeze: wheeze reported in two or more 3-month intervals between 6 and 18 months of age (data not shown). The associations with exposure to folic acid supplements in first trimester were similar for any wheeze and recurrent wheeze. Exclusion of low birthweight children and multiple births did not materially alter any of the findings (data not shown). Also, results were robust against adjustment for previous maternal stillbirths and spontaneous abortions.

DISCUSSION

Folic acid supplements in pregnancy were associated with a slight increase in the risk of early respiratory infections and wheeze. The increased risk was associated primarily with exposure during the first trimester.

Folic acid supplementation has been found to influence early embryogenesis, and is thus recommended in the first months of pregnancy to reduce the risk of neural tube and other congenital defects.[2] We found the association between folic acid and respiratory outcomes to be attributable to exposure early in pregnancy. The difference by timing of exposure might reflect different mechanisms for effects of folate on the developing fetus. A recent study revealed that periconceptional dietary inputs to the methionine/folate cycle in sheep can lead to widespread epigenetic alterations in offspring and influence health related phenotypes.[15]

Many factors related to supplement use may also potentially influence risk of disease. Thus, unmeasured and residual confounding may influence associations. We found exposure to folic acid supplements in pregnancy to be associated with several characteristics in both mothers and children related to a lower risk of respiratory illness, including higher maternal educational level, longer duration of breastfeeding and less smoking. Residual confounding by these factors should result in a negative bias, suggesting that associations could be stronger than estimated. However, supplement users may be more health oriented and have greater disease awareness than non-users and in general report more health problems. This could result in a positive bias of associations between intake and disease. We did not find that supplement users in general reported more health outcomes than non-users. For example, folic acid supplements were not associated with an increased risk of colic before 6 months of age.

Maternal health problems during pregnancy may influence risk of respiratory disease in children, and increased disease vulnerability may influence the pattern of supplement use. We attempted to address this by performing analyses accounting for maternal atopy, low birthweight, multiple births, previous maternal stillbirths and spontaneous abortions, and the findings remained essentially unchanged.

We did not consider dietary intake of folate in foods, or genetic polymorphisms in folate metabolism in mothers or children suggested to be associated with both atopy and intake of folate supplements.[11, 12] In a recent study from Norway in which folate supplementation in pregnancy was found to protect against cleft palate risk, the cut-point for the highest quartile of folate from food sources in pregnancy was 265 μg, well below the 400μg contained in many supplements.[1] Thus, especially in Norway where food is not fortified with folate as it is in several other countries, intake from supplements predominates over intake from diet alone. In the recent Norwegian study, the beneficial effect of folate supplementation on cleft palate risk was not altered by adjustment for dietary folate. A validation study of report of dietary supplements in our cohort found biomarkers and self-reported use of folic acid supplements in pregnancy to correspond. [16]

Respiratory symptoms in the age group investigated may be transient and not necessarily represent chronic respiratory disease. However, for some children early wheezing may be related to a predisposition for asthma, especially for children with persistent wheezing.[17] Persistent wheezing have also been associated to elevated IgE-levels, indicating a relation with atopy.[17] We attempted to identify children with persistent symptoms by investigating children with reports of wheeze at more than one age-interval, and found similar associations with folic acid supplement exposure in early pregnancy. However, information on wheezing was only available for children between six and 18 months of age, which is a short period for addressing persistent symptoms. The children in MoBa will be followed to older ages when more reliable diagnoses of subtypes of asthma and other atopy-related outcomes can be made.

The positive association with folic acid supplement exposure is of interest in light of recent findings in mouse models demonstrating that intake of folic acid and other methyl donors in pregnancy leads to epigenetic influences in the offspring.[7, 8] Methylation is involved in early differentiation of T-cells and regulation of the immune response, thus a high intake of methyl-donors in pregnancy or after birth may affect the immune system in several ways. [18, 19] While there are few data on respiratory and immune outcomes, a methyl-rich diet in pregnant mice has also been found to influence gestational length, coat color and weight of offspring via differential methylation.[20–23] A recent experimental study in mice showed that supplementation with methyl donors, including folic acid, during pregnancy, led to increased gene methylation and allergic asthma phenotypes in offspring via epigenetic

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mechanisms.[10] Thus it is plausible that a high intake of folate and other methyl donors during pregnancy could influence immune phenotypes in children via epigenetic mechanisms.

Folic acid supplements may also influence disease phenotypes by other mechanisms. For example, folate participates as a substrate in the methionine cycle which is central in cell metabolism.[20] The impact of altering this cycle is not fully understood. Genetic polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) in the methionine cycle have been suggested to influence development of atopy related outcomes, but findings are conflicting.[11, 12] One study found an increased risk of atopy in children carrying the T-allele when the mother reported folate supplementation in pregnancy, and also higher risk of allergy in mothers with the TT genotype who took folate supplements in pregnancy, [11, 12] but these were suggested to be chance findings.

Synthetic folic acid (PteGlu), the most commonly used folate form in supplements, is different from folates in food, and may act differently than natural occurring folates.[24–26] Absorption of PteGlu is a saturable process,[27] and regular intake of folic acid supplements will in many subjects result in circulating unmetabolized folic acid,[28] which may have possible effects on immune-cells.[26]

Exposure to folate supplements in first trimester of pregnancy was associated with a slightly increased risk of respiratory illness in early childhood. Effects were small, and unmeasured confounding may influence the associations found. The findings are in agreement with the hypothesis that early childhood respiratory health may be affected by possible epigenetic influences of methyl donors in maternal diet during pregnancy.

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What is already known on this topic

- Folic acid supplements in the first trimester of pregnancy influence early embryogenesis. In pregnant mice, supplementation with methyl donors, including folic acid, led to increased gene methylation and allergic asthma phenotypes in offspring via epigenetic mechanisms

What this study adds

- Exposure to folate supplements in the first trimester of pregnancy may be associated with increased risk of wheeze and lower respiratory tract infections up to 18 months of age.
- Early childhood respiratory health may be affected by possible epigenetic influences of methyl donors in maternal diet during pregnancy.

TABLE 1

Prevalence (%) of children exposed to folic acid supplements in pregnancy in different strata of characteristics in the Norwegian Mother and Child Study, for children born 2000–2005.

		Folic acid supplements
	n	**%**
Overall	32,077	79.3
Prenatal maternal smoking		
no	26,745	81.2
yes	3,260	67.0
Postnatal parental smoking		
no	21,932	81.8
yes	7,903	73.9
Sex		
boy	16,305	79.2
girl	15,733	79.5
Maternal education (years)		
≤ 12	12,481	71.1
>12 and < 16	13,188	83.9
≥ 16	5,697	87.2
other	594	78.8
Birthweight (grams)		
< 2500	1,223	83.3
2500 – 4500	29,243	79.3
> 4500	1,537	76.4
Maternal history of atopy		
no	22,665	78.5
yes	9,412	81.6
Season born		
winter	7,534	79.0
spring	9,038	79.6
summer	7,971	79.2
fall	7,496	79.4
Breastfeeding (months)		
< 6	5,919	74.3
≥ 6	26,158	80.5
Maternal age (years)		
< 25	4,001	72.9
25 – 30	14,638	81.5
> 30	13,438	79.0
Parity		
0	14,448	84.5
1	11,329	78.5

	Folic acid supplements	
	n	%
> 1	6,300	69.1
Type of daycare		
parent	9,978	75.5
nanny/private home	10,148	79.7
kindergarten	11,861	82.4

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Table 2

Incidence proportions (%) and adjusted* relative risks (aRR) with 95% confidence intervals (CI) for wheeze, lower respiratory tract infections (LRTI), and hospitalizations for LRTIs up to 18 months of age according to exposure to folic acid supplements in pregnancy for 32,077 children born 2000–2005 in the Norwegian Mother and Child Study.

Folic acid supplements in pregnancy			Wheeze 6 – 18 months			LRTI 0 – 18 months			LRTI hospitalized 0 – 18 months		
before week 12	after week 12	n	%	aRR	95%CI	%	aRR	95%CI	%	aRR	95%CI
No	No	6,835	38.2	1.00		16.7	1.00		4.3	1.00	
No	Yes	4,431	39.5	1.01	0.96, 1.07	16.0	0.97	0.88, 1.08	3.8	0.92	0.73, 1.15
Yes	No	7,145	41.0	1.07	1.03, 1.12	17.3	1.10	1.01, 1.20	5.0	1.28	1.07, 1.53
Yes	Yes	13,666	41.2	1.07	1.02, 1.12	16.8	1.07	0.98, 1.16	4.2	1.08	0.90, 1.29

*Adjusted for other vitamin supplements and cod liver oil in pregnancy, vitamin supplements and cod liver oil at 6 months of age, and for maternal age, maternal atopy, maternal smoking in pregnancy, maternal educational level, postnatal parental smoking, sex, parity, birthweight, season born, breastfeeding, and type of daycare.

TABLE 3

Incidence proportions (%), and crude (c) and adjusted* (a) relative risks (RR) with 95% confidence intervals (CI), for wheeze, lower respiratory tract infections (LRTI), and hospitalizations for LRTIs according to exposure to folic acid supplements in pregnancy for 32,077 children born 2000 – 2005 in the Norwegian Mother and Child Study.

	Wheeze 6 – 18 months n = 12,656				LRTI 0 – 18 months n = 5,089				LRTI hospitalized 0 – 18 months n = 1,319			
	%	**cRR**	**aRR**	**95%CI**	**%**	**cRR**	**aRR**	**95%CI**	**%**	**cRR**	**aRR**	**95%CI**
Folic acid in first trimester												
No	38.8	1.00	1.00	–	16.4	1.00	1.00	–	4.1	1.00	1.00	–
Yes	41.1	1.06	1.06	1.03, 1.10	17.0	1.04	1.09	1.02, 1.15	4.5	1.09	1.24	1.09, 1.41
Folic acid after first trimester												
No	39.7	1.00	1.00	–	17.0	1.00	1.00	–	4.6	1.00	1.00	–
Yes	40.8	1.03	1.00	0.97, 1.03	16.6	0.98	0.98	0.92, 1.04	4.1	0.89	0.86	0.75, 0.97

*Exposures in first and after first trimester adjusted for each other, and in addition adjusted for other vitamin supplements and cod liver oil in pregnancy, vitamin supplements and cod liver oil at 6 months of age, and for maternal age, maternal atopy, maternal smoking in pregnancy, maternal educational level, postnatal parental smoking, sex, parity, birthweight, season born, breastfeeding, and type of daycare.

TABLE 4

Incidence proportions (%) and adjusted relative risks (aRR) with 95% confidence intervals (CI) for lower respiratory tract infections (LRTI) and hospitalizations for LRTIs at different ages according to exposure to folic acid supplements in pregnancy, for 32,077 children born 2000–2005 in the Norwegian Mother and Child study.

	LRTI 0 – 6 months n = 1,566			**LRTI hospitalized 0 – 6 months n = 614**			**LRTI 6 –18 months n = 4,240**			**LRTI hospitalized 6 –18 months n = 893**		
	%	**aRR**	**95%CI**	**%**	**aRR**	**95%CI**	**%**	**aRR**	**95%CI**	**%**	**aRR**	**95%CI**
Folic acid in first trimester												
No	5.1	1.00	–	1.8	1.00	–	13.1	1.00	–	2.8	1.00	–
Yes	5.1	1.11	0.99, 1.24	2.1	1.28	1.06, 1.55	13.7	1.08	1.01, 1.16	2.9	1.19	1.02, 1.40
Folic acid after first trimester												
No	5.3	1.00	–	2.1	1.00	–	13.5	1.00	–	3.0	1.00	–
Yes	5.0	0.98	0.87, 1.10	1.9	0.88	0.73, 1.06	13.6	1.00	0.93, 1.07	2.7	0.86	0.74, 1.01

* Exposures in first and after first trimester adjusted for each other, and in addition adjusted for other vitamins and cod liver oil in pregnancy, and for maternal age, maternal atopy, maternal smoking in pregnancy, maternal educational level, postnatal parental smoking, sex, parity, birthweight, season born and breastfeeding. Estimates for age 6 –18 months also adjusted for type of daycare and supplement use at 6 months of age (cod liver oil and vitamins).