EDITOR'S CHOICE

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 up to 18 months of age.

Methods: In the Norwegian Mother and Child Cohort Study, questionnaire data collected at several time points during pregnancy and after birth on 32 077 children born between 2000 and 2005 were used to assess the effects of folate supplements during pregnancy on respiratory outcomes up to 18 months of age, while 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 for wheeze for children exposed to folic acid supplements in the first trimester was 1.06 (95% CI 1.03 to 1.10), the relative risk for lower respiratory tract infections was 1.09 (95% CI 1.02 to 1.15) and the relative risk for hospitalisations for lower respiratory tract infections was 1.24 (95% CI 1.09 to 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. The results suggest that methyl donors in the maternal diet during pregnancy may influence respiratory health in children consistent with epigenetic mechanisms.

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.

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 led 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, it is recommended that pregnant women take 400 μg of folic acid daily as supplements before and during 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.

It is also recommended that Norwegian women 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] However, not all women follow the recommendations for supplement use, which means the Norwegian population of the early 2000s is suitable for research on the 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 offspring by epigenetic mechanisms. In mouse models, the intake of methyl donor micronutrients during pregnancy can alter methylation levels in offspring, and thereby influence gene expression and disease phenotypes.[7 8] Although the impact of methylation in immune and respiratory diseases has not been comprehensively studied, recent evidence implicates methylation as crucial in the development and function of T regulatory cells, and it could influence early childhood airway inflammation by this and other mechanisms.[9] In mice, a high intake of folic acid and other methyl donors in pregnancy led to increased global methylation and the development of allergic asthma phenotypes in offspring.[10] There are few data on humans on the possible effects of folate supplementation in pregnancy on 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 study which includes 100 000 pregnancies enrolled up to 2008, and is described elsewhere.[13] The study population for the current analyses included all children born between the beginning of 2000 and June 2005 who had reached 18 months of age, and for whom the 17-week and the 30-week questionnaires in pregnancy, and the 6-month and the18-month questionnaires had been processed as of April 2007 (see online supplement for further details). 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 enquired about. Mothers were also asked at which age (in 3-month intervals) wheezing occurred but were not asked about the 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 hospitalisations for any of these conditions were classified as "hospitalised for LRTI". LRTIs, with or without hospitalisation, 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 to 30 in pregnancy. The pregnant women recorded in which 4-week period they used different supplements, according to the label on their supplement container. Exposure to folic acid in any 4-week-period during weeks 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 vitamins 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, birth weight, month of birth, and maternal atopy, maternal educational level, parity, maternal smoking in pregnancy, type of day care, parental smoking in first 3 months after birth, breast feeding at 6 months, and exposure to vitamin supplements or cod liver oil at 6 months of age.

Statistical analyses

Data were analysed 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 generalised 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, exposure after first trimester or exposure in 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 during the first 6 months of age, we adjusted for other supplements in pregnancy. For outcomes at 6–18 months we additionally controlled for supplements at age 6 months. In Norway, kindergarten usually starts around 1 year of age, so type of day care was included in analyses for respiratory outcomes between 6 and 18 months. We ran models including adjustment for factors that might be associated with a higher risk of health problems and supplement use, such as maternal atopy, previous stillbirths and spontaneous abortions, and models excluding low birth weight 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, 4.3% for LRTIs at 0–6 months, and 2.3% for LRTIs at 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 day care outside the home were 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 6 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 6 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 hospitalisations 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 in infancy, and associations with exposure in the first trimester remained significant (table 3). We also analysed LRTIs before 6 months and from 6 to 18 months separately, adjusting the later outcomes for infant supplement use up to 6 months and

Table 1 Prevalence (%) of children exposed to folic acid supplements in pregnancy by various characteristics

	n (% exposed to folic acid supplements)
Overall	32 077 (79.3%)
Prenatal maternal smoking	
No	26 745 (81.2%)
Yes	3260 (67.0%)
Postnatal parental smoking	
No	21 932 (81.8%)
Yes	7903 (73.9%)
Sex	
Boy	16 305 (79.2%)
Girl	15 733 (79.5%)
Maternal education (years)	
⩽12	12 481 (71.1%)
>12 to <16	13 188 (83.9%)
⩾16	5697 (87.2%)
Other	594 (78.8%)
Birth weight (g)	
<2500	1223 (83.3%)
2500–4500	29 243 (79.3%)
>4500	1537 (76.4%)
Maternal history of atopy	
No	22 665 (78.5%)
Yes	9412 (81.6%)
Season born	
Winter	7534 (79.0%)
Spring	9038 (79.6%)
Summer	7971 (79.2%)
Autumn	7496 (79.4%)
Breast feeding (months)	
<6	5919 (74.3%)
⩾6	26 158 (80.5%)
Maternal age (years)	
<25	4001 (72.9%)
25–30	14 638 (81.5%)
>30	13 438 (79.0%)
Parity	
0	14 448 (84.5%)
1	11 329 (78.5%)
>1	6300 (69.1%)
Type of day care	
Parent	9978 (75.5%)
Nanny/private home	10 148 (79.7%)
Kindergarten	11 861 (82.4%)

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 birth weight 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 the 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 the 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 breast feeding 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 the 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 birth weight, 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

Table 2 Incidence proportions (%) and adjusted* relative risks with 95% CI for wheeze, lower respiratory tract infections (LRTIs) and hospitalisations for LRTIs up to 18 months of age according to prenatal exposure to folic acid supplements for children born in 2000–2005

Folic acid supplements in pregnancy		Wheeze, 6–18 months			LRTI, 0–18 months		LRTI hospitalised, 0–18 months	
Before week 12	After week 12	n	%	aRR (95% CI)	%	aRR (95%CI)	%	aRR (95%CI)
No	No	6835	38.2	1.00	16.7%	1.00	4.3%	1.00
No	Yes	4431	39.5	1.01 (0.96 to 1.07)	16.0%	0.97 (0.88 to 1.08)	3.8%	0.92 (0.73 to 1.15)
Yes	No	7145	41.0	1.07 (1.03 to 1.12)	17.3%	1.10 (1.01 to 1.20)	5.0%	1.28 (1.07 to 1.53)
Yes	Yes	13 666	41.2	1.07 (1.02 to 1.12)	16.8%	1.07 (0.98 to 1.16)	4.2%	1.08 (0.90 to 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, birth weight, season born, breast feeding and type of day care.
aRR, adjusted relative risk; LRTI, lower respiratory tract infection.

Table 3 Incidence proportions (%), crude relative risks and adjusted* relative risks with 95% CI, for wheeze, lower respiratory tract infections (LRTIs) and hospitalisations for LRTIs according to prenatal exposure to folic acid supplements for children born in 2000–2005

	Wheeze, 6–18 months, n = 12 656			LRTI, 0–18 months, n = 5089			LRTI hospitalised, 0–18 months, n = 1319		
	%	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 to 1.10)	17.0%	1.04	1.09 (1.02 to 1.15)	4.5%	1.09	1.24 (1.09 to 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 to 1.03)	16.6%	0.98	0.98 (0.92 to 1.04)	4.1%	0.89	0.86 (0.75 to 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, birth weight, season born, breast feeding and type of day care.
aRR, adjusted relative risk; cRR, crude relative risk; LRTI, lower respiratory tract infection.

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 400 μg 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 reports of dietary supplements in our cohort found that biomarkers corresponded with self-reported use of folic acid supplements in pregnancy.[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 has also been associated with elevated IgE levels, indicating a relationship 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 6 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 are possible.

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 offspring.[7 8] As methylation is involved in early differentiation of T cells and regulation of the immune response, 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 colour 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 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 methylenetetrahydrofolate reductase (MTHFR) in the methionine cycle have been suggested to influence the 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 a higher risk of allergy in mothers with the TT genotype who

Table 4 Incidence proportions (%) and adjusted relative risks with 95% CI for lower respiratory tract infections (LRTI) and hospitalisations for LRTIs at different ages according to prenatal exposure to folic acid supplements for children born in 2000–2005

	LRTI, 0–6 months, n = 1566		LRTI hospitalised, 0–6 months, n = 614		LRTI, 6–18 months, n = 4240		LRTI hospitalised, 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 to 1.24)	2.1%	1.28 (1.06 to 1.55)	13.7%	1.08 (1.01 to 1.16)	2.9%	1.19 (1.02 to 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 to 1.10)	1.9%	0.88 (0.73 to 1.06)	13.6%	1.00 (0.93 to 1.07)	2.7%	0.86 (0.74 to 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, birth weight, season born and breast feeding. Estimates for age 6–18 months also adjusted for type of day care and supplement use at 6 months of age (cod liver oil and vitamins).
aRR, adjusted relative risks; LRTI, lower respiratory tract infection.

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 unmetabolised folic acid,[28] which may have possible effects on immune cells.[26]

Exposure to folate supplements in the 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. These findings are in agreement with the hypothesis that early childhood respiratory health may be affected by the possible epigenetic influences of methyl donors in maternal diet during pregnancy.

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Competing interests: None.

Ethics approval: 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.

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preference would be for some of the information to be presented in diagrammatic form rather than bullet points. Also, pictures of different inhaler, nebuliser and non-invasive ventilation devices would have been useful. I have the same criticism of the common clinical procedures section. Again, it is comprehensive but I would have appreciated illustrations of procedures such as chest drain insertion, ciliary brushings and tracheostomy changes. Finally, there is an Appendix section which covers the measurement of lung function from spirometry to plethysmography and gas dilution techniques.

This book certainly achieves its aim and is a valuable resource for any paediatrician specialising or with an interest in respiratory medicine. It is best used as a handbook although the opening section would be a worthwhile read for any paediatric trainee as it provides a common sense approach to a variety of respiratory presentations. Overall this is an excellent book full of useful and eminently practical information. At only £35, it would be a well-advised addition to the shelf just above your desk.

N Sargant

CORRECTION

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S E Håberg, S J London, H Stigum, *et al*. Folic acid supplements in pregnancy and early childhood respiratory health. *Arch Dis Child* 2009;**94**:180–4. In table 2 of this paper the column labelled ''n'' refers to number of children within each exposure group for folic acid supplements in pregnancy, and not to number of children with wheeze. The heading ''wheeze, 6–18 months'' applies only to the % and aRRs (95% CI).