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Folic acid in pregnancy

Is there a link with childhood asthma or wheeze?

Background

Folic acid supplementation has an established role in early pregnancy for preventing neural tube defects. However, there is controversy over a possible link between late pregnancy folic acid supplementation and childhood asthma.

Objective

To review the evidence exploring the association between maternal folate exposure in pregnancy and childhood asthma or wheeze.

Results

Four relevant observational studies were identified. Two found statistically significant associations between childhood asthma and late (but not early) pregnancy maternal folic acid exposure. Another found a statistically significant association between childhood wheeze and early (but not late) pregnancy maternal folic acid exposure. A fourth study found little association between maternal dietary folate in pregnancy and infantile wheeze.

Discussion

The currently available evidence regarding an association between folate in pregnancy and childhood asthma or wheeze is conflicting. We offer suggestions for discussing the potential risk with patients and recommend further research on this subject be conducted.

Keywords: folic acid; pregnancy; dietary supplements; asthma

Folate is a water soluble B vitamin that must be obtained in the diet or through supplementation. For more than 50 years it has been known that folate plays an integral role in embryonic development.¹ Periconceptional folic acid in doses of at least 0.36 mg has been shown to prevent approximately 72% of neural tube defects,^{2,3} and therefore a daily dose of 0.4 mg is widely recommended for all women at average risk from at least 1 month preconception to 12 weeks pregnancy.⁴ Despite this, many Australian women do not have sufficient folate intake in pregnancy,⁵ thus mandatory folic acid fortification of flour was introduced in Australia in September 2009.⁶

The Generation 1 Cohort Study,⁷ published in 2009, found that the use of folic acid in late pregnancy was associated with an increased risk of childhood asthma. This was widely reported in the popular media, both in Australia⁸ and overseas,⁹ leading to concern about the safety of folic acid in late pregnancy. Many women take pregnancy multivitamins throughout pregnancy to achieve the recommended intake of micronutrients.^{10,11} As all such multivitamins seem to include folic acid, their use in late pregnancy would present a dilemma if folic acid were unsafe.

There is a plausible explanation for the association between folate intake and childhood asthma. A laboratory study in mice showed that maternal exposure to a high methyl donor diet, which included folic acid, increased the severity of inherited allergic airway disease in offspring through increased DNA methylation. This predisposition appeared to be partially transmitted into subsequent generations.¹² However, findings in animal models are not necessarily applicable to

humans. Folic acid, which is the synthetic form of the B vitamin, is a potentially more potent methyl donor than naturally occurring folate and so may have different effects.⁷

Method

We conducted a narrative review of studies that investigate the association between maternal dietary folate intake and/or folic acid supplementation exposure and childhood asthma or wheeze. We considered performing a meta-analysis, but decided this was inappropriate due to heterogeneity of populations studied, exposure measurements, and outcome measure reporting. The first author (ES) searched MEDLINE (Ovid and PubMed) and CinAHL, using the strategy '(Folic Acid OR Folate) AND pregnancy AND (asthma OR respiratory health)', as well as '(Folate OR Folic Acid) AND late pregnancy'. Further citation searches were undertaken using Web of Science. The second author (BM) independently searched PubMed using the strategy '(asthma OR wheeze OR respiratory) AND (folate OR folic) AND pregnancy'. We identified four relevant studies, all of which were observational cohort studies.

Results

The main results from the different studies included in this review are summarised in *Table 1*.

Norwegian Mother and Child study

Håberg et al reported the Norwegian Mother and Child Cohort Study that involved 32 077 children.¹³ This study measured maternal use of folic acid supplements in early and late pregnancy, and child lower respiratory tract infections and wheeze up to the age of 18 months. Data were collected using questionnaires that were completed by participating mothers at 17 weeks and 30 weeks gestation as well as 6 months and

Table 1. Review of the associations between folic acid intake during pregnancy and childhood asthma or wheeze

Cohort (study year)	Sample size	Exposure	Outcome	Adjusted* OR (95% CI)
Avon Longitudinal Study of Parents and Children ¹⁵ (2008)	6090 (at 18 weeks)	Supplemental folic acid intake at 18 weeks and 32 weeks pregnancy	Asthma at 7.5 years	1.17 (0.91–1.51) at 18 weeks
	6078 (at 32 weeks)			1.24 (1.02–1.51) at 32 weeks
Generation 1 ⁷ 2009	490 (at 3.5 years)	Supplemental folic acid (mg/day) intake at <16 weeks and at 30–34 weeks pregnancy	Asthma at 3.5 years	0.92 (0.79–1.08) at <16 weeks
	423 (at 5.5 years)			1.26 (1.09–1.47) at 30–34 weeks
Norwegian Mother and Child ¹³ 2009	32 077	Supplemental folic acid intake at 0–12 weeks and 12–30 weeks pregnancy	Wheeze at 6–18 months	0.92 (0.79–1.08) at <16 weeks
				1.16 (0.94–1.43) at 30–34 weeks
Norwegian Mother and Child ¹³ 2009	32 077	Supplemental folic acid intake at 0–12 weeks and 12–30 weeks pregnancy	Wheeze at 6–18 months	1.06 (1.03–1.10) at 0–12 weeks 1.00 (0.97–1.03) at 12–30 weeks
Osaka Maternal and Child Health Study ¹⁴ 2010	763	Dietary folate intake during pregnancy	Wheeze at 16–24 months	1.28 (0.65–2.50)

* See list of confounding factors used in each individual study in Results section

18 months postpartum. Exposure to folic acid supplements was assessed from weeks 0–30 gestation. Analysis was stratified by timing of folic acid exposure (first trimester [0–12 weeks] or after first trimester). Mothers were asked in the postpartum questionnaires about their child's experience of wheeze or lower respiratory tract infection. Results were adjusted for a number of confounding factors including gender, birth weight, maternal atopy and education level, maternal smoking (both in pregnancy and postpartum) and breastfeeding.

An association was found between the use of folic acid in the first trimester and wheeze at 6–18 months (adjusted relative risk (aRR) 1.06, 95% CI: 1.03–1.10), but no association was found with folic acid exposure after the first trimester (aRR 1.00 95% CI: 0.97–1.03).¹³ Positive associations were also noted between first trimester folic acid exposure and lower respiratory tract infections, but no significant associations were found between such infections and later pregnancy folic acid exposure.

Generation 1 Cohort Study

The study by Whitrow et al⁷ was a prospective cohort study that recruited 605 women from antenatal clinics in Adelaide. The women were interviewed using validated food questionnaires in early (<16 weeks) and late (30–34 weeks) pregnancy to estimate dietary folate intake and supplemental folic acid use. Follow up postal questionnaires at 3.5 and 5.5 years included questions about child asthma diagnosis. Results were adjusted for a number of confounding factors including maternal age, education, smoking and asthma status, other vitamin supplementation, breastfeeding, gravida and parity.

The primary result from this study was that for every 1 mg increase in supplemental folic acid in late pregnancy, the adjusted relative risk of asthma at 3.5 years was 1.26 (95% CI: 1.09–1.47). This effect was attenuated at 5 years (aRR 1.16, 95% CI: 0.94–1.43). The study showed no increase in asthma with early pregnancy folic acid (aRR 0.92, 95% CI: 0.79–1.08). It should

be noted that the relative risks were expressed per 1 mg/day dose of folate, whereas the recommended dose for low risk women is 400 µg/day.⁶ This means that the increase in childhood asthma risk for women on a typical dose of folic acid would be much smaller than these relative risks imply.

Osaka Maternal and Child Health Study

A recent Japanese study¹⁴ involving 763 mother and child pairs from the Osaka Maternal and Child Health Study measured dietary intake of B vitamins, including folate, and examined associations with childhood atopy including wheeze and eczema as defined by responses to a standardised maternal questionnaire.

Folate intake was quantified using a detailed dietary questionnaire, and mothers were then followed up with a survey at 2–9 months and 16–24 months postpartum. Folate intake was divided into quartiles of amount consumed (quartile medians: Q1=206.8 µg/day; Q2=255.1 µg/day; Q3=291.2 µg/day; Q4=370.6 µg/day), and there were no data on timing in pregnancy. Even in the highest quartile, intake was still below the World Health Organization recommended daily intake of 400 µg/day.⁴ The study authors did not include supplemental folic acid intake as this was uncommon among the cohort (<10%).

Results were adjusted for a number of factors including maternal and paternal history of asthma, atopic eczema and allergic rhinitis; maternal age, child gender and birth weight, gravida, parity, household smoking, breastfeeding and maternal and paternal education. Little evidence of an association was observed between maternal dietary folate during pregnancy and childhood wheeze at age 16–24 months (Q4 aRR 1.28, 95% CI: 0.65–2.50).¹⁴

Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population based birth cohort study in the United Kingdom which enrolled 14 541 pregnant women in the early 1990s. Granell et al¹⁵ used data from 7356 mothers and 5364 children to study the link between mother and child MTHFR C677T polymorphisms, dietary folate intake and childhood atopy, finding no link

between folate metabolism genotype and allergy. (The authors of this ALSPAC sub-study did not aim to study associations between maternal folate intake and childhood asthma, but as we noted that data had been collected on these factors, the ALSPAC study authors were approached for more information.)

The collected data included maternal dietary folate intake ($\mu\text{g}/\text{day}$) at 32 weeks of pregnancy, as well as folic acid supplementation (yes/no) at 18 and 32 weeks. Childhood asthma was measured at 7.5 years of age and defined as maternal recall of physician diagnosis of asthma together with wheeze within the previous 12 months. Analysis of these data yields the previously unpublished results presented in *Table 2*. Logistic regression models were used to evaluate the association between children's asthma and maternal dietary/supplemental folate intake. Results were adjusted for gender, maternal history of asthma or allergy, exposure to prenatal and postnatal maternal smoking and mothers' education. There was no association between children's asthma and maternal dietary folate intake at 32 weeks. However, there was moderate evidence of a positive association between children's asthma and maternal supplemental folic acid intake at 32 weeks (adj OR 1.24, 95% CI: 1.02–1.51, $p=0.03$).¹⁵

Limitations of the studies

As the included articles were all cohort studies, a shared limitation is that, despite attempting to adjust for plausible measurable confounders, some confounding factors may exist. Several of the studies did not adjust for paternal atopy, asthma and smoking.^{7,13,15} Some confounders may not be easily measured. For example, we speculate that a 'health conscious' mother might be more likely to take folic acid, attend a doctor for concerns regarding child respiratory health (increasing the chance of a diagnosis), and emphasise childhood hygiene, a putative risk factor for asthma.¹⁶ Neither the Norwegian nor the ALSPAC studies quantified folic acid supplement intake beyond a 'yes/no' measure, and the Norwegian study did not measure dietary folate intake. The Japanese study may have been underpowered, and it did not measure supplemental folic acid intake. The four studies measured respiratory outcomes at different ages, and ascertained outcomes differently, making direct comparison difficult. In addition, children with infantile wheeze do not necessarily develop asthma. The results from the ALSPAC are post hoc, and therefore should be interpreted with caution.

Folate in late pregnancy in context

Although outside the scope of this review, folic acid intake in late pregnancy has been

suggested to be neutral or beneficial for a number of other pregnancy outcomes including gestational hypertension, pre-eclampsia, birth weight, neurodevelopment, preterm birth, placenta praevia¹ and paediatric malignancy.¹⁷ The vast majority of this evidence comes from observational studies, as there are few randomised controlled trials of folic acid supplementation in late pregnancy.

Conclusion

The current available evidence of an association between late pregnancy folate intake and childhood asthma or wheeze is conflicting. The Norwegian study suggested a risk for wheeze from early, but not late pregnancy folic acid intake. In contrast, the Australian and English studies suggested a risk for asthma from late, but not early pregnancy folic acid intake. The Japanese study found no significant risk of wheeze with dietary folate, but did not study folic acid supplementation. We are unaware of any other relevant research.

We feel that an association between childhood asthma and late pregnancy folic acid supplementation at standard doses is possible. However, given the evidence at present is drawn from cohort studies, it has limitations. A randomised controlled trial of

Table 2. Association between asthma and maternal dietary folate intake or folic acid supplementation in the ALSPAC cohort¹⁵

				OR (95% CI), <i>p</i> value for children's asthma at 7.5 years	
	Number of children with asthma/no asthma	Mean (SD) for asthmatics	Mean (SD) for nonasthmatics	Crude	Adjusted
Continuous variables					
A) Maternal dietary folate intake at 32 weeks (per 100 $\mu\text{g}/\text{day}$)	599/5503	254.9 (68.2)	255.7 (7.07)	0.98 (0.87, 1.11) $p=0.77$	0.97 (0.86, 1.10) $p=0.65$
Binary variables					
B) Maternal supplemental folic acid intake at 18 weeks gestation	599/5491	NA	NA	1.20 (0.94, 1.55) $p=0.14$	1.17 (0.91, 1.51) $p=0.22$
B) Maternal supplemental folic acid intake at 32 weeks gestation	599/5503	NA	NA	1.25 (1.04, 1.49) $p=0.02$	1.25 (1.04, 1.49) $p=0.02$
C) Maternal supplemental folic acid intake at 32 weeks gestation	598/5480	NA	NA	1.26 (1.05, 1.50) $p=0.01$	1.24 (1.02, 1.51) $p=0.03$

A) Adjusted for gender, maternal history of asthma or allergy, maternal supplemental folic acid at 32 weeks gestation, exposure to prenatal and postnatal maternal smoking and mother's education

B) Adjusted for gender, maternal history of asthma or allergy, maternal dietary folate intake at 32 weeks gestation, exposure to prenatal and postnatal maternal smoking and mother's education

C) Adjusted as in 'B', but also adjusted for maternal supplemental folic acid intake at 18 weeks gestation

folic acid supplementation in late pregnancy would offer more reliable evidence. Considering the range of possible benefits and risks from folate supplementation, and the fact that such supplementation is commonly used, such a study could be considered but would face challenges of adequate power and ethical acceptability.

Implications for practice

We will continue to recommend periconceptional and early pregnancy folic acid supplementation for the prevention of neural tube defects. Given the possible association with asthma, we would not recommend supplements containing only folic acid in late pregnancy. However, given the uncertainty of this risk, and the possible benefits of other micronutrients (which are outside the scope of this article but reviewed elsewhere^{18,19}) we would not dissuade a pregnant woman from taking a standard pregnancy multivitamin.

We would remind women that respiratory risks from late pregnancy folic acid are unproven, but that even if they are real, the absolute increase in risk to an individual child would be fairly small. Hypothetically, if the relative risk increase of asthma from standard dose late pregnancy folic acid was 10–20% (consistent with the Australian and English studies), and assuming an Australian childhood asthma prevalence of 20%,²⁰ a pregnant woman taking folic acid in late pregnancy would increase her child's risk of asthma by 2–4%. Couching the statistics in these terms may help patients make an informed decision.

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