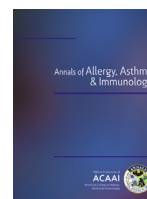




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Relationship between prenatal antibiotic use and asthma in at-risk children

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ABSTRACT

Background: Asthma prevalence has doubled in developed countries during the past 30 years. Pre- and perinatal events are essential in shaping the development of the immune system and systemic antibiotic use during this time could alter the maternal or placental microbiome, leading to an increase in the child's risk of developing asthma.

Objective: To determine whether prenatal antibiotic use is associated with asthma and wheezing in children at risk for asthma.

Methods: Using data from a randomized education intervention of families at risk for asthma from 1998 followed through 2009 in urban Chicago, asthma was defined as ever having a physician asthma diagnosis by year 3 and wheezing in the third year. Logistic regression models controlling for confounders investigated the effect of antibiotic use during pregnancy on these outcomes.

Results: After adjustment, prenatal antibiotic use was a risk factor for asthma (odds ratio 3.1, 95% confidence interval 1.4–6.8) but was only weakly associated with wheezing (odds ratio 1.8, 95% confidence interval 0.9–3.3). Analyses of the effects of timing of prenatal antibiotic use on asthma and wheezing showed the relation remained consistent for antibiotic use later in pregnancy, but the outcomes were not associated with antibiotic use in the first trimester.

Conclusions: This study suggests prenatal antibiotic use might be associated with the development of asthma in children at risk for asthma. Although the relation with prenatal antibiotics does not hold for wheezing in this study, there might be a trend that could be delineated further within a larger cohort study.

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Introduction

Prevalence of asthma has doubled in developed countries during the past 30 years.¹ The factors causally driving these temporal increases remain essentially unknown, with poor and minority children in the United States presenting with a disproportionately

greater burden of asthma morbidity.² Concurrent increases in antibiotic use to treat infections in children have led to speculation of a causal relation. Retrospective studies have shown strong correlations between early antibiotic use and asthma, but the findings suggest the possibility of reverse causation or confounding by indication.^{3,4} Conversely, prenatal antibiotics have been found to be associated with the development of asthma and wheezing in early life.^{5–11} The hygiene hypothesis suggests that birth into an environment with fewer microbial exposures can alter development of the immune system, leading to a greater risk of atopy.¹² Data have suggested that antibiotics in utero could change the maternal or placental microbiome and increase the child's risk of developing allergic disease.^{13,14} Factors that modify microbial exposure pre- and perinatally could have a long-term impact on the risk of developing subsequent atopic disease.^{7,15,16} Research using prospective birth cohorts has been limited, especially in impoverished urban residents.

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Controlling for maternal and child confounders within a prospective study, the authors investigated the effects of prenatal antibiotic use with the subsequent development of asthma by year 3 and wheezing in the third year within a high-risk urban cohort. Because this relation could be confounded by maternal asthma or by antibiotic use in the child, the authors investigated the associations within subsets of mothers without asthma and within children who did not use antibiotics. They also investigated the impact of antibiotics during different trimesters of pregnancy.

Methods

The Peer Education in Pregnancy Study is a randomized education intervention examining the effect of community educators working with pregnant women at risk for having children with asthma on modification of factors in the home known to exacerbate the disease. From 1998 to 2004, at-risk families living in disadvantaged areas of urban Chicago were identified to participate in the study if the unborn child had a first-degree relative with asthma, hay fever, or eczema. Mothers were followed and surveyed in each trimester of pregnancy and soon after delivery, and 301 children were followed from 4 weeks through 3 years of age. The intervention did not address antibiotic usage. All women in the study received general health education. Half the women also received a series of home visits from a community health educator to identify and decrease in-home asthma triggers. The complete outline of participant flow through the study has been published elsewhere.^{17,18}

A total of 298 mother–child pairs from the Peer Education in Pregnancy Study had information concerning systemic antibiotic use and were followed through the child's third year of life. The primary end points of the study were asthma diagnosis by year 3 and reported wheezing in the third year of life. Asthma was defined as ever having an asthma diagnosis by a physician by 3 years of age based on the self-reported answer to the question, "Has a doctor ever told you that your child has asthma?" Secondary end points included eczema and other respiratory symptoms in the third year:

exercise-induced wheezing, sleep disturbed by wheezing, wheezing without a cold, and emergency department visits for breathing problems. Development of the primary end point of wheezing and the secondary end points of eczema and other respiratory symptoms were determined by a positive response within the year before their third-year visit based on the following questions: "Has your child's chest sounded wheezy or whistling?" "Has a physician ever told you that your child has eczema?" "Has your child's chest sounded wheezy or whistling during or shortly after vigorous exercise?" "Has your child been awakened at night by wheeze or by shortness of breath?" "Has your child had episodes of wheezing or whistling without a cold?" "Was your child treated in the emergency department for breathing problems (coughing, congestion, runny nose, wheezing)?" Prenatal risk factors during pregnancy, such as antibiotic use, infections, and smoking status, were evaluated by questionnaire at enrollment in the first trimester, at 4 to 5 months of gestation, and at 7 to 8 months of gestation. Other potential confounders, including history of asthma, maternal age, maternal ethnicity, and acetaminophen and ibuprofen use, were evaluated by questionnaire during pregnancy and 5 times throughout the child's first year of life. Information on the reason for antibiotic use in the child was separated into respiratory vs nonrespiratory infections. If the 2 infection types occurred, the reason was considered respiratory. Reason for prenatal antibiotic use was not captured, but only systemic antibiotics were noted. Antibiotic use during each trimester of pregnancy was investigated as early use in the first trimester or mid-to-late use in the second to third trimester. Information on type of delivery and antibiotic use during delivery was not available in this cohort.

The study was approved by the university's institutional review board. All enrolled participants provided written informed consent. Maternal characteristics during pregnancy, child characteristics through the first year, and third-year outcomes were compared across prenatal antibiotic uses. Frequency counts and percentages are shown for categorical variables and were compared using χ^2 or the Fisher exact test. Continuous variables are presented as mean with SD and were compared using *t* test. Multivariable logistic

Table 1
Maternal and child characteristics by prenatal antibiotic use (N = 298)

	Total	Prenatal antibiotic use	No antibiotic use	P value
Total, n (%)	298	103 (34.6)	195 (65.4)	
Study intervention, n (%)	148 (49.7)	51 (49.5)	97 (49.7)	.97
Maternal characteristics during pregnancy				
Maternal age (y), mean (SD)	25.9 (5.9)	26.0 (6.3)	25.8 (5.7)	.78
Mexican ancestry, n (%)	201 (67.5)	66 (64.1)	135 (69.2)	.37
Any smoking, n (%)	30 (10.1)	13 (12.6)	17 (8.7)	.29
Any acetaminophen, n (%)	204 (68.7)	74 (71.8)	130 (67.0)	.39
Any ibuprofen, n (%)	42 (14.1)	12 (11.7)	30 (15.4)	.38
Any infections, n (%)	270 (90.6)	94 (91.3)	176 (90.3)	.78
Any respiratory infections, n (%)	258 (86.6)	87 (84.5)	171 (87.7)	.44
Any fevers, n (%)	148 (49.8)	58 (56.3)	90 (46.4)	.10
Vitamin use, n (%)	84 (28.6)	38 (36.9)	46 (24.1)	.020
Mother has asthma, n (%)	98 (32.9)	45 (43.7)	53 (27.2)	.004
Child characteristics, n (%)				
Firstborn child	108 (36.2)	39 (37.9)	69 (35.4)	.67
Boy	155 (52.0)	58 (56.3)	97 (49.7)	.28
Low birth weight (<2,500 g)	25 (8.4)	10 (9.7)	15 (7.7)	.55
Premature birth (<36 wk)	14 (4.7)	4 (3.9)	10 (5.1)	.63
Breast-fed	264 (88.6)	92 (89.3)	172 (88.2)	.77
First year of life exposures, n (%)				
Exposed to cigarette smoke in home	53 (17.8)	22 (21.4)	31 (15.9)	.24
Any antibiotics	161 (54.0)	61 (59.2)	100 (51.3)	.19
Any acetaminophen	284 (95.6)	96 (94.1)	188 (96.9)	.25
Any ibuprofen	108 (36.2)	45 (43.7)	63 (32.3)	.052
Any infections	285 (95.6)	101 (98.1)	184 (94.4)	.14
Ear infections	111 (37.3)	41 (39.8)	70 (35.9)	.51
Respiratory infections	276 (92.6)	99 (96.1)	177 (90.8)	.09
Any fevers	86 (28.9)	35 (34.0)	51 (26.2)	.16

Table 2
Child outcomes by prenatal antibiotic use^a

	Total, n (%)	Prenatal antibiotic use, n (%)	No antibiotic use, n (%)	P value
Outcomes				
Asthma by year 3	44 (14.8)	23 (22.3)	21 (10.8)	.008
Wheezing in year 3	65 (21.8)	29 (28.2)	36 (18.5)	.054
Other symptoms in year 3				
Exercise-induced wheezing	35 (11.7)	17 (16.5)	18 (9.2)	.06
Sleep disturbed by wheezing	26 (8.7)	14 (13.6)	12 (6.2)	.03
Wheezing without a cold	27 (9.1)	14 (13.6)	13 (6.7)	.048
ED visit for breathing problems	46 (15.4)	21 (20.4)	25 (12.8)	.09
Eczema	58 (19.5)	23 (22.3)	35 (18.0)	.36

Abbreviation: ED, emergency department.

^aThe χ^2 test was used to compare third-year outcomes by prenatal antibiotic use.

regression models for asthma and wheezing were constructed by including all variables predictive at the univariate level ($P < .10$) and study intervention. Effect modification was evaluated using interaction terms (with $P < .20$ considered a potential interaction) between probable confounders and prenatal antibiotic use and with subset analyses within mothers with no history of asthma and within children who did not use antibiotics in the first year. Prenatal antibiotic use was split into any use throughout the pregnancy, first-trimester use, or second-to third-trimester use, and 3 separate adjusted regression models investigated the effect of antibiotics used during these different trimesters of pregnancy on asthma and wheezing. Table footnotes list variables included in adjustment. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Maternal characteristics, child characteristics, and first year of life exposures by prenatal antibiotic use are presented in Table 1. One hundred three mothers (35%) used antibiotics during their pregnancy. Most mothers in the study were of Mexican ancestry (68%) and the average age was 26 years. There were no differences for antibiotic use by maternal age, Mexican ancestry, smoking status, acetaminophen or ibuprofen use, or infections or fevers. Mothers who took antibiotics during pregnancy also were more likely to take vitamins (37% vs 24%, $P = .02$). Prenatal antibiotic use also was significantly higher in mothers with asthma (44% vs 27%, $P < .01$). Child characteristics, including low birth weight and prematurity, did not differ by prenatal antibiotic use. There also were no differences in first-year exposures to antibiotic or acetaminophen use in children born to mothers who took antibiotics. First-year ibuprofen use and respiratory infections were higher in children whose mothers took antibiotics (44% vs 32%, $P = .052$, and 96% vs 91%, $P = .09$, respectively).

Table 3
Multivariable regression model to predict asthma^a by year 3 (N = 295, 42 with asthma)

	OR (95% CI)	P value
Study intervention	0.96 (0.44–2.09)	.92
Maternal Mexican ancestry	0.37 (0.17–0.82)	.014
Any smoking in pregnancy	2.34 (0.86–6.35)	.10
Any antibiotics in pregnancy	3.12 (1.44–6.77)	.004
Any ibuprofen in pregnancy	1.37 (0.52–3.58)	.53
Mother has asthma	2.66 (1.22–5.84)	.015
Child exposed to smoke in the home	0.79 (0.30–2.07)	.63
Child took antibiotics for respiratory infections	2.53 (1.67–3.82)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

^aVariables include study intervention and significant variables ($P < .10$) from univariate analysis.

Third-year outcomes varied by antibiotic use during pregnancy (Table 2). Asthma diagnosed by year 3 occurred in 23 children (22%) born to mothers who took antibiotics vs 21 children (11%) born to mothers who did not take antibiotics ($P < .01$). Wheezing occurred in 28% of children whose mothers took antibiotics vs 19% with no antibiotics ($P = .054$). Eczema in year 3 and all respiratory symptoms in year 3 increased with prenatal antibiotic use, but only sleep disturbed by wheezing and wheezing without a cold reached conventional statistical significance.

In a multivariable regression model, independent predictors of asthma by year 3 included any antibiotic use during pregnancy (adjusted odds ratio [aOR] 3.12, 95% confidence interval [CI] 1.44–6.77), maternal asthma, and child antibiotic use for respiratory reasons in the first year of life (Table 3). Mexican ancestry was significantly protective against an asthma diagnosis. Variables related to wheezing during the third year differed slightly from those related to asthma (Table 4). Low birth weight and smoking during pregnancy were significant independent predictors of wheezing ($P = .048$ and $.018$, respectively). Antibiotic use during pregnancy was associated with an increased odds (aOR 1.76, 95% CI 0.94–3.28) of wheezing that approached significance, as did lack of breast-feeding and antibiotic use for respiratory reasons in the first year of life.

There were no significant interactions with prenatal antibiotic use in either multivariable model. The significant association between prenatal antibiotic use and asthma by year 3 remained intact within a subset analysis of mothers with no history of asthma (aOR 5.75, 95% CI 1.78–18.60, $P < .01$) and within a subset of children who did not use antibiotics in the first year (aOR 3.62, 95% CI 1.09–12.05, $P = .04$; Table 5). However, the association with wheezing was eliminated within these subsets.

Forty-three mothers took antibiotics during the first trimester, early in pregnancy, whereas 75 mothers took antibiotics in the

Table 4
Multivariable regression model to predict wheezing^a during third year of life (N = 295, 64 with wheezing)

	OR (95% CI)	P value
Study intervention	0.75 (0.40–1.39)	.36
Maternal Mexican ancestry	0.61 (0.31–1.19)	.14
Any smoking during pregnancy	2.83 (1.20–6.70)	.018
Any antibiotics during pregnancy	1.76 (0.94–3.28)	.08
Any ibuprofen during pregnancy	1.80 (0.81–4.03)	.15
Mother has asthma	1.43 (0.75–2.71)	.28
Child has low birth weight (<2,500 g)	2.56 (1.01–6.50)	.048
Child is breast-fed	0.45 (0.19–1.09)	.08
Child exposed to smoke in home	1.56 (0.73–3.34)	.27
Child takes antibiotics for respiratory infections	1.33 (0.97–1.84)	.08

Abbreviations: CI, confidence interval; OR, odds ratio.

^aVariables include study intervention and significant variables ($P < .10$) from univariate analysis.

Table 5

Adjusted regression models^a for subset analyses of prenatal antibiotic use as a predictor of asthma and wheezing

	Asthma by year 3		Wheezing in year 3	
	OR (95% CI)	P value	OR (95% CI)	P value
No maternal asthma (n = 200)	5.75 (1.78–18.60)	.004	1.50 (0.65–3.46)	.34
No first-year antibiotics (n = 137)	3.62 (1.09–12.05)	.036	1.61 (0.60–4.31)	.35

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted analysis includes study intervention and significant variables ($P < .10$) from univariate analysis. Asthma is adjusted for study intervention, Mexican ancestry, smoking during pregnancy, ibuprofen during pregnancy, mother having asthma, exposure to smoke in the home in the first year of life, and child antibiotic use for respiratory reasons. Wheezing is adjusted for study intervention, Mexican ancestry, smoking during pregnancy, ibuprofen during pregnancy, mother having asthma, low birth weight, any breast feeding, exposure to smoke in the home in the first year of life, and child antibiotic use for respiratory reasons.

second to third trimester. Analyses of the effects of the timing of prenatal antibiotic use on asthma and wheezing showed the relation remained consistent for antibiotic use in the second to third trimester of pregnancy (Table 6). These outcomes were not significantly associated with antibiotic use in the first trimester of pregnancy.

Discussion

This study found that prenatal systemic antibiotic use was a significant predictor of incident asthma, and weakly associated with wheezing, in at-risk children by 3 years of age after controlling for confounders. Similarly, McKeever et al⁷ used a birth cohort to show a relation between prenatal antibiotics exposure and an increase in the child's risk of allergic disease. Several other studies also have shown an increased risk of asthma and wheezing with pre- and perinatal antibiotic use.^{5,6,8,10,19} To the authors' knowledge, only 1 cohort study did not find an association between prenatal antibiotic exposure and wheeze or atopic sensitization but did find an association between eczema and prenatal antibiotic use.²⁰

The association between prenatal antibiotic use and subsequent asthma suggests an etiologic relation because the issue of reverse causality is naturally avoided. However, the relation could be confounded by maternal asthma, infections, smoking, premature birth, or antibiotic use in infancy because mothers who use antibiotics might be more apt to ask for antibiotics for their infants.⁵

Table 6

Three adjusted^a regression models for asthma and wheezing by timing of prenatal antibiotic use

	Asthma by year 3		Wheezing in year 3	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1: any antibiotics during pregnancy	3.12 (1.44–6.77)	<.01	1.76 (0.94–3.28)	.08
Model 2: antibiotics during first trimester	2.23 (0.90–5.49)	.08	1.32 (0.58–3.02)	.50
Model 3: antibiotics during second to third trimester	3.33 (1.52–7.27)	<.01	1.77 (0.92–3.39)	.09

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted analysis includes study intervention and significant variables ($P < .10$) from univariate analysis. Asthma is adjusted for study intervention, Mexican ancestry, smoking during pregnancy, ibuprofen during pregnancy, mother having asthma, exposure to smoke in the home in first year of life, and child antibiotic use for respiratory reasons. Wheezing is adjusted for study intervention, Mexican ancestry, smoking during pregnancy, ibuprofen during pregnancy, mother having asthma, low birth weight, any breast feeding, exposure to smoke in the home in the first year of life, and child antibiotic use for respiratory reasons.

This study attempted to identify and minimize the sources of confounding through model adjustment, effect modification, and subgroup analyses. In the present cohort, the authors found no correlation between infant antibiotic use and maternal antibiotic use. They showed there was no effect modification by maternal asthma, respiratory infections, or smoking within multivariable models of asthma and wheezing. In the subset analyses of mothers without asthma and of infants who did not take antibiotics, prenatal antibiotics remained a significant predictor of asthma. However, the association with wheezing was weaker. Owing to the large number of maternal and child infections, the authors could not look at a subset of mothers or children without infections. The Copenhagen Prospective Study on Asthma in Childhood found an association between prenatal antibiotic use and asthma within a cohort of children born to mothers with asthma.⁸ These investigators were able to replicate the findings in a subgroup of mothers using antibiotics for nonrespiratory infections. They concluded the effect was not confounded by the mother's asthma or infections and could be due to a disturbed bacterial ecology that could trigger the disease process in perinatal life. Data on specific infections for which antibiotics were used in the Peer Education in Pregnancy Study were not precise enough to rule out the possibility of confounding by infection.

Antibiotics taken in the second to third trimester of pregnancy, but not in the first trimester, were significant predictors of asthma in this study. These results are in agreement with a cohort study that also found that antibiotic use only in the second and third trimesters was associated significantly with persistent wheezing in 1-year-old children.⁹ In addition, studies have found that the composition of maternal vaginal and intestinal bacteria is related to an increased risk of wheeze in infants.^{5,13} Contrary to the previously held belief that the womb is sterile, recent studies have shown that maternal microbial transfer starts during pregnancy.¹⁵ Aagaard et al¹⁴ recently published a study demonstrating the placental microbiome is affected by maternal antenatal infections. It is unknown whether the infection itself, an inflammatory response, or antibiotic use for the infection causes this placental microbiome change. Prenatal antibiotic use could modify the placental, vaginal, or maternal gut microbiome, which can increase a child's risk of developing asthma.

The present study design offered many pertinent risk factors for childhood asthma and wheezing, and the prospectively collected measurements of maternal and child confounders strengthened the study results. This unique population of disadvantaged urban, mostly Hispanic, mothers was closely followed from the first trimester of pregnancy through the child's third year of life. However, there are some limitations to this study. Given the highly selected population, the generalizability of the study results are limited to disadvantaged children at risk for allergy and asthma. Asthma is a complex clinical disease that is difficult to assess critically before 6 years of age.¹ The present study included diagnoses before 3 years of age, when the nature of the disease progression can still be unpredictable. Because there was a high rate of infections in the mothers and children, there could be a co-variation effect between infections and antibiotic use that the authors were unable to separate. Also, the use of antibiotics and type of infections are based on parental recall and are prone to recall bias. Nurses administered the surveys multiple times throughout the pregnancy and 5 times within the child's first year to ensure recall was limited to the prior few months. Another limitation is that the authors do not have access to the number of days antibiotics were taken or the reasons antibiotics were taken by the mothers. Moreover, they do not know the types of antibiotics used in the children or the pregnant mothers. Broad-spectrum antibiotics became more prevalent in the 1980s and might alter microbiomes more than the narrower-spectrum antibiotics used previously.²¹ The study findings

could be limited to certain types of antibiotics, which should be investigated further. The authors do not have information on confounders, such as chorioamnionitis during pregnancy, or information on childbirth, such as caesarean section, which might be associated with prophylactic use of antibiotics.

This study suggests an association between prenatal antibiotic use and the development of asthma in at-risk children. Modification of microbial load could be occurring prenatally, affecting the maturation of the infant immune system and increasing a child's risk for developing asthma. Although the relation with prenatal antibiotics does not hold for wheezing in this study, there might be a trend that could be delineated further within a larger cohort study.

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