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The Relationship between Prenatal Antibiotic Use and Asthma in At-Risk Children

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Introduction

Prevalence of asthma has doubled in developed countries over the last 30 years¹. The factors causally driving these temporal increases remain essentially unknown, with poor and minority children in the United States suffering a disproportionately higher burden of asthma morbidity². Concurrent increases in antibiotic use to treat infections in children have led to speculation of a causal relationship. Retrospective studies have shown strong

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Contributor's Statement Page

Brittany Lapin: Brittany conceptualized and designed the study, conducted the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Julie Piorkowski: Julie coordinated and managed the database, conceptualized the study, critically revised the manuscript, and approved the final manuscript as submitted.

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Victoria Persky: Dr. Persky conceptualized and designed the study, critically revised the manuscript, and approved the final manuscript as submitted.

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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 may alter development of the immune system leading to a greater risk of atopy¹². Data have suggested that antibiotics in utero may 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 may have a long-term impact on the risk of developing subsequent atopic disease^{7,15,16}. Research utilizing prospective birth cohorts has been limited, especially among impoverished urban residents.

Controlling for maternal and child confounders within a prospective study, we investigated the effects of prenatal antibiotic use with the subsequent development of asthma by year three and wheezing in the third year within a high-risk urban cohort. Since this relationship may be confounded by maternal asthma or by antibiotic use in the child, we investigated the associations within subsets of mothers without asthma and within children who did not use antibiotics. We 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 of age through age three years. The intervention did not address antibiotic utilization. All women in the study received general health education. Half of 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 have information concerning systemic antibiotic use and were followed through the child's third year of life. The primary endpoints of the study are asthma diagnosis by year three 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 endpoints include eczema, as well as other respiratory symptoms in the third year: exercise induced wheezing, sleep disturbed by wheezing, wheezing without a cold, and emergency room visits for breathing problems. Development of the primary endpoint of wheezing and the secondary endpoints of eczema and other respiratory symptoms were determined by a positive response within the year prior to their third year visit based on the following questions: "Has your child's chest sounded wheezy or whistling?"; "Has a doctor 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 room 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 4–5 months of gestation, and at 7–8 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 reason for antibiotic use in the child was separated into respiratory infections versus non-respiratory infections. If both infections 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 use. Frequency counts and percentages are shown for categorical variables and compared using chi-square or Fisher's exact test. Continuous variables are presented as means with standard deviations and were compared using t-test. Multivariable logistic regression models for asthma and wheezing were constructed by including all variables predictive at the univariate level ($p < 0.10$), as well as study intervention. Effect modification was evaluated using interaction terms (with $p < 0.20$ considered potential interaction) between probable confounders and prenatal antibiotic use, as well as 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 three separate adjusted regression models investigated the effect of antibiotics utilized during these different trimesters of pregnancy on asthma and wheezing. Table footnotes list variables included in adjustment. Statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc, 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 and three (35%) mothers used antibiotics during their pregnancy. The majority of mothers in the study were of Mexican ancestry (68%) and the average age was 26. There were no differences between antibiotic use by maternal age, Mexican ancestry, smoking status, acetaminophen or ibuprofen use, or infections or fevers. Mothers who took antibiotics during pregnancy were more likely to also take vitamins (37% vs. 24%, $p = 0.02$). Prenatal antibiotic use was also significantly higher within mothers with asthma (44% vs. 27%, $p < 0.01$). Child characteristics, including low birth weight and prematurity, did not differ by prenatal antibiotic use. There were also no differences in first year exposures of antibiotic or acetaminophen use within children born to

mothers who took antibiotics. First year ibuprofen use as well as respiratory infections were higher within children whose mothers took antibiotics (44% vs. 32%, $p=0.052$ and 96% vs. 91%, $p=0.09$, respectively).

Third year outcomes varied by antibiotic use during pregnancy (Table 2). Asthma diagnosed by year three occurred in 23 (22%) children born to mothers who took antibiotics versus 21 (11%) children born to mothers who did not take antibiotics ($p<0.01$). Wheezing occurred in 28% of children whose mothers took antibiotics versus 19% with no antibiotics ($p=0.054$). Eczema in year 3, as well as all respiratory symptoms in year 3, was 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 three included any antibiotic use during pregnancy (aOR: 3.12; 95% 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 for asthma diagnosis. The 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 ($p=0.048$ and $p=0.018$, 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 three remained intact within a subset analysis of mothers with no history of asthma (aOR: 5.75; 95% CI: 1.78, 18.60, $p<0.01$) and within a subset of children who did not use antibiotics in the first year (aOR: 3.62; 95% CI: 1.09, 12.05, $p=0.04$) (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 second to third trimester. Analyses of the effects of the timing of prenatal antibiotic use on asthma and wheezing showed the relationship 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

Our study found that prenatal systemic antibiotic use was a significant predictor of incident asthma, and weakly associated with wheezing, in at-risk children by age three after controlling for confounders. Similarly, McKeever et al. utilized a birth cohort to show a relationship between prenatal antibiotics exposure and an increase in the child's risk of allergic disease⁷. Several other studies have also shown an increased risk of asthma and wheezing with pre- and perinatal antibiotic use^{5,6,8,10,19}. To our knowledge, only one cohort

study did not find an association between prenatal antibiotic exposure and wheeze or atopic sensitization, but they did find an association between eczema and prenatal antibiotic use²⁰.

The association between prenatal antibiotic use and subsequent asthma suggests an etiologic relationship since the issue of reverse causality is naturally avoided. However, the relationship could be confounded by maternal asthma, infections, or smoking, premature birth, or antibiotic use in infancy as mothers who use antibiotics may be more apt to ask for antibiotics for their infants⁵. Our study attempted to identify and minimize the sources of confounding through model adjustment, effect modification, and subgroup analyses. In our cohort we found no correlation between infant antibiotic use and maternal antibiotic use. We showed there was no effect modification by maternal asthma, respiratory infections, or smoking within multivariable models of asthma and wheezing. In our subset analyses within mothers without asthma and within infants who did not take antibiotics, prenatal antibiotics remained a significant predictor of asthma. The association with wheezing, however, was reduced. Due to the large number of maternal and child infections, we 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 asthma⁸. These investigators were able to replicate the findings in a subgroup of mothers using antibiotics for non-respiratory infections. They concluded the effect was not confounded by the mother's asthma or infections and could be due to a disturbed bacterial ecology which may 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 our study. These results are in agreement with a cohort study which also found that antibiotic use in the second and third trimester only were associated significantly with persistent wheezing in one year olds⁹. Additionally, studies have found that the composition of maternal vaginal and intestinal bacteria was 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 pregnancy¹⁵. Aagard et al. recently published a study demonstrating the placental microbiome is affected by maternal antenatal infections¹⁴. 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 may increase a child's risk of developing asthma.

Our study design offered many pertinent risk factors for childhood asthma and wheezing, and the prospectively collected measures 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. There are some limitations with this study, however. 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 which is difficult to critically assess before age 6¹. Our study included diagnoses prior to age three when the nature of the

disease progression may still be unpredictable. Since there was a high rate of infections in the mothers and children, there may be a co-variation effect between infections and antibiotic use that we 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 we do not have access to the number of days antibiotics were taken or the reason antibiotics were taken by the mothers. Nor do we know the types of antibiotics used in either the children or the pregnant mothers. Broad-spectrum antibiotics became more prevalent in the 1980s and may alter microbiomes more than the narrower-spectrum antibiotics used in the past²¹. The study findings may be limited to certain types of antibiotics, which should be investigated further. Finally, we do not have information on confounders such as chorioamnionitis during pregnancy, or information on childbirth such as caesarean section which may be associated with prophylactic use of antibiotics.

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

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Table 1

Maternal and child characteristics by prenatal antibiotic use (n=298)

	Total N (%)	Prenatal Antibiotic Use N (%)	No Antibiotic Use N (%)	P-Value
Total Number	298	103 (34.6)	195 (65.4)	
Study Intervention	148 (49.7)	51 (49.5)	97 (49.7)	0.97
Maternal Characteristics during Pregnancy				
Maternal Age (Years) –Mean (SD)	25.9 (5.9)	26.0 (6.3)	25.8 (5.7)	0.78
Mexican Ancestry	201 (67.5)	66 (64.1)	135 (69.2)	0.37
Any Smoking	30 (10.1)	13 (12.6)	17 (8.7)	0.29
Any Acetaminophen	204 (68.7)	74 (71.8)	130 (67.0)	0.39
Any Ibuprofen	42 (14.1)	12 (11.7)	30 (15.4)	0.38
Any Infections	270 (90.6)	94 (91.3)	176 (90.3)	0.78
Any Respiratory Infections	258 (86.6)	87 (84.5)	171 (87.7)	0.44
Any Fevers	148 (49.8)	58 (56.3)	90 (46.4)	0.10
Vitamin Use	84 (28.6)	38 (36.9)	46 (24.1)	0.020
Mother has Asthma	98 (32.9)	45 (43.7)	53 (27.2)	0.004
Child Characteristics				
First Born Child	108 (36.2)	39 (37.9)	69 (35.4)	0.67
Male Gender	155 (52.0)	58 (56.3)	97 (49.7)	0.28
Low Birth Weight <2500g	25 (8.4)	10 (9.7)	15 (7.7)	0.55
Premature Birth <36 weeks	14 (4.7)	4 (3.9)	10 (5.1)	0.63
Breast Fed	264 (88.6)	92 (89.3)	172 (88.2)	0.77
First Year of Life Exposures				
Exposed to Cigarette Smoke in the Home	53 (17.8)	22 (21.4)	31 (15.9)	0.24
Any Antibiotics	161 (54.0)	61 (59.2)	100 (51.3)	0.19
Any Acetaminophen	284 (95.6)	96 (94.1)	188 (96.9)	0.25
Any Ibuprofen	108 (36.2)	45 (43.7)	63 (32.3)	0.052
Any Infections	285 (95.6)	101 (98.1)	184 (94.4)	0.14
Ear Infections	111 (37.3)	41 (39.8)	70 (35.9)	0.51
Respiratory Infections	276 (92.6)	99 (96.1)	177 (90.8)	0.09
Any Fevers	86 (28.9)	35 (34.0)	51 (26.2)	0.16

Table 2Child 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)	0.008
Wheezing in Year 3	65 (21.8)	29 (28.2)	36 (18.5)	0.054
Other Symptoms in Year 3				
Exercise Induced Wheezing	35 (11.7)	17 (16.5)	18 (9.2)	0.06
Sleep Disturbed by Wheezing	26 (8.7)	14 (13.6)	12 (6.2)	0.03
Wheezing without a Cold	27 (9.1)	14 (13.6)	13 (6.7)	0.048
ER Visit for Breathing Problems	46 (15.4)	21 (20.4)	25 (12.8)	0.09
Eczema	58 (19.5)	23 (22.3)	35 (18.0)	0.36

^a Chi-square tests compare third year outcomes by prenatal antibiotic use.

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

	OR [95% CI]	P-Value
Study Intervention	0.96 [0.44, 2.09]	0.92
Maternal Mexican Ancestry	0.37 [0.17, 0.82]	0.014
Any Smoking in Pregnancy	2.34 [0.86, 6.35]	0.10
Any Antibiotics in Pregnancy	3.12 [1.44, 6.77]	0.004
Any Ibuprofen in Pregnancy	1.37 [0.52, 3.58]	0.53
Mother has Asthma	2.66 [1.22, 5.84]	0.015
Child Exposed to Smoke in the Home	0.79 [0.30, 2.07]	0.63
Child took Antibiotics for Respiratory Infections	2.53 [1.67, 3.82]	<0.001

^aVariables include study intervention as well as significant variables (p<0.10) from univariate analysis.

Table 4

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

	OR [95% CI]	P-Value
Study Intervention	0.75 [0.40, 1.39]	0.36
Maternal Mexican Ancestry	0.61 [0.31, 1.19]	0.14
Any Smoking in Pregnancy	2.83 [1.20, 6.70]	0.018
Any Antibiotics in Pregnancy	1.76 [0.94, 3.28]	0.08
Any Ibuprofen in Pregnancy	1.80 [0.81, 4.03]	0.15
Mother has Asthma	1.43 [0.75, 2.71]	0.28
Child Low Birth Weight <2500g	2.56 [1.01, 6.50]	0.048
Child Breast Fed	0.45 [0.19, 1.09]	0.08
Child Exposed to Smoke in the Home	1.56 [0.73, 3.34]	0.27
Child takes Antibiotics for Respiratory Infections	1.33 [0.97, 1.84]	0.08

^a Variables include study intervention as well as significant variables (p<0.10) 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]	0.004	1.50 [0.65, 3.46]	0.34
No First Year Antibiotics (n=137)	3.62 [1.09, 12.05]	0.036	1.61 [0.60, 4.31]	0.35

^a Adjusted analysis includes study intervention as well as significant variables (p<0.10) 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.

Table 6Three 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 in Pregnancy	3.12 [1.44, 6.77]	<0.01	1.76 [0.94, 3.28]	0.08
Model 2: Antibiotics in the First Trimester	2.23 [0.90, 5.49]	0.08	1.32 [0.58, 3.02]	0.50
Model 3: Antibiotics in the Second to Third Trimester	3.33 [1.52, 7.27]	<0.01	1.77 [0.92, 3.39]	0.09

^a Adjusted analysis includes study intervention as well as significant variables (p<0.10) 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.