

THE PRENATAL USE OF ANTIBIOTICS AND THE DEVELOPMENT OF ALLERGIC DISEASE IN ONE YEAR OLD INFANTS. A PRELIMINARY STUDY

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Abstract

Objectives: Recent research has suggested that the protective effect of natural infections may be due to their influence on the development of the immune system in early life. The purpose of the study was to determine whether maternal use of antibiotics during pregnancy is a risk factor for wheezing and allergy in early infancy. **Materials and Methods:** Non-smoking women, aged 18–35 years, were enrolled in 2000/2001 from prenatal clinics during the second or third trimester of pregnancy. After delivery, newborns were followed-up every three months over one year and trained interviewers conducted a standardized interview with mothers on infants’ health at each visit held every three-month. In total, 102 infants were followed over a one-year period and questionnaires on the use of various medications during pregnancy and potential risk factors for allergy and asthma were completed. Relative risk for persistent wheezing (9+ days over the follow-up) adjusted for potential confounders was significantly associated with the duration of antibiotic therapy, however, it was significant only if the antibiotic treatment took place in the second and the third trimester. **Results:** The adjusted relative risk was increasing by 14% with each day of using antibiotics compared with the reference group (RR = 1.14; 95%CI: 1.01–1.27). When usage of antibiotics was regarded as a dichotomous variable in the logistic model (cut-off point at 5 days), the estimated adjusted risk for persistent wheezing was 4.42 (95%CI: 1.05–18.8). The risk for hay fever due to exposure to antibiotics was 2.65 (95%CI: 1.03–6.81) and a corresponding estimate for eczema was 2.30 (95%CI: 0.91–5.80). **Conclusions:** The study suggests that maternal use of antibiotics during pregnancy may prove to be a risk factor for persistent wheezing and development of allergy in early infancy.

Key words: Epidemiology, Perinatal exposures, Asthma, Hay fever, Eczema

INTRODUCTION

There is a good body of evidence that the prevalence of asthma and allergic diseases has increased markedly in the developed world during the second half of the 20th century, particularly in children and young adults [1–3]. The recent analysis of hospitalization trends in asthma among children in Poland [4] showed a consistent upward trend over the last two decades, and in the years 1984–1996, the rates doubled for both genders. Among boys the rates

were 1.6 times higher than in girls. On average, the rates increased annually by 12% for boys and 11% for girls. The fastest increase was noted in the youngest children aged less than 4 years.

One of the hypotheses trying to explain this trend over time is often linked with the effects of the “Western lifestyle”. The hygiene context of this hypothesis is associated with the decreasing prevalence of childhood infections, which are assumed to exert a protective effect for the develop-

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ment of asthma and allergy. It has been suggested that the increase in allergy-related diseases is in part due to reduced microbial exposure in early childhood, increased immunization, improved sanitary conditions and smaller family size [5–14]. Another important factor possibly related to the reduced exposure to infectious agents is the use of antibiotics in early childhood [15].

Recent research has suggested that the protective effect of natural infections may be due to their influence on the development of the immune system in early life [16–19]. Since infants who subsequently become allergic have an altered immune response at birth, it should draw our attention to prenatal factors that can influence the development of the allergic phenotype.

Beside transplacental sensitization [20], one of potential candidates may be prenatal exposure to antibiotics that may modify microbial exposure and development of the immune system. This may subsequently have a long-term impact on the risk of developing allergic diseases.

In this study, we used a birth cohort of 102 infants in order to investigate the relationship between antibiotic treatment of infections during pregnancy and the incidence of asthma, eczema, and hay fever in the early infancy.

MATERIALS AND METHODS

This study used the data from the Kraków birth cohort of children established earlier as a part of the collaborative study with the Columbia University in New York City. The design of the study and the detailed selection of the population have been described previously [21]. In brief, between November 2000 and September 2002, a total of 294 women recruited from ambulatory prenatal clinics, and healthy pregnant women in the first and the second trimester of pregnancy were eligible for the study. The enrolment included only non-smoking women with singleton pregnancies at the age of 18–35 years, without illicit drug use and HIV infection, free from chronic diseases, such as diabetes or hypertension, and living in Kraków for at least one year prior to pregnancy. Recruited women were interviewed and given a description of the study and requirements for participation in

the project. Upon enrollment, a detailed questionnaire was administered to each subject at the entry to the study to solicit information on demographic data, house characteristics, date of the last menstrual period (LMP), medical and reproductive history, use of prescribed medications during pregnancy, occupational hazards, alcohol consumption, and smoking habits of household members. All subjects gave informed consent and the study design was approved by the Ethical Committee of the Jagiellonian University.

The data on prescriptions of antibiotics were collected in the course of the prenatal interviewing of pregnant women before the delivery. Questions on the use of antibiotics during pregnancy were related to the type of antibiotics used, trimester of pregnancy, and duration of antibiotic therapy.

After delivery, newborns were followed-up every three months over one year and trained interviewers conducted a standardized interview with mothers on infants' health at each visit held every three-month. In total, 102 infants were followed over a one-year period and questionnaires on the use of various medications during pregnancy and potential risk factors were completed. The results of our study based on the subsample of the enrolled subjects are well represented in regard to the prenatal use of antibiotics. In the study group, one third of the mothers were prescribed one or more courses of antibiotics during pregnancy, and 11% of women had antibiotic treatment in the first trimester, 17% in the second trimester, and 13% in the third trimester. The corresponding frequencies of prenatal antibiotics usage in the sample, not included in the analysis, were 14%, 15% and 15%.

Information about wheezing symptoms was derived from the question "has your infant ever in the last three months had wheezing?" If "yes", "how many episodes and over how many days the symptoms occurred?" Persistent wheezing was regarded if symptoms were present at least 9 days over the follow-up. Questions about allergy symptoms were "has your child ever in the last three months had hay fever?" and "has your child ever in the last three months had eczema?"

Statistical analysis

The use of antibiotics was compared with regard to the outcome variables, such as wheezing, hay fever and eczema. To identify potential confounders, association between population characteristics and outcome variables were investigated using 2 by 2 tables. Differences between subgroups with and without antibiotics use were tested by the Chi-square statistics. Multiple logistic regression models were used to analyze the association between the use of antibiotics and the occurrence of wheezing and allergy, with adjustment to potential confounding variables. Two approaches were applied in the analysis of the effect of prenatal antibiotics on the occurrence of wheezing and allergy. In the first approach, antibiotics medication was used as a continuous variable expressed in days of antibiotic use, and in the second approach as a binary variable (shorter and longer use of antibiotics at the cut-off point of 5 days). Exposure to prenatal antibiotics was initially examined in a series of univariate analyses as binary “exposed or unexposed” indicator variables and then as ordered categorized variables by the duration of antibiotic use and by trimester of pregnancy in which antibiotics were used. As association between the use of antibiotics and wheezing or hay fever may be due to respiratory infections in the follow-up, all regression analyses were additionally adjusted for respiratory infections in the first year of life. Statistical analyses were performed with BMDP software for Windows [22].

RESULTS

The completed one-year cohort of 102 infants comprised slightly less males than females (48 vs. 52%). Characteristics of the groups of users and non-users of antibiotics during pregnancy is presented in Table 1. In total, about one third of the mothers were prescribed one or more courses of antibiotics during pregnancy, and 11% of women had antibiotic treatment in the first trimester, 17% in the second trimester, and 13% in the third trimester. Mothers who used antibiotics in pregnancy reported higher prevalence of allergy than those who did not confirm antibiotic treatment (38.7 vs. 22.5%, $P = 0.092$) and more

Table 1. Characteristics of the infants by perinatal exposure to antibiotics (whenever in pregnancy)

Variables	Antibiotics (-) n = 71 (%)	Antibiotics (+) n = 31 (%)	Significance level
Age of mother (years) mean (SD)	28.1 (3.6)	26.2 (4.0)	$P = 0.018$
Education level of mother			$\text{Chi}^2 = 6.377$; $P = 0.271$
Elementary	14	10	
Secondary	28	35	
Higher	58	55	
Parity			$\text{Chi}^2 = 1.793$; $P = 0.180$
0	43.7	58.1	
1+	56.3	41.9	
Allergy in mother	22.5	38.7	$\text{Chi}^2 = 2.834$; $P = 0.092$
Allergy in father	16.9	22.6	$\text{Chi}^2 = 0.459$; $P = 0.498$
Boys	50.7	41.9	$\text{Chi}^2 = 0.664$; $P = 0.415$
Gestational age (weeks) mean (SD)	39.3 (2.0)	39.2 (1.83)	$P = 0.894$
Wheezing (episodes)			$\text{Chi}^2 = 3.466$; $P = 0.325$
0	81.7	71.0	
1	11.3	19.4	
2+	7.0	9.6	
Wheezing (days)			$\text{Chi}^2 = 2.970$; $P = 0.396$
0	81.7	71.0	
1–3	4.2	3.2	
4–9	4.2	3.2	
9>	9.9	22.6	
Respiratory infections (number of episodes)			$\text{Chi}^2 = 4.322$; $P = 0.229$
0	31.0	12.9	
1	7.0	9.2	
2+			
Hay fever	46.5	61.3	$\text{Chi}^2 = 1.894$; $P = 0.168$
Eczema	29.6	41.9	$\text{Chi}^2 = 1.483$; $P = 0.223$

SD – standard deviation; Chi^2 – Chi square value; P – probability level;
n – sample size.

frequently reported wheezing symptoms in their infants (29.0 vs. 18.3%). In wheezy children, the symptoms over one-year lasted 16.7 days on average (95%CI: 8.2–25.4). While the mothers of infants without wheezing reported to have used antibiotics for 2 days, those of infants presenting wheezing symptoms reported the average use of antibiotics for at least 5 days. Wheezing lasting at least 9 days/year was reported in 22.6% of infants exposed to antibiotics compared to 9.9% of those

non-exposed. Hay fever in infants was also more frequently reported by mothers who used antibiotics than by non-users (61.3 vs. 46.5%) and the corresponding frequency of eczema ever occurring in the follow-up was 41.9 vs. 29.6%. There were no significant differences in characteristics of mothers of children with persistent wheezing, hay fever, or eczema except for prenatal use of antibiotics (Table 2). Persistent wheezing and allergy (hay fever, eczema) occurred slightly more frequently in boys than in girls. Antibiotic treatment over at least 5 days was much more frequently reported in the group of infants with wheezing (50.0 vs. 23.9%, $P = 0.036$) and hay fever (36.5 vs. 18.0%, $P = 0.036$) or eczema (38.2 vs. 22.1%, $P = 0.084$). There was evident association between persistent wheezing and allergy and the duration of antibiotic therapy (Table 3), however, it was significant only in the group of infants with wheezing ($P = 0.046$).

Relative risk (RR) of persistent wheezing (at least 9 days) adjusted for potential confounders (maternal education, child's gender, maternal allergy, number of respiratory infections) increased with increasing duration of antibiotic therapy, however, it was significant only if the treatment took place in the second or the third trimester of pregnancy (Table 4). In the total sample, the adjusted relative risk was increasing by 14% with each day of prenatal treatment with antibiotics as compared to the reference group (OR = 1.14; 95%CI: 1.01–1.27). The statistical model was stable, and adjusted for additional variables like maternal age, environmental tobacco smoke (ETS) or paternal allergy did not affect the results.

In the second approach (Table 5), we applied the same multiple logistic model, but duration of antibiotic therapy was treated as a dichotomous variable (cut-off point at 5 days). The adjusted RR for persistent wheezing and antibiotic

Table 2. Characteristics of the study sample by persistent wheezing (9+ days in a year), allergy, hay fever, and eczema

Variables	Wheezing n = 14		Hay fever n = 52		Eczema n = 34	
	–	+	–	+	–	+
Age of mother (years)	29.8 (3.8)	25.9 (3.4) $P = 0.088$	27.8 (4.0)	27.3 (3.7) $P = 0.437$	27.5 (4.0)	27.6 (3.4) $P = 0.884$
Gestational age (weeks)	39.3 (1.9)	39.1 (2.1) $P = 0.802$	39.2 (2.2)	39.4 (1.7) $P = 0.597$	39.1 (2.0)	39.6 (1.8) $P = 0.284$
Boys (%)	45.5	64.3 $\text{Chi}^2 = 1.716$ $P = 0.190$	54.0	42.3 $\text{Chi}^2 = 1.396$ $P = 0.237$	44.1	55.9 $\text{Chi}^2 = 1.257$ $P = 0.262$
Allergy in mother (%)	25.0	42.9 $\text{Chi}^2 = 1.933$ $P = 0.164$	22.0	32.7 $\text{Chi}^2 = 1.463$ $P = 0.226$	25.0	32.4 $\text{Chi}^2 = 0.615$ $P = 0.432$
Allergy in father (%)	17.1	28.6 $\text{Chi}^2 = 1.058$ $P = 0.303$	18.0	19.2 $\text{Chi}^2 = 0.025$ $P = 0.873$	19.1	17.7 $\text{Chi}^2 = 0.032$ $P = 0.857$
Respiratory infections (episodes)						
0	69.3	50.0	68.0	65.4	67.7	64.7
1	26.1	21.4	28.0	23.1	23.5	29.4
2+	4.5	28.6 $\text{Chi}^2 = 9.670$ $P = 0.021$	4.0	11.5 $\text{Chi}^2 = 2.115$ $P = 0.549$	8.8	5.9 $\text{Chi}^2 = 0.587$ $P = 0.899$
Use of antibiotics whatever the doses (%)	27.3	50.0 $\text{Chi}^2 = 2.949$ $P = 0.086$	24.0	36.5 $\text{Chi}^2 = 1.894$ $P = 0.169$	26.5	38.2 $\text{Chi}^2 = 1.482$ $P = 0.233$
Use of antibiotics (5+ days) (%)	23.9	50.0 $\text{Chi}^2 = 4.399$ $P = 0.036$	18.0	36.5 $\text{Chi}^2 = 4.399$ $P = 0.036$	22.1	38.2 $\text{Chi}^2 = 2.978$ $P = 0.084$

Chi^2 – Chi square value; P – probability level; Standard deviation (SD) in parenthesis.

treatment lasting 5 or more days was 4.42 (95%CI: 1.05–18.8). Tables 6 and 7 present the adjusted relative risk estimates for the occurrence of hay fever and eczema in infants ever observed in the follow-up period. The estimated risk for

Table 3. Association between persistent wheezing, allergy and days of prenatal use of antibiotics

Prenatal use of antibiotics	Persistent wheezing	Hay fever	Atopic dermatitis
0 (n = 71)	9.9%	46.5%	29.6%
1–5 days (n = 9)	11.1%	55.6%	22.2%
6+ (n = 22)	27.3%	63.6%	50.0%
	Chi ² (trend), df = 1 P = 0.046	Chi ² = 2.06, df = 1 P = 0.151	Chi ² = 2.60, df = 1 P = 0.107

Chi² – Chi square value; df – degree of freedom; P – probability level.

Table 4. Relative risk (RR) for wheezing due to antibiotics used in pregnancy trimesters, adjusted for maternal education level, child’s gender, maternal allergy, and the number of respiratory infections

Trimester of pregnancy	OR and 95% CL for dose of antibiotics (days of treatment)	P
First	1.09 (0.90–1.31)	0.354
Second	1.13 (0.99–1.29)	0.066
Third	1.28 (1.01–1.63)	0.041
Second or third	1.18 (1.04–2.94)	0.032
Total (whenever in pregnancy)	1.14 (1.01–1.27)	0.024

OR – odds ratio; CL – confidence limits.

Table 5. Multiple logistic regression for wheezing (9+ days) and prenatal use of antibiotics (5+ days over pregnancy) adjusted for potential confounders
Chi²(5) = 19.767; P = 0.001;

Model estimates	Maternal education	Child’s gender	Respiratory infections	Maternal allergy	Use of antibiotics (5+ days)
Wald’s statistics	5.405	1.916	7.394	3.451	4.234
P	0.020	0.166	0.006	0.063	0.039
OR *	0.722	0.392	3.309	4.360	4.415
-95%CL	0.547	0.102	1.381	0.904	1.053
+95%CL	0.953	1.500	7.926	21.029	18.500

* Adjusted for the other variables in the table: maternal education (0 – elementary, 1 – secondary, 2 – higher), child’s gender (1 – boys, 2 – girls), respiratory infections over the pregnancy (number of episodes), maternal allergy (0 – no allergy, 1 – allergy present), prenatal use of antibiotics (0 – no prenatal exposure or use of antibiotics for 4 days or less, 1 – use of antibiotics for 5 days or longer);
–95%CL – lower 95% confidence limit; OR – odds ratio;
+95%CL – upper 95% confidence limit.

Table 6. Multiple logistic regression for hay fever (whenever in the follow-up) and prenatal use of antibiotics (5 days or more during pregnancy) adjusted for potential confounders
Chi²(3) = 7.7932; P = 0.050

Model estimates	Maternal education	Child’s gender	Use of antibiotics (5 days or more)
Wald’s statistics	2.107	1.234	4.202
P	0.146	0.266	0.040
OR	0.893	1.581	2.650
-95%CL	0.765	0.697	1.031
+95%CL	1.042	3.588	6.809

Maternal education: 0 – elementary, 1 – secondary, 2 – higher;
–95%CL – lower 95% confidence limit; OR – odds ratio;
+95%CL – upper 95% confidence limit.

Table 7. Multiple logistic regression for eczema (whenever in the follow-up) and prenatal use of antibiotics (5+ days during pregnancy) adjusted to potential confounders
Chi²(3) = 4.6384, P = 0.200

Model estimates	Maternal education	Child’s gender	Use of antibiotics
Wald’s statistics	0.167	1.590	3.210
P	0.681	0.207	0.073
OR	1.033	0.578	2.302
-95%CL	0.881	0.244	0.914
+95%CL	1.211	1.368	5.800

Maternal education: 0 – elementary, 1 – secondary, 2 – higher;
–95%CL – lower 95% confidence limit; OR – odds ratio;
+95%CL – upper 95% confidence limit.

using antibiotics (dichotomous variable) and hay fever was found to be 2.65 (95%CI: 1.03–6.81) and the corresponding estimate for eczema was 2.30 (95%CI: 0.91–5.80).

DISCUSSION

Our results suggest that prenatal exposure to antibiotics is associated not only with the increased risk of the child’s persistent wheezing, but also with the development of hay fever and eczema, however, to a smaller extent. Relative risk for persistent wheezing (at least 9 days) adjusted for potential confounders was related to the duration of antibiotic therapy, although it was significant only if antibiotic therapy was applied in the second or in the third pregnancy trimester. The adjusted risk of wheezing was increasing by 14% with each day of prenatal use of antibiotics as compared to the reference group (OR = 1.14; 95%CI:

1.01–1.27). If the use of antibiotics during pregnancy was treated as a binary variable (cut-off point at 5 days), the estimated risk of persistent wheezing due to prenatal use of antibiotics reached 4.42 (95%CI: 1.05–18.8). The estimated risk for hay fever was 2.65 (95%CI: 1.03–6.81) and the corresponding estimate for eczema was 2.30 (95%CI: 0.91–5.80).

The study has some limitations, which mainly result from the fact that the prenatal use of antibiotics and the occurrence of symptoms in infants were based only on interviews. Neither information about specific medical indications for prescription of antibiotics nor data on the severity of given infections were collected. The interviews with mothers on wheezing may be biased with the tendency to over-reporting by those who are possibly preoccupied with the infant's health. It was difficult to exclude these potential confounding factors, therefore, symptoms, which recurred over the study period and lasted at least nine days were considered in our analysis.

Our research results are in good agreement with the recently published paper by McKeever et al. [23] who studied the impact of change in microbial exposure during pregnancy on the child's risk for developing allergic disease. Using a birth cohort of 24 690 children derived from the general practice research database, the authors investigated a number of perinatal exposures and their effects on the incidence of asthma, eczema, and hay fever. The findings showed that exposure to antibiotics *in utero* was associated with an increased risk of asthma in a dose-related manner (more than two courses of antibiotics compared with none). The mean adjusted hazard ratio was 1.68 (95%CI: 1.51–1.87), and similar ratios were found for eczema – 1.17 (95%CI: 1.06–1.29) and hay fever – 1.56 (95%CI: 1.22–2.01). Exposure to a wide range of infections *in utero* was also associated with a small increase in the risk for developing allergic disease.

The findings of both these studies on the role of antibiotic therapy during pregnancy in the etiology of allergic disease in infants are consistent with the hygiene hypothesis, which suggests the protective effect of natural infections due to their influence on the development of the immune system in early life [19,20,23,24]. Reducing exposure to in-

fectious agents may distort the balance between T cell sub-populations from normal Th1 cell responses to atopic Th2 cell responses, including an increased production of IgE. Moreover, a lower Th1-like immune response in early life may be a marker of an inherited predisposition to allergic disease. Therefore, it is understandable that the effects of antibiotics in early life could occur particularly in children with a genetic predisposition to an allergy-type of immune response.

CONCLUSIONS

The study suggests that exposures, which reduce and modify microbial load during pregnancy may increase a child's risk for developing allergic disease. To what extent the results may have practical implications for prevention of allergic diseases is the problem to be further elucidated.

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