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Prenatal antibiotic exposure increases the risk of infant atopic dermatitis: data from a Greek cohort

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Key words

Antibiotics; atopic dermatitis; cesarean section; children; prenatal.

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Impact statement

Prenatal use of antibiotics was associated with an increased risk of infant atopic dermatitis only when antibiotics were given by intravenous route.

Summary

Background. *The human microbiome is important due to the impact it has on host immunologic development and allergy-associated diseases. This study aimed to investigate the impact of prenatal exposure to antibiotics on the incidence of atopic dermatitis (AD) in children at 18 months of age.* ***Methods.*** *Mothers were interviewed at baseline, in the maternity ward and by phone questionnaire after 18 months. Demographic data, mode of delivery, yoghurt consumption, antibiotic and other drug use during pregnancy, atopic history, diagnosis of AD and history of infections in the offspring were noted.* ***Results.*** *385 mothers were interviewed at baseline. 231 (60%) mothers with 236 children responded at follow up. Cesarean section was reported in 116 (50.2%) deliveries while antibiotic use during pregnancy in 55/231 (23.8%) women. 43/236 (18.22%) infants were diagnosed with AD. Intravenous antibiotic use was associated with a 7.7 increased risk of AD diagnosis in the offspring (95%CI 1.23-48.27, p = 0.029). An increased odd for AD was recorded for mothers 30-40 years of age (OR 4.50, 95%CI 1.08-18.7, p = 0.039). No significant association between cesarean section and AD (p = 0.70) was recorded. In multivariate analysis, reported food allergy (OR 8.03, 95%CI 2.30-27.97, p = 0.001) and otitis media episodes in children (OR 3.76, 95%CI 1.60-8.83, p = 0.002) were significantly associated with AD diagnosis.* ***Conclusions.*** *An increased risk of AD was recorded only when antibiotics were given prenatally by intravenous route and in women between 30-40 years of age. Children with food allergy had an increased risk for AD. The relatively high percentage of cesarean sections was not a risk factor for AD.*

Introduction

The human microbiome, starting *in utero*, is extremely important for the normal immune and metabolic function later in life, according to Barker's Hypothesis for the developmental origin of chronic diseases (1). Environmental factors that affect microbial exposure during pregnancy, birth, and early infancy, such as antibiotic use, mode of delivery, breastfeeding and early life feeding, can influence the infant gut microbiome. Reduction in the abundance and diversity of microbial communities, described as dysbiosis and caused by changes in modern life (increased exposure to urban environment, cesarean sections, antibiotic use), is associated with the pathogenesis of allergic diseases, *i.e.*, asthma, rhinitis, and eczema (1, 2).

Placental microbiome is formulated during normal-term, healthy pregnancies and is mainly composed by non-pathogenic commensal bacteria. Direct presentation of maternal bacterial components to the fetus has been recognized as a potential route for immune imprinting. Intestinal B and T cells present from 12-14 weeks of gestation and, at birth, up to

5-10% of neonatal T cells are differentiated into either memory or effector cells, suggesting activation *in utero* (3). Moreover, prenatal environmental exposures may alter gene expression via epigenetic mechanisms. Maternal exposure to higher endotoxin levels in farms during pregnancy confers protection against sensitization and allergic diseases and has been associated with increased DNA demethylation of the Foxp3 locus in cord blood cells and enhanced neonatal regulatory T-cell function (3). A recent systematic review concluded that individuals with atopic dermatitis (AD) − the earliest manifestation of allergic diseases − have different gut and skin microbial compositions compared to individuals without AD (4). Dysbiosis reflects and may explain the imbalance of the immune system towards Th2 response, resulting in an increase of allergic diseases and can be detected even before the onset of clinical signs and symptoms (5).

The increase in antibiotic use in parallel with the increase in the prevalence of allergic diseases has led to the hypothesis of a causal relationship, either by changing the natural course of infections or by altering the microbiota in various body sites (6). It has been shown that even prenatal antibiotic use, especially when used in both the 1st, 2nd and 3rd trimester, is associated with atopic dermatitis, mainly in the presence of maternal atopy (4, 6-9). Recent meta-analysis concluded that maternal exposure to antibiotics is associated with eczema in the offspring by the age of one year, although such an effect might be even more prolonged (10). Most recent studies also confirm that association between prenatal antibiotic use and atopic dermatitis that can depend on the trimester of pregnancy and is confounded by familial factors (11, 12).

The primary outcome of our study was to investigate the impact of pregnant women's prenatal exposure to antibiotics on the incidence of AD in their offspring up to the age of 18 months, in the environment of our island, located in the southern part of Greece and Europe. Secondary outcomes included assessing the effect of several confounding factors in relation to the mother or the infant on the occurrence of AD.

Materials and methods

This was a prospective study, including mothers who gave birth to one or more children at Venizeleion General Hospital in Heraklion, a city with a population of almost 200,000 people, from January 2018 to August 2018. The study was approved by the Ethical Committee of the Hospital and a written informed consent was obtained from each mother. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The primary investigator, a pediatric allergologist, interviewed women during the first days after labor while they were still in hospital. Participants answered a questionnaire including demographic data, such as age at birth, pre-pregnancy body mass index (BMI), education level, home location; smoking in pregnancy, mode of delivery, sex; use of antibiotics (trimester, route and type of oral antibiotic − prophylactic antibiotic treatment for cesarean section not included), paracetamol and any drug use during pregnancy, birth weight of the baby, number of older siblings, family history of allergy-associated diseases, prenatal exposure to pets, and basic elements of mother's diet during pregnancy, focusing on yoghurt consumption (type, frequency).

A second telephone interview was performed when babies were 18 months old. Mothers were asked whether their child had ever been diagnosed with atopic dermatitis (AD) by a doctor. More specifically, questions involved whether their child presented any recurrent, itchy rash affecting one or more of the following areas: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes and persistently dry skin for the documentation of AD diagnosis, while age of onset, severity (frequent emollient use, any need for topical corticosteroid treatment) and present activity of AD were also recorded (9).

Breastfeeding, personal history of upper and lower respiratory infections, acute otitis media, urinary tract infections, gastrointestinal infections, admissions, antibiotic use (< 12 months and > 12 months), any wheezing episodes, any food allergy (mother-perceived or diagnosed by doctor), and current weight were also noted.

In statistical analysis, most of the variables that were analyzed were categorical, and, in majority, they were no/yes valued. Descriptive statistics were given in the form of count data (%). Regarding scale variables, descriptive statistics were given in the form of median (25^{th}-75^{th} percentile). For inference, potential associations between categorical variables were tested with Pearson's Chi-Squared test of independence. Subgroup values of scale variables were compared using Wilcoxon Rank-Sum test. A multivariate analysis was performed with logistic regression modeling and the estimation of the odds ratios was visualized with the use of a forest plot. Various predictors were excluded from the multivariate analysis, due to the multicollinearity issue. Associating potential child AD presence with respective predictors was split into 2 models (mother- *vs* child-related predictors), due to lack of degrees of freedom. Sample power analysis for the two logistic regression processes yielded to the conclusion that at least a power of 90% is achieved, given that our dataset possesses 236 subjects. Given our set of data, we achieved an effect size of 0.152 in the former regression task (with maternal predictors), and 0.250 in the latter regression task (with children's predictors), which both fall in the moderate category of effect sizes for logistic regression. Assuming that the number of the predictors is no bigger than 15, an 80% of power is achieved with 156 subjects,

and a 90% of power is achieved with 190 subjects using the R software and the "pwr" library. "rms" library was moreover used for the calculation of the pseudo R^2 for the two logistic regression models (13). All statistical tests were considered two-sided, while statistical significance was taken as $p < 0.05$. For the statistical analysis, the R software for statistical computing and the R studio IDE were used.

Results

At baseline, 385 mothers were enrolled. At re-evaluation, 231 mothers (60%) and their 236 infants (5 pairs of twins) participated, and these were analyzed at both time points. Participants and dropouts were homogenous in respect to baseline characteristics (data not shown).

AD was diagnosed in 43/236 (18.2%) of the children at the age of 18 months. In 80% of the cases, AD was considered as mild and in 20%, as moderate.

55/231 (23.81%) of mothers received antibiotics during pregnancy. Among the 48 women (87.27%) who could accurately recall, 41.66% received the antibiotic in the 3rd trimester and 33.33% in the 2nd trimester. 36/48 (75%) of the women received an oral regimen of antibiotic and in 27/36 (75%), this was a 2nd-generation cephalosporin.

116/236 (50.2%) babies were born by cesarean section. 184/231 (79.6%) of the women breastfed; however, 71% stopped after 3 months. 131/236 (55.5%) children had received antibiotic by the time of re-evaluation and 46.56% of them more than twice.

A description of all attributes regarding either the child or the mother/family is depicted in **table I**.

Multivariate analysis was performed to assess the impact of attributes on child AD occurrence. Two separate models were used, one for child attributes and one for mother attributes. Although the association of oral antibiotic use during pregnancy was not significant in respect to AD incidence, intravenous administration of antibiotics in the prenatal period was significantly associated with AD occurrence in the offspring (OR 7.70, 95%CI 1.23-48.27, p = 0.03). AD occurrence was significantly associated with mother's age > 30 years (OR 4.50, 95%CI 1.08-18.79, p = 0.04), otitis media episodes in children (OR 3.76, 95%CI 1.60-8.83, p = 0.002), reported concurrent history of food allergy in the child (OR 8.03, 95%CI 2.30-27.97, p = 0.001) and absence of child gastroenteritis (OR 0.14, 95%CI 0.02-0.74, p = 0.02). **Figures 1** and **2** visualize the outcomes of the two models.

Discussion

This study highlights a significant association between intravenous prenatal antibiotics use in pregnant women. Women over 30, given intravenous antibiotics, are at the highest risk of having offspring suffering from AD up to the 18 months of age. Furthermore, AD is significantly associated with a history of food allergy, otitis media episodes and the absence of gastroenteritis in children at the age of 18 months.

The lack of a significant association between prenatal use of antibiotics (before making a distinction by route and mother's age) and AD at a median age of 18 months in our study agrees with previous studies in the same age group reporting a positive association only under certain circumstances, *i.e.*, presence of maternal positive history of atopy and administration of antibiotics in the 3rd trimester or intrapartum antibiotic exposure > 24 h in women who gave a vaginal birth (7, 8).

The increased risk of AD in the offspring inflicted by intravenous antibiotic use can be attributed to the increased impact the latter has on the gut microbiome compared to treatment by oral route, as has been shown in animal studies for a number of antibiotics, such as ampicillin (14, 15). Moreover, the increased occurrence of AD in infants of mothers more than 30 years of age most probably reflects the fact that this age group comprises the majority of the mother population.

The increased risk of a positive food-allergy history and AD might be attributed to the well-established association between AD and food allergy, regardless of severity. Increasing evidence supports that AD predisposes to FA and not *vice versa*. AD facilitates the development of food sensitization and allergy by presentation of food allergens to the immune system through the inflamed and disrupted skin barrier in the eczematous skin. In population-based studies, the likelihood of food sensitization was up to 6 times higher in AD patients *versus* healthy controls at 3 months of age (16-18). The fact that food allergy in this study is reported by history and not confirmed by oral challenge only partially influences the association between food allergy and AD.

Although previous data confirm the positive association of AD occurrence in infants presenting with more than one otitis media episodes, it is still debated whether early infection or parallel antibiotic use causing dysbiosis influence the immune system response (19). In our study, all children with otitis media episodes received antibiotic treatment because they were < 2 years of age. Moreover, the increased odd for AD in children with no history of gastroenteritis might reflect the protective role of atopy against the occurrence of enteric infections, although data are inconclusive (20).

No statistical significance was recorded between prenatal antibiotic use and food allergy in the offspring. The first study to prove such an association was a large study in rural populations in central Europe (21). In our study, this could not be proven, potentially due to the small number of children with reported food allergy (%) and/or because our population was mainly from an urban environment.

Table I *- Characteristics of children assessed at the age of 18 months (n = 236) and mothers included in the study (n = 231).*

Characteristics	Descriptives	n (%)	Characteristics	Descriptives	n (%)
Children					
Atopic dermatitis (AD), yes	43	(18.22%)	Antibiotic use (< 18 months) (schemes)		
AD severity mild, yes	32	(80%)	1	70	(30.43%)
Gender, male	103	(43.64%)	2	29	(12.61%)
Birth weight at birth (g), median	3,255	(CI)	3	21	(9.13%)
Breastfeeding, yes	184	(79.65%)	> 3	11	(4.74%)
Wheezing episodes, yes	77	(33.19%)	Antibiotic use (< 12 months) (schemes)		
Lower respiratory infections, yes	32	(14.16%)	1	29	(17.47%)
Upper respiratory infections, yes	48	(20.69%)	2	15	(9.04%)
Acute otitis media episodes, yes	71	(30.47%)	3	3	(1.81%)
Gastrointestinal infections, yes	35	(15.15%)	> 3	2	(1.2%)
Urinary tract infections, yes	11	(4.74%)	History of food allergy, yes	15	(6.44%)
Maternal					
Antibiotic use, yes	55	(23.81%)	Route of antibiotic, IV	10	(4.5%)
Age (years), 30-40	190	(82.25%)	Pets, yes	90	(38.96%)
BMI			Animals outside house, yes	1	(0.43%)
Underweight	12	(5.56%)	Yoghurt consumption, yes	142	(61.47%)
Normal	119	(55.09%)	Yoghurt frequency		
Overweight	66	(30.56%)	1-2 times /week	20	(8.66%)
Obese	19	(8.8%)	2-3 times /week	10	(4.33%)
Home location			3-4 times /week	39	(16.88%)
Heraklion	147	(63.64%)	Every day	73	(31.6%)
Other town	62	(26.84%)	Type of yoghurt		
Village	22	(9.52%)	Cow	57	(24.68%)
Mode of birth, cesarean section	116	(50.22%)	Sheep	22	(9.52%)
Smoking, yes	93	(40.26%)	Strained	63	(27.27%)
Maternal allergies, yes	16	(6.93%)	Trimester of antibiotic use		
Other children, yes	188	(81.39%)	1st	9	(4.13%)
Number of children (median)	1		1st,3rd	1	(0.46%)
Allergies in other children	52	(27.81%)	2nd	16	(7.34%)
Paternal allergies	2	(0.87%)	2nd, 3rd	2	(0.92%)
Pregnancy paracetamol use > 1	64	(27.71%)	3rd	20	(9.17%)

The prevalence of eczema in our study is in line with percentages worldwide (22) and only slightly higher than the 14% recorded as the odd for eczema in the first year of life in the RHEA study, conducted also in Crete almost 10 years ago (23). It is also higher than the respective percentage recorded recently in central Greece (24). Also, the severity of AD was mild in 80% of the cases. Severe AD is quite rare in our island, which is located in the southernmost part of Greece, probably due to the mild climate. Moreover, the mild AD phenotype might be differently related to prenatal antibiotic exposure in comparison with AD in central and northern Europe. The high rate of cesarean sections in the participating women agrees with the percentage of cesarean section in central Greece (24), but is significantly increased compared to the

Figure 1 - *A forest plot that illustrates the outcome of a logistic regression model that uses the children's attributes as predictors and child atopic dermatitis (AD) as target, in terms of the produced odds ratios (ORs) with their 95% confidence intervals.*

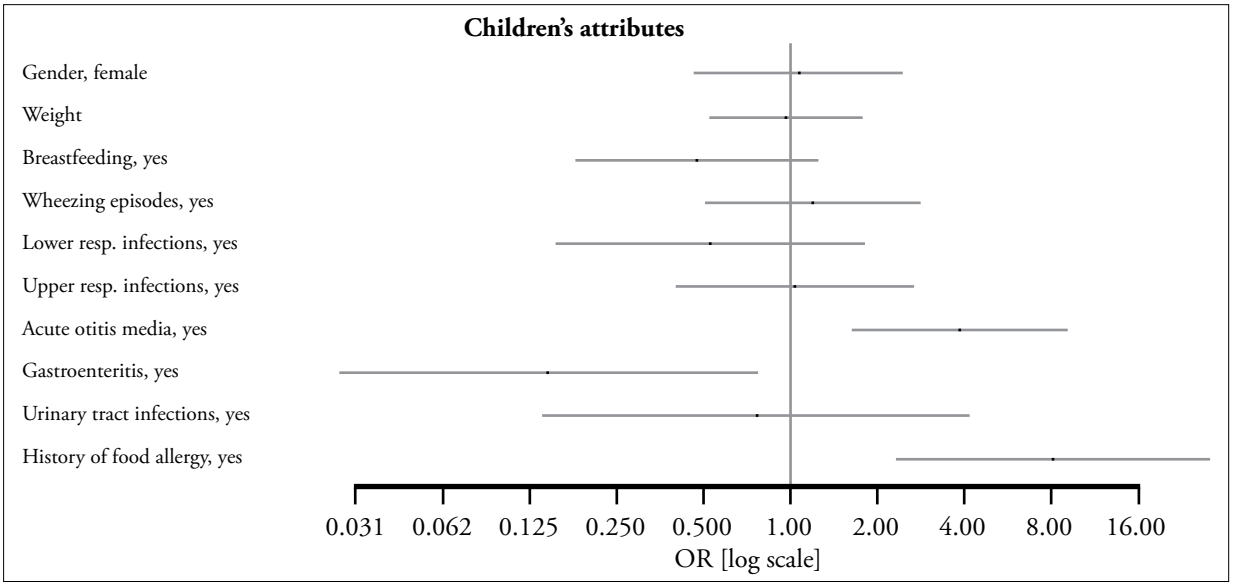
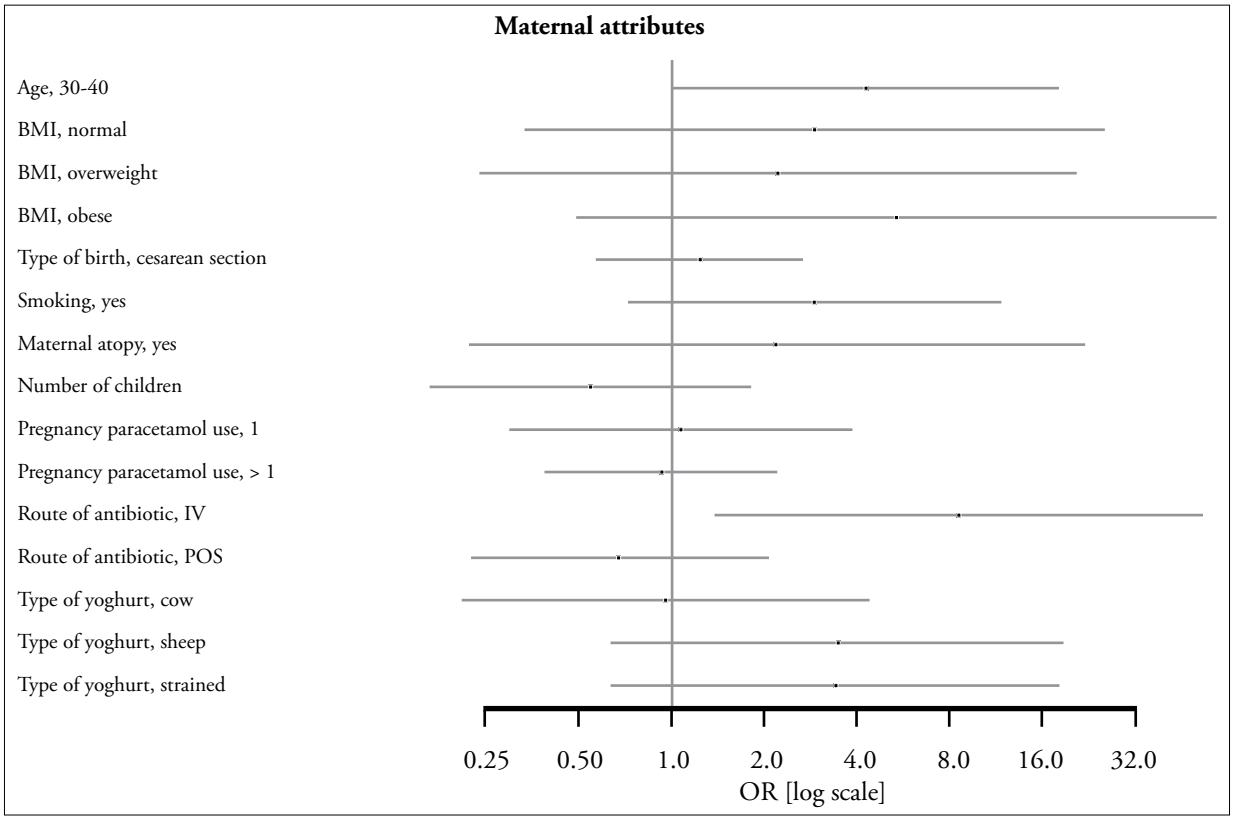


Figure 2 - *A forest plot that illustrates the outcome of a logistic regression model that uses the maternal attributes as predictors and child atopic dermatitis (AD) as target, in terms of the produced odds ratios (ORs) with their 95% confidence intervals.*



respective ratios noted in central (19.1%) (21) and northern Europe (15%) (8). Cesarean section by itself relates to infant's gut dysbiosis and is correlated to AD (25). In addition, all women giving birth by cesarean section receive a short course of antibiotics as prophylactic treatment, which might disrupt the mother's microbiome even more.

A major limitation of our study is the high dropout rate, since only 60% of the women participated in the second interview, mainly due to limited responsiveness to phone communication. Nevertheless, sample power analysis yielded that at least 90% power is achieved. Similar (59-60%) or lower (44.3%) participation rates are recorded in similar prospective cohort studies (6-8). Another limitation is the self-reported use of antibiotics in pregnancy and the fact that the clinical reason for intravenous antibiotic use was not routinely recorded. In 4 out of 10 cases, intravenous antibiotics were used, because of obstetric complications. In addition, the sample sizes are too small to present robust evidences for the studied associations. On the other hand, the fact that the reported AD in the offspring was medically diagnosed and that questions about AD were asked by a pediatric allergologist strengthens our study. Furthermore, incidence of medically diagnosed AD in another study in central Greece is only slightly lower than incidence in our own study (13.5%) (23).

In conclusion, prenatal use of antibiotics was associated with an increased risk of infant atopic dermatitis only when antibiotics were given by intravenous route and in women between 30-40 years of age. The relatively high percentage of cesarean sections in our study population did not significantly change the odds for atopic dermatitis. The study supports the rational use of antibiotics during pregnancy due to potential and diverse effects in the offspring.

Fundings

None.

Contributions

ES: investigation, writing – original draft. IK, MA: investigation. JL: formal analysis. EG: writing – review and editing. PX: conceptualization, writing – review & editing.

Conflict of interests

PX has accepted support as member of advisory board from Novartis, research support from Friesland and support as a speaker from Novartis, Uriach, Nestle, Nutricia, GlaxoSmithKline, Menarini, and Galenica. The rest of the authors declare that they have no conflict of interests.

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