Antibiotics administration during last trimester of pregnancy is associated with atopic dermatitis – a cross-sectional study

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Financial Support: M. P. was supported by the Sectoral Operational Programme Human Resources Development (SOP-HRD), financed from the European Social Fund and by the Romanian Government under the contract numbers POSDRU/89/1.5/S/64331.

Introduction. Studies regarding antibiotics administration during pregnancy and atopic dermatitis (AD) in children are only few. In this context, the objective of our study was to investigate the potential association between the timing of intrauterine exposure to antibiotics or prenatal antibiotic administration in general and AD occurrence in children.

Methods. This was a cross-sectional study in 1046 subjects. The exposure to antibiotics during pregnancy was initially evaluated using simple logistic regressions. Then, each period of antibiotics administration was adjusted with the other periods of antibiotics exposure (model 1) and with the other variables associated with AD in our database (model 2).

Results. In simple logistic regression analysis, the administration of antibiotics during pregnancy, as a whole period, presented a trend of association with AD (OR = 1.28, %CI: 0.99 – 1.65). When we analyzed antibiotic administration during each trimester of pregnancy, only antibiotherapy during the 3rd trimester was associated with AD (OR = 2.94, %CI: 1.21 – 7.12). After adjusting with all the other important risk factors associated with AD in the database, antibiotics administration during the 3rd trimester of pregnancy was still independently associated with AD (OR=2.64, %CI: 1.01 – 6.91).

Conclusion. Antibiotic administration during the 3rd trimester of pregnancy was independently associated with AD in children.

Key words: atopic dermatitis, atopic eczema, antibiotics, antibiotherapy.

INTRODUCTION

Atopic dermatitis (AD) is the first clinical manifestation of atopic march towards allergic rhinitis and asthma [1]. Primary prevention of AD and the atopic march is based on the discovery of AD risk factors. One factor suggested to favor AD occurrence was the early antibiotics exposure [2]. This is very interesting since during the last decade the antibiotic use across the European Union increased considerably in parallel with the incidence of AD [3, 4]. In addition, in 2010 at least 41.5% of all deliveries were exposed to antibiotic therapy during pregnancy [5]. Moreover, studies suggested that exposure to antibiotics during pregnancy could alter

the microbiome of the mother and could enter the fetal circulation via placenta modifying the fetal intestinal microbiota before birth [6]. These changes of the intestinal microbiota produce a delay in the development of immune system, leading to the persistence of Th2 immune status, characteristic for AD [7]. However, the studies performed up to now, regarding the role of prenatal antibiotics administration in the development of AD, have not come to an agreement [8, 9]. In addition, studies which analyzed the moment of maternal antibiotics use during pregnancy are only few [10–12].

In this context, the main objective of our study was to investigate the potential association between timing of intrauterine exposure to antibiotics

and AD occurrence in children. Secondly, we aimed to test if prenatal antibiotic exposure, without accounting for the trimester of administration, was associated with AD.

MATERIALS AND METHODS

Study design

This study on the potential link between antibiotics exposure during pregnancy and AD is part of a cross-sectional survey performed during January–June 2012 aiming to investigate the potential association between early life environment and AD occurrence later in childhood.

Power calculation

We planned a cross-sectional study in general population of children 0 to 18 years. In this population, we considered a mean estimated prevalence of AD of 10% [13]. If the true odds ratio for disease in subjects exposed to antibiotics during pregnancy relative to unexposed subjects was estimated to be 2.15, we needed at least 97 patients with AD and 969 subjects without AD to be able to reject the null hypothesis (odds ratio equals 1) with probability (power) 0.8 [9, 14] [2, 3]. The accepted type I error probability associated with this test of this null hypothesis was 0.05. We used a multiple logistic regression analysis to evaluate this null hypothesis.

Participants

The participants were children up to 18 years old. The study was carried out in schools and kindergartens located in the southern counties of Romania (Arges, Vâlcea, Olt, Constanța and Bucharest). The schools and kindergartens were randomly selected from each County School Inspectorate's listings. All children from each school or kindergarten were invited to participate. The study had institutional ethical approval in all centers and was performed according to the Declaration of Helsinki. For all subjects included in the study, parents signed an informed consent.

The only inclusion criterion in the survey was for subjects to be less than 18 years old. The only exclusion criteria was if parents or subjects have lived outside the country during pregnancy or for at least one year before as well as during their child life since the environmental risk factors may be different in this case.

Questionnaires

Our study was based upon the model of the surveys undertaken by ISAAC (International Study of Asthma and Allergies in Childhood) and consisted of filling in questionnaires by mothers. The questionnaires were structured in two parts. The first part comprised ISAAC "core" questions translated into Romanian. The second part comprised questions related to the risk factors involved in AD occurrence.

Questionnaire distribution and recovery

All questionnaires were distributed and redeemed by teachers from schools and kindergartens. Teachers' participation in the study was voluntary as well. In order to avoid repeated enrolment each study subject received a coupon with an unique number, which they were asked to give back with the completed questionnaire. The questionnaires recovery rate achieved was 52.3%.

Diagnosis of AD

AD diagnosis was made according to the ISAAC criteria and involved positive answers to the following 3 questions within the ISAAC questionnaire translated into Romanian: 1) Has your child ever had an itchy rash which was coming and going for at least 6 months? 2) Has your child had this itchy rash at any time in the past 12 months? 3) Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

Exposure to antibiotics

The questionnaire included special questions regarding the use of antibiotics during pregnancy. The questions investigated the usage of antibiotics during pregnancy and the trimester of pregnancy when they were used. Antibiotic therapy during pregnancy was defined as administration of antibiotics at any time from conception to birth. In addition, another variable was the trimester of antibiotics administration.

Variables

Patient's residence area was defined as rural or urban area. Maternal and paternal allergy history

was considered as having at least one of the following conditions: asthma, allergic rhinitis or atopic eczema. Infection during first year of life was defined as any microbiologically documented bacterial, viral or parasitic infection with agents not normally colonizing the body during the first year of life. Maternal smoking during pregnancy and in the first year of life was considered as tobacco inhalation during these periods whether this was an active or passive process. Mode of birth was either vaginal or caesarean section delivery. Gestational age was considered the time measured from the first day of the mother's last menstrual cycle until the child's birth. Birth weight was defined as the weight of the child at birth and was declared by the mother. Breastfeeding was registered if the infant received breast milk for at least one month. Exclusive breastfeeding was considered if the child received only his mother's milk for at least 3 months. Solid food introduction was identified as the moment of food diversification declared by the mother. Exposure to furry pets was defined as living in the same place with a furry pet during the first year of life.

Statistical analysis

Normally distributed continuous variables are presented as mean $\pm$ standard deviation. Non-normally distributed variables are presented as median and interquartile range. Categorical variables are presented as percentage (%). Comparison of means for normally distributed variables was performed using the t-test for independent samples. Comparison of medians for non-normally distributed variables was done by Kruskal–Wallis test. Categorical variables were compared using the chi-square test. To test the association of antibiotics exposure during pregnancy with AD occurrence we first used four simple logistic regressions having as explanatory variables either the pregnancy trimester of antibiotic administration or antibiotic therapy during the whole pregnancy period, while the dependent variable was AD diagnosis. Then adjustments were performed for two models of covariates: model 1 and model 2. Model 1 comprised exposure to antibiotics in the first year of life as well as in any of the other trimesters of pregnancy than the tested one. Model 2 consisted of the most important risk factors for AD in our database including the upper mentioned exposure to antibiotics. Model 2 was built from all variables associated with AD in the simple logistic regression analysis using the following algorithm. At first, all potential risk factors in the database

were tested for their association with AD using simple logistic regressions. Then we tested all significantly associated variables ($p < 0.05$), as well as those potential confounding factors ($p \leq 0.20$), in a multiparametric logistic regression analysis with a forward selection of covariates where the variables were removed from the model if $p > 0.10$, to keep in the model also the potential important confounders (Figure 1). Co-linearity in the models was estimated by the variance inflation factor (VIF) and tolerance. The cut-off values for $VIF < 5$, for tolerance > 0.5 were considered acceptable. The analysis was performed with MedCalc software, version 16.4.3.

Figure 1. Description of the statistical analysis algorithm. The complete description of the algorithm is presented in the methods section. AD – atopic dermatitis, model 1 – model comprising the other periods of antibiotic exposure excepting the one tested (e.g. For the 3rd trimester of pregnancy the model 1 comprised the following variables: antibiotic administration during the 1st, 2nd trimester of pregnancy and during the 1st year of life). Model 2 – model comprising the main variables associated with AD from the database, including for the periods of antibiotics exposure, after forward section of covariates.

RESULTS

We enrolled 1,046 subjects and 11.19% of them were diagnosed with AD. The two groups of children were different regarding allergy occurrence in parents. In addition, when compared with healthy subjects patients with AD presented a higher maternal and paternal history of allergic diseases. Significant differences among children with and without AD were recorded when we analysed birth weight, gestational age, birth by cesarean section. The number of subjects

receiving antibiotics during the 3rd trimester of pregnancy was also higher in the AD group compared with healthy subjects. There was no difference between

study groups regarding the other studied factors. The complete description of subjects' characteristics is presented in Table 1.

Table 1

General characteristics of the studied population

Variable	Healthy controls N = 929	Atopic dermatitis N = 117	P
Female/Male (N/%)	490/439 (52.74/47.25)	61/56 (52.13/47.86)	0.90
Region type [Urban/Rural (%)]	65.48/34.51	74.36/25.64	0.06
Age of the child (months)	104 ± 49	96 ± 52	0.09
Maternal history of allergy (%)	8.97	16.37	0.01
Eczema (%)	2.92	9.48	0.0004
Asthma (%)	1.51	0.00	0.18
Rhinitis (%)	4.10	6.03	0.34
More allergies (%)	0.43	0.8	0.58
Paternal history of allergy (%)	7.35	19.82	<0.0001
Eczema (%)	2.48	6.89	0.008
Asthma (%)	1.51	3.44	0.13
Rhinitis (%)	3.13	8.62	0.003
More allergies (%)	0.2	0.86	0.20
Antibiotic administration during pregnancy	10.54	15.38	0.12
1 st trimester (%)	4.20	6.00	0.37
2 nd trimester (%)	4.20	3.42	0.69
3 rd trimester (%)	2.15	6.00	0.01
Infections during pregnancy (%)	12.82	16.52	0.26
Active smoking during pregnancy (%)	15.19	14.52	0.85
Passive smoking during pregnancy (%)	28.91	29.91	0.82
Mode of birth [vaginal/caesarean (%)]	68.43/31.57	56.42/43.58	0.009
Gestational age			
<37 weeks (%)	11.87	9.56	0.47
37–40 weeks (%)	80.24	75.65	0.25
>40 weeks (%)	7.88	14.78	0.01
Birth weight (%)			
<2500 g (%)	8.11	10.25	0.43
2500–4000 g (%)	88.09	80.34	0.02
>4000 g (%)	3.78	9.40	0.005
Breast feeding (%)	80.92	84.48	0.35
Solid food introduction (%)			
<4 months	50.38	39.47	0.03
4–6 months	38.08	42.98	0.31
>6 months	11.53	17.54	0.06
Antibiotic therapy during first year (%)	40.15	47.86	0.11
Smoking in the first year of life (%)	21.71	25.64	0.33
Infections in the first year of life (%)	42.45	48.71	0.19
Brothers (%)	54.69	58.11	0.48
Furry pets (%)	14.68	19.65	0.15
Cat (%)	6.48	11.20	0.06
Dog (%)	7.24	10.25	0.24

Continuous normally distributed variables are presented as Mean ± SD. Categorical variables are presented as percentage (%). Continuous normal distributed variables are compared using the t test for independent samples. Categorical variables are compared using the chi-square test. N – number of subjects, P – statistical significance (considered significant if $p < 0.05$).

In unadjusted analysis the administration of antibiotics during pregnancy presented a trend of association with AD occurrence (OR = 1.28, %CI 0.99–1.65). Administration of antibiotics during the 1st and 2nd trimesters of pregnancy was not a risk factor for AD occurrence (OR_{T1} = 1.51, %CI 0.65–3.46 and OR_{T2} = 0.93, %CI 0.55–1.57) while the administration

of antibiotics during the 3rd trimester of pregnancy was associated with AD (OR_{T3} = 2.94, %CI 1.21–7.12) (Table 2).

Since only the antibiotics administration during the 3rd trimester of pregnancy was associated with the presence of AD, just this variable was used for further adjustments to test its independent

association with AD. When we adjusted the 3rd trimester of antibiotics administration for exposure to antibiotics in any of the other trimesters of pregnancy, as well as in the first year of life

(model 1), administration of antibiotics in the 3rd trimester of pregnancy was independently associated with AD (OR_{T3} = 2.81, 95%CI 1.16–6.84) (Table 3).

Table 2

Simple regression analysis of the association of the periods of antibiotics administration with atopic dermatitis

No.	Variable	OR	95 %CI	P
SLR 1	Antibiotherapy during pregnancy	1.28	0.99–1.65	0.06
SLR 2	Antibiotherapy during 3 rd trimester of pregnancy	2.94	1.21–7.12	0.02
SLR 3	Antibiotherapy during 2 nd trimester of pregnancy	0.93	0.55–1.57	0.78
SLR 4	Antibiotherapy during 1 st trimester of pregnancy	1.51	0.65–3.46	0.33

Simple logistic regressions (SLR 1 to SLR4) with the periods of antibiotics administration (1st, 2nd, 3rd trimester of pregnancy or during pregnancy as whole period) as explanatory variables and AD as dependent variable. No. – Number of the SLR, OR – odds ratio, 95% CI – 95% confidence interval, P – statistical significance (considered significant if $p < 0.05$), SLR – simple logistic regression.

Table 3

The 3rd trimester of pregnancy adjusted for model 1 (the other periods of antibiotics administration)

Variable	OR	95%CI	P
Antibiotherapy during 3 rd trimester of pregnancy	2.81	1.16 – 6.84	0.02
Antibiotherapy during 2 nd trimester of pregnancy	0.81	0.28 – 2.34	0.70
Antibiotherapy during 1 st trimester of pregnancy	1.43	0.62 – 3.30	0.40
Antibiotherapy during first year	1.33	0.90 – 1.97	0.15

Multivariable logistic regression analysis having the 3rd trimester of pregnancy adjusted for model 1 variables comprising the other trimesters of antibiotics administration and antibiotics exposure during the first year of life as explanatory variables. AD is the dependent variable in the regression. OR – odds ratio, 95% CI – 95% confidence interval, P – statistical significance (considered significant if $p < 0.05$).

Finally, the model (model 2) built out of all variables potentially associated with AD in our database (including the upper described antibiotic administration) comprised the following variables: maternal history of AD, paternal allergy history, caesarean section delivery, cat exposure during the first year of life, time of solid food introduction

(Table 4). Antibiotics administration during the 3rd trimester of pregnancy was still independently associated with AD (OR_{T3} = 2.64, 95%CI 1.01–6.91) after adjustment with model 2 of covariates (Table 4). It is worth noticing that antibiotics administration during the 1st and 2nd trimesters as well as in the first year of life was not retained in model 2.

Table 4

The association of antibiotics exposure during the 3rd trimester of pregnancy and atopic dermatitis, adjusted for model 2.

Variable	OR	%CI	P
Antibiotherapy during 3 rd trimester of pregnancy	2.64	1.01–6.91	0.046
Maternal history of AD	2.72	1.24–5.95	0.01
Paternal history of allergy	1.52	1.22–1.89	0.0002
Caesarian section	1.57	1.04–2.37	0.03
Cat exposure during first year of life	1.99	1.03–3.85	0.03
Time of solid food introduction	1.42	1.08–1.86	0.009

Multivariable logistic regression having antibiotics administration in the 3rd trimester of pregnancy adjusted for variables in model 3 (maternal history of AD, paternal history of allergy, caesarian section delivery, cat exposure during the first year of life, time of solid food introduction) as explanatory variables. The dependent variable in this regression is AD. OR – odds ratio, 95% CI – 95% confidence interval, P – statistical significance (considered significant if $p < 0.05$).

The categories of antibiotics administered during the 1st trimester of pregnancy were: aminopenicillins (ampicillin and amoxicillin) and fluoroquinolone (ciprofloxacin). In the 2nd trimester of pregnancy

the administered antibiotics were: aminopenicillins (ampicillin and amoxicillin), aminoglycosides (gentamicin), macrolides (azithromycin, erythromycin) and cephalosporins (ceftriaxone). In the 3rd trimester

of pregnancy the administered antibiotics were: aminopenicillins (ampicillin and amoxicillin), cephalosporins (cefuroxime and ceftriaxone) and aminoglycosides (gentamicin). The reasons for antibiotics prescription were urinary, respiratory and genital infections.

DISCUSSION

This study showed that antibiotics administration during the 3rd trimester was associated with AD. Another finding of this study was that antibiotics administration during the other two pregnancy trimesters was not associated with AD.

One potential explanation for the lack of association between antibiotics administration in pregnancy as a whole period and AD seen in this study may be due to the dilution effect of the other two trimesters on the effect exercised by the administration during the 3rd trimester of pregnancy. This hypothesis is sustained by the small percentage of patients with antibiotics administration during the 3rd trimester of pregnancy from total population (2.6%) and from population with antibiotic administration during pregnancy (23.27%).

Our result regarding the role of antibiotics administration during pregnancy as a whole period is similar to that of Kurzius-Spencer and Tsakok [8, 15], who found no association between antibiotics administration during pregnancy and the risk of AD occurrence and is different from other surveys [9, 16–18]. One potential explanation for the mixed results of these studies analyzing antibiotics administration in pregnancy as a whole period may be that these studies did not specifically accounted for the trimesters of administration. These studies could potentially have had different percentages of populations with antibiotics exposure during 1st, 2nd or 3rd trimester of pregnancy which could lead to a dilution or strengthening of the effect of antibiotics administration in the 3rd trimester according to the percent of subjects receiving antibiotics during this trimester.

Regarding the association of the timing of antibiotics administration in pregnancy and AD we found a study conducted in a Danish population where maternal use of antibiotics in the 3rd trimester did not influence the child's risk of eczema (OR = 0.65, %CI: 0.35–1.22) [11]. Some possible explanations could be the different study design, the type of cohort and the criteria of AD diagnosis. The Danish survey was realized in a birth cohort of 411 children born from mothers with asthma and the diagnosis of AD

was made using criteria of Hanifin and Rajka. Our study is an observational survey based on the answers given by the children's parents. We evaluated the role of antibiotics administration in the general population and the diagnosis criteria for AD were the ISAAC criteria. The replication of the Danish survey in the general population did not find any association between AD and antibiotics during the 3rd trimester of pregnancy either (HR 0.68, 95%CI: 0.43–1.09) [10]. This could potentially be explained by the fact that the diagnosis of eczema in this second study was made by using an algorithm Youden J index 62.7 and a positive answer of parents to the question „Does your child have eczema?”. In our study the diagnosis was made by a positive answer to three questions from the ISAAC questionnaires. Other possible explanation of the different result of our study was the fact that it was performed on subjects until 18 years old while the Danish study had a prospective follow-up of 3 years leading to different frequencies of eczema between these two studies.

Another study performed in Danish population did not find any association between antibiotics exposure during 1st–2nd or 3th trimesters of pregnancy and AD occurrence among 18 month – old children. In this study, independent of timing, showed increase odds of AD only among children born by atopic mothers. The same study showed no differences between different classes of antibiotics and the risk of AD [12]. Notably, the design of our study was different being performed in general population. In addition, our study enrolled patients up to 18 years old since AD onset may be possible later in childhood. Thus, these design differences may potentially account for these different results.

The association between AD and antibiotic exposure during 3rd trimester of pregnancy is interesting since antibiotics administration in this trimester is very likely to influence the AD occurrence. A potential mechanistic explanation for this association may be that the fetus swallows large quantities ~400 mL/d of amniotic liquid during the last trimester of pregnancy which subsequently reaches the distal small intestine, an organ that is significantly more sensitive to inflammatory stimuli than postnatal infant intestine. Also, in the third trimester of pregnancy the fetal intestine is developed having a potential role in immunity development [19, 20]. It was believed that the intrauterine environment and the fetus were sterile and microbial colonization is initiated when the infant is exposed to the microbes from the mother or surrounding environment during birth [21]. Recently, the presence of bacterial isolates and/or

DNA in meconium [22], amniotic fluid [23], fetal membranes [24], umbilical cord blood [25] and placenta [26] of the healthy mothers and infants, without any clinical signs of infection or inflammation suggests that fetuses are not sterile and gut colonization may start before birth. These studies raised the hypothesis that maternal – fetal exchange of commensal microbiota may occur before birth thereby seeding the intestinal microbiome of the fetus, which may stimulate the fetal intestinal mucosal immune system in utero [27]. Maternal – fetal exchange may occur via translocation through the chorioamniotic intracellular junctions, maternal intestinal translocation or haematogenous spread from periodontal tissue [20]. In this context, antibiotics taken in pregnancy, which can cross the placenta and enter the fetal circulation, might disrupt normal colonization of the developing intestinal microbiome in utero and potentially influence the immune system development and its response later in life [6].

A potential strength of this study was the large studied sample of more than 1,000 subjects which was considered sufficient for this type of study. In addition, the sample was representative for the south part of Romania since the schools and kindergartens were randomly selected and all children from each school or kindergarten were asked to participate.

Although our population comprised 1,046 subjects, the number of patients with antibiotics administered in the 1st (46 subjects), 2nd (43 subjects) or 3rd

(27 subjects) trimester was not very large raising a potential power issue. However, in order to avoid this potential limitation, we used for the adjustment models a forward selection of covariates in order to include in the adjustment models the minimum number of covariates. Another possible limitation of this study is that our data were obtained from questionnaires. However, since the diagnosis section of our questionnaires was built upon the model of ISAAC we assume that this may not be that important to influence our result. More than that, these criteria are the most used criteria for epidemiological studies and are the most cited AD criteria [28]. Since the children were up to 18 years old, a potential recall bias among mother may be possible in regards to if, and when they took antibiotics during pregnancy. Hopefully, this memory problem could be the same among all mothers due to the cross-sectional design of the study, the way the diagnosis was made in the study and the emotional effect of drug administration during pregnancy for any mother which makes the recall very probable. However, no registry for antibiotic prescription was available to certainly verify the antibiotic exposure.

CONCLUSION

This study showed that antibiotics administration during 3rd trimester of pregnancy was independently associated with AD in children.

Introducere. Există doar câteva studii privind administrarea de antibiotic în timpul sarcinii și riscul apariției dermatitei atopice (DA) la copil. În acest context, obiectivul studiului nostru a fost de a analiza posibila asociere între administrarea prenatală de antibiotic, în general, precum și între momentul expunerii intrauterine la antibiotic și apariția DA la copil.

Metode. Acesta este un studiu cross-sectiional pe 1046 subiecți. Expunerea la antibiotic în timpul sarcinii a fost inițial evaluată folosind o regresie logistică simplă. Apoi, fiecare perioadă a administrării de antibiotice a fost ajustată cu celelalte perioade ale expunerii la antibiotic (model 1) și cu celelalte variabile asociate cu DA din baza de date (model 2).

Rezultate. În analiza prin regresie logistică simplă, administrarea de antibiotice în timpul sarcinii, ca și perioadă, a prezentat un trend de asociere cu DA (OR = 1,28, %CI: 0,99 – 1,65). Când am analizat administrarea de antibiotic în fiecare trimestru de sarcină, doar antibioterapia în trimestrul 3 a fost asociată cu DA (OR = 2,94, %CI: 1,21 – 7,12). După ajustarea cu ceilalți factori de risc importanți asociați cu DA în baza de date, administrarea de antibiotic în trimestrul 3 de sarcină a rămas asociată independent cu DA (OR=2,64, %CI: 1,01 – 6,91).

Concluzie. Administrarea de antibiotic în trimestrul 3 de sarcină a fost asociată independent cu DA la copil.

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Conflict of interest disclosure: The authors declare that there are not conflicts of interest.

Authors contribution: MP, BAG, LGS, NMP, AME, BC, CC, AP, GP, MR participated in the study design and implementation. MP, AME, AP and NMP performed the statistical analysis. MP wrote and edited the manuscript. BAG, LGS, AME, BC, CC, AP, GP, MR and NMP edited the manuscript. MP and NMP had the full access to the database and statistical analysis and are the guarantors of the study.

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Received January 16th 2020