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Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood

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ABSTRACT PAGE

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Background: Delivery by cesarean section (CS) may predispose to allergic disorders, presumably due to alterations in the establishment of normal gut microbiota in early infancy. In this study, we sought to investigate the association between CS and physician-diagnosed food allergy and atopic dermatitis during the first three years of life, using data from a homogeneous, population-based, birth cohort.

Methods: A total of 459 children born and cared for in the same tertiary maternity unit were examined at birth and followed up at 1, 6, 12, 18, 24, 30 and 36 months of age. Participants with symptoms suggestive of food allergy or atopic dermatitis were evaluated by a pediatric allergy specialist to confirm the diagnosis based on well-defined criteria.

Results: The rate of CS was 50.8 % (N=233). Food allergy was diagnosed in 24 participants (5.2%) while atopic dermatitis was diagnosed in 62 children (13.5%). Cesarean section (OR 3.15; 95%CI 1.14-8.70), atopic dermatitis of the child (OR 3.01; 95%CI 1.18-7.80), parental atopy (OR 4.33; 95%CI 1.73-12.1) and gestational age (OR 1.57; 95%CI 1.07-2.37) were significant and independent predictors of food allergy. Children with at least one allergic parent delivered by CS, had higher probability of developing food allergy compared to vaginally-delivered children of non-allergic

parents (OR 10.0; 95%CI 3.06-32.7). Conversely, the effect of CS on atopic dermatitis was not significant (OR 1.35; 95%CI 0.74-2.47).

Conclusions: Delivery by CS predisposes to development of food allergy but not atopic dermatitis in early childhood. Cesarean section delivery seems to up-regulate the immune response to food allergens, especially in children with allergic predisposition.

Keywords: atopic dermatitis, cesarean section, food allergy

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Introduction

Since the second half of the 20th century, industrialized societies have experienced an epidemic increase in the prevalence of pediatric allergic disorders (1). By the 2000s, however, the prevalence of respiratory allergies reached a plateau or even declined (1), while food allergy (FA) emerged as the 'new allergic epidemic' (2). Initially, the most accepted explanation of these phenomena was the 'hygiene hypothesis', stressing that decreased exposure to microorganisms in early life may have shifted immune responses toward allergic inflammation (3). Intensive subsequent research highlighted the contribution of total microbial burden and intestinal microbiota in the development of allergic disorders (4). Indeed, it has been shown that the composition of gut microbiota differs between allergic and non-allergic children, and that these differences may precede the development of allergic disorders (4, 5). There is also evidence that optimal gut colonization plays a crucial role in down-regulating atopic response to environmental allergens and promotes immunologic tolerance (6).

Delivery by cesarean section (CS) is one of numerous factors associated with 'western lifestyle', and since its rate has also increased during the past decades, its role in the development of pediatric allergic disorders has attracted considerable interest (7). Several studies suggest that CS is associated with aberrant gut colonization, presumably due to the lack of exposure to vaginal and perianal bacteria, which may predispose to allergic sensitization and development of allergic diseases (2, 8-12). Others, however, have failed to reveal such an association (13, 14), thus increasing the uncertainty about the true influence of CS on the development of allergic disorders in childhood.

The aim of this birth-cohort study was to investigate the association between CS and physician-diagnosed FA and atopic dermatitis (AD) during the first 3 years of life, after taking into account a series of confounding factors known or presumed to be associated with development of allergic disorders. Based on the existing evidence, we hypothesized that children born by CS may be at increased risk of developing FA and/or AD in early childhood.

Methods

Study population and design

This was a prospective birth-cohort study of children born at ≥ 34 weeks of gestation at the University Hospital of Patras, Greece, between August 2009 and March 2011. The families of the children were recruited prenatally (maternity wards) on Tuesdays and Thursdays between 7:00 a.m. and 7:00 p.m. Exclusion criteria included non-Greek origin, congenital or chromosomal anomalies and admission to Neonatal Intensive Care Unit. Children who received antibiotics for neonatal infections were included. In case of twins, only the first born was considered for the analysis. All children were followed up by structured telephone interviews at 1, 6, 12, 18, 24, 30 and 36 months of age. Participants with symptoms suggestive of FA or AD were invited to attend our Pediatric Allergy Unit to confirm the diagnosis. Participants who failed to attend the first or last telephone interview, or two consecutive intermediate interviews, were excluded. Children who were invited for

diagnosis confirmation and did not attend the appointment were also excluded. The Regional Ethics Committee approved the study protocol and informed consent was obtained from the parents.

Data collection

Prenatal and perinatal data were collected by structured interviews and included demographics, parental allergic diseases (physician-diagnosed asthma, eczema, allergic rhinitis and FA), smoking exposure, number of siblings, pregnancy complications including antibiotic use during the 3rd trimester, gestational age, birth weight, mode of delivery, and perinatal complications. The gestational age of the neonates was determined by the early second-trimester ultrasound in conjunction to the date of the last menstrual period, as per standard practice in our hospital. Neonates delivered between 34^{0/7} and 36^{6/7} weeks of gestation were considered as late preterm, while those delivered at $\geq 37^{0/7}$ weeks as born at term. Cesarean section deliveries were classified as elective, i.e. programmed CS performed prior to onset of labor, and non-elective. All data were confirmed by reviewing the obstetrical and neonatal clinical files. After hospital discharge, data were collected by structured telephone interviews at 1, 6, 12, 18, 24, 30 and 36 months of age, and included information on breast feeding, symptoms suggestive for FA or AD, antibiotic prescription, and hospital admissions. Telephone calls were performed by the same investigator (EP) on afternoon hours.

Diagnosis of FA and AD

Children who experienced erythema, flushing, rash, hives, lip and/or facial edema and/or any generalized symptom (cough, wheezing, stridor, vomiting, hypotonia) immediately or at least within 2 hours after any food ingestion were invited to attend the local Pediatric Allergy Unit and evaluated by a pediatric allergy specialist (MT). All children underwent skin prick tests (SPTs) and/or blood sampling for serum specific IgE (sIgE) detection against the suspected food. Participants were tested for the major food allergens (cow milk, egg, wheat, cod and peanut) irrespectively of the

history. SPTs were performed with commercial extracts (Solu-prick, ALK-Abello, Madrid, Spain), using histamine (10mg/ml) and saline as positive and negative controls, respectively. An SPT wheal size of at least 3mm greater than the negative control was considered as positive. Serum specific IgE was measured with CAP system (ImmunoCAP 100, Phadia, Thermo Fisher Scientific Inc, Uppsala, Sweden); a concentration of ≥ 0.35 KUA/L in the presence of a convincing history was regarded as positive.

Atopic dermatitis was defined by the presence of a persistent for at least 2 weeks and/or chronically relapsing dry itchy skin lesion in any body area except that of the diaper, in conjunction with a relevant diagnosis (including prescription of medication) established by a physician. When the history was inconclusive, the diagnosis was confirmed by a pediatric allergy specialist (MT) according to standard criteria (15).

Statistical analysis

Details on sample size estimation are presented in the online supplement. Simple and multivariable logistic regression analysis was applied to explore the effect of gender, gestational age, birth weight, maternal age, parity, smoking in pregnancy, duration of membranes rupture, delivery by CS, breast feeding, antibiotics exposure during the last trimester of pregnancy and early infancy, and parental atopy (separate models for father, mother, and any parent) on FA (any FA) and AD. Analyses were performed with IBM SPSS software version 20.0 (IBM Corp., Armonk, NY).

Results

A total of 536 eligible children were initially included in the study. Of them, 77 (14.4%) failed to attend the 3 year follow up and were excluded from the analysis (see online supplement for a detailed description). The characteristics of the remaining 459 children are presented in Table 1. The rate of CS was 50.8 % (N = 233); 198 CSs (85%) were elective and 35 (15%) non-elective. Maternal atopy was reported in 43 participants (9.4%) and paternal atopy in 41 (8.9%); 77 children (16.8%)

had at least one atopic parent (parental atopy). Food allergy was noted in 24 participants (5.2%). Details on parental atopy and FA are presented in the online supplement. Atopic dermatitis was identified in 62 children (13.5%); 45 of them attended the local Pediatric Allergy Unit for further diagnostic confirmation. Eight children (1.7%) were diagnosed with both FA and AD; they represented the 33.3% of participants with FA and the 12.9% of those with AD.

The effect of various factors on the development of FA is presented in Table 2. Cesarean section, parental atopy, AD, and gestational age were significant and independent predictors of FA. The effect of CS remained significant when maternal and paternal atopy were considered separately (Online supplement - Table E3). In children born exclusively by CS, only parental atopy, AD, and gestational age were associated with higher probability of FA, while the effect of the type of CS was not significant (Table 3). The combined effect of CS and parental atopy is presented in Table 4. Children who were born by CS and had at least one atopic parent, presented higher probability to develop FA compared to participants without atopic parents who were delivered vaginally; the probability was higher when only term-born children were analyzed (Table 4).

The effect of the same factors on the development of AD is presented in Table 5. Parental atopy and paternal atopy (Online supplement – Table E4) were the only predictors of AD after adjustment for other confounders. The effect of CS on the development of AD was not significant (Table 5).

Discussion

In this population-based birth-cohort study we examined the association between CS and physician-diagnosed FA and AD during the first 3 years of life. We found that children born by CS had a 3-fold higher probability of FA, independently of other confounding factors. Parental atopy, AD, and gestational age were also significant and independent predictors of FA in our cohort. Children with at least one allergic parent delivered by CS had a 10-fold higher probability of developing FA

compared to children of non-allergic parents who were born vaginally; this relationship was stronger among participants born at term. Conversely, CS delivery was not related to the development of AD in our study.

There are conflicting data in the literature concerning the influence of CS on the development of FA (2, 16). Earlier studies have shown an association between mode of delivery and sensitization to food allergens (17, 18), while a later report suggested a direct relationship between CS and IgE-mediated cow's milk allergy (10). In a population-based birth cohort, CS was not directly associated with confirmed egg (11) or cow's milk (12) allergy. However, children of allergic mothers who were born by CS had a significantly higher probability of FA (11, 12). In line with our results, these findings suggest that the effect of CS is more pronounced among infants with allergic predisposition. On the contrary, other studies have failed to show an association between CS and physician-diagnosed FA in early childhood (13, 14).

The inconsistency in the results of these reports could be attributed to methodological differences, including heterogeneity of the studied populations, lack of a consistent definition of FA (e.g., parent-reported symptoms versus physician-confirmed FA, FA versus food sensitization), and the confounders taken into account in the multivariable analyses (2). Our study included a homogeneous birth-cohort in terms of genetic background (participants of solely Greek origin), lifestyle conditions (families from a single urban/suburban area) and health-care access. Moreover, all participants were born and cared for in the same maternity unit; this is important since emerging evidence suggests that the place of delivery may contribute to the development of allergic diseases by affecting the composition of neonatal microbiota (9, 19). Finally, all children underwent a meticulous 3-year follow-up, while allergic disorders were diagnosed by a specialized physician.

Perturbation of gut microbiota plays a key role in the dysregulation of immune response and subsequent development of allergic disorders (5, 6). Since normal intestinal colonization begins at birth, the effect of perinatal factors is particularly important. There is now evidence that vaginally-delivered newborns harbor microbial communities that resemble maternal vaginal microbiota, while

infants born by CS acquire nonmaternal bacteria from the hospital environment (19). Although the establishment of gut microbiota is a dynamic process, also involving environmental exposures beyond the neonatal period (20), delayed colonization with beneficial bacteria appears to be the first of a series of events that predispose to allergic manifestations later in life (8, 9).

Cesarean section may also influence the maturation of the immune system by altering the level of stress at birth (21). During vaginal delivery, uterine contractions and fetal hypoxia initiate a potent stress response characterized by increased release of cortisol in fetal circulation, thus promoting the maturation of various organs (22). Infants delivered by CS lack this beneficial effect, which is thought to affect the adaptation and maturation of the immune system at the long term (21). Our results do not support a relationship between type of CS and FA; it should be noted, however, that the quantification of birth-related stress is difficult and far more complex than the simplistic classification of CS as elective or non-elective.

We found no association between CS and AD, which is in line with the findings of previous reports (7, 23, 24). Two recent studies using mediation statistical analysis, have shown that perturbations of gut microbiota may have an intermediate role in the relationship between mode of delivery and AD (8, 9); however, the impact of CS *per se* was significant only in one of these two reports (8). Atopic dermatitis is a heterogeneous disorder, the pathogenesis of which involves a complex cross-talk between cutaneous and systemic immune responses, environmental exposures, and skin barrier defects (25). Therefore, the effect of CS on AD by means of alterations in gut microbiota is unlikely to be revealed in observational studies like ours.

The present study included children born late-preterm and our findings suggest that this 'marginal' prematurity had a protective effect on FA but not AD. Current evidence supports that prematurity is not a risk factor for FA (26); however, data focusing exclusively on late-preterm infants are lacking. It has been shown that the amniotic fluid of mothers delivering prematurely is abundant in bacterial rDNA (27), and that the gastrointestinal tract of preterm-born infants has been

already colonized at birth (28). Earlier colonization might contribute to the earlier maturation of the developing immune system, thus explaining the protective effect of prematurity against FA.

Other perinatal factors which are thought to alter normal gut microbiota, such as use of antibiotics and prolonged rupture of membranes (2), did not have a significant effect in our cohort. Exposure to vaginal flora after rupture of membranes may lead to early colonization of the fetus regardless of the subsequent method of delivery (29), while perinatal or postnatal administration of broad-spectrum antibiotics could affect the establishment of normal microbiota (2, 29). However, the independent contribution of these factors in the development of allergic diseases is difficult to be proven.

As expected, the family history of atopy was a significant predictor of FA in our cohort, while parental AD had the strongest effect among parental allergic disorders (Table 2). On the other hand, AD of the child, which represents a known risk factor for food sensitization in childhood (30, 31) was also associated with a significantly higher probability of FA. Inclusion of both variables (i.e., parental and children's AD) in the multivariable analysis model resulted in a decrease of the ORs for parental AD (and family history of atopy in general) (Table 2). These findings suggest that the effect of parental AD on child's FA was mediated – at least in part – through the development of AD. The significant and independent effect of the other parental allergic disorders (i.e., allergic asthma, allergic rhinitis and food allergy) on the development of FA in the offspring should also be highlighted (Table 2).

The limitations of the present work should be acknowledged. First, we provide data from a single center and a limited urban/suburban area, therefore, our results may not be generalizable to other populations or different settings. Nevertheless, this design permitted for the marked homogeneity of our cohort, which should be considered a critical condition to interpret the results of similar reports. Second, our study sample was small, but with enough statistical power to allow for the multivariable analyses presented herein. Third, we did not have data on the socioeconomical status of the families, thus the effect of this parameter cannot be assessed. Previous experience in

our setting has shown that the inclusion of relevant questions may decrease the rate of consent to participate, thus we decided not to include such information in the structured interviews. The high rate of CS (i.e., 50.8%) reflects the dramatic rise of CS deliveries in Greece over the last years (32) and should not be considered the result of selection bias. Finally, although the reported association between CS and FA is straightforward, the proposed intermediate role of gut microbiota remains an assumption.

To conclude, using data from a homogeneous, population-based, birth cohort, we report a direct association between delivery by CS and development of FA in early childhood, independently of other confounding factors known or presumed to predispose to the development of allergic disorders. Of note, CS delivery seems to potentiate the immune response to food allergens particularly in children with allergic predisposition. Conversely, CS had no significant effect on the development of AD in our cohort.

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Conflicts of interest: The authors have no conflicts of interest to disclose

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Table 1. Characteristics of the study population

N	459
Male gender	246 (53.6)
Gestational age, weeks	38.2 ± 1.5
Late preterm	80 (17.4)
Birth weight, g	3190 ± 470
Maternal age, years	30.2 ± 5.6
Multiparae	234 (51.0)
Smoking in pregnancy	136 (29.6)
Duration of membrane rupture, hours	2.8± 13
Prolonged membrane rupture*	18 (3.9)
Cesarean section	233 (50.8)
Elective	198 (43.1)
Non-elective	35 (7.7)
Exclusive breast feeding†	98 (21.4)
Antibiotics exposure	
Pregnancy‡	50 (10.9)
Early infancy§	40 (8.7)
Family history of atopy	
Mother	43 (9.4)
Father	41 (8.9)
Any parent	77 (16.8)
Allergic disorders	
Food allergies	24 (5.2)
Atopic dermatitis	62 (13.5)

Data are number of cases (%) or mean $\pm$ SD

* membrane rupture >18 hours, † exclusive breast feeding for at least 6 months, ‡ antibiotics exposure during the 3rd trimester of pregnancy, § antibiotics exposure from birth up to the 6th month of age

Table 2. Effect of various factors on the development of food allergy

N = 459	Unadjusted OR	Adjusted OR	
Male gender	1.47 (0.63-3.44)	1.53 (0.62-3.72)	1.54 (0.60-3.96)
Gestational age	1.21 (0.90-1.61)	1.57 (1.07-2.37)	1.54 (1.04-2.28)
Birth weight	1.05 (0.43-2.52)	0.53 (0.16-1.62)	0.58 (0.18-1.77)
Maternal age	1.04 (0.97-1.12)	1.03 (0.95-1.12)	1.03 (0.94-1.12)
Parity	0.80 (0.35-1.84)	0.98 (0.37-2.64)	0.92 (0.33-2.05)
Smoking in pregnancy	0.61 (0.22-1.67)	0.55 (0.19-1.54)	0.55 (0.19-1.59)
Duration of membrane rupture	0.99 (0.94-1.05)	1.00 (0.94-1.08)	1.00 (0.92-1.08)
Delivery by cesarean section	3.07 (1.20-7.88)	3.15 (1.14-8.70)	3.04 (1.12-7.50)
Exclusive breast feeding*	1.03 (0.38-2.84)	0.83 (0.30-2.38)	0.75 (0.24-2.31)
Antibiotics exposure in pregnancy†	0.73 (0.17-3.21)	0.78 (0.16-3.74)	0.79 (0.14-4.39)
Antibiotics exposure in early infancy‡	0.44 (0.06-3.36)	0.68 (0.11-5.25)	0.69 (0.11-5.45)
Family history of atopy§	5.69 (2.45-13.2)	4.33 (1.73-12.1)	-
None	Reference	-	Reference
Atopic dermatitis	7.49 (2.69-33.4)	-	5.04 (1.36-26.2)
Other allergic disorders¶	4.74 (1.85-12.2)	-	3.90 (1.39-10.6)

Multivariable logistic regression models. Unadjusted OR refers to the crude effect of each factor separately. Adjusted OR refers to the effect of each factor adjusted for the effect of the others.

* exclusive breast feeding for at least 6 months; † exposure during the 3rd trimester of pregnancy; ‡ exposure from birth up to the 6th month of age; § any parent with atopy; ¶ allergic asthma, allergic rhinitis or food allergy

Table 3. Effect of various factors on the development of food allergy in children born by cesarean section

N = 233	Unadjusted OR	Adjusted OR
Male gender	1.20 (0.45-3.21)	1.36 (0.41-4.09)
Gestational age	1.34 (0.95-1.87)	1.56 (1.05-3.08)
Birth weight	0.99 (0.40-2.47)	0.48 (0.16-1.53)
Maternal age	1.01 (0.92-1.11)	1.00 (0.90-1.11)
Parity	0.82 (0.31-2.15)	1.32 (0.33-5.42)
Smoking in pregnancy	0.48 (0.14-1.73)	0.41 (0.12-1.64)
Duration of membrane rupture	0.98 (0.87-1.10)	0.91 (0.73-1.18)
Elective cesarean section	1.91 (0.59-6.21)	2.39 (0.44-11.9)
Exclusive breast feeding*	1.79 (0.60-5.32)	1.56 (0.50-4.94)
Antibiotics exposure		
Pregnancy†	0.49 (0.06-3.86)	0.43 (0.04-4.16)
Early infancy‡	0.54 (0.07-4.29)	0.98 (0.10-8.95)
Parental atopy§	5.31 (1.97-14.3)	4.11 (1.69-18.5)

Atopic dermatitis of the child **2.87 (1.43-8.44)** **3.20 (1.79-9.23)**

Multivariable logistic regression models. Unadjusted OR refers to the crude effect of each factor separately. Adjusted OR refers to the effect of each factor adjusted for the effect of the others.

* exclusive breast feeding for at least 6 months; † exposure during the 3rd trimester of pregnancy; ‡ exposure from birth up to the 6th month of age; § any parent with atopy

Table 4. Combined effect of type of delivery and parental atopy on the development of food allergy

	All neonates	Term-born neonates
Group	(N = 459)	(N = 379)
Vaginal delivery - No parental atopy	Reference group	Reference group
Cesarean section - No parental atopy	2.02 (0.58 - 7.06)	2.84 (0.72 - 11.2)
Vaginal delivery - Parental atopy	3.05 (0.54 - 17.36)	3.76 (0.60 - 23.5)
Cesarean section - Parental atopy	10.0 (3.06 - 32.7)	11.3 (2.93 - 43.5)

Logistic regression models.

Parental atopy refers to the presence of atopy in any parent.

Table 5. Effect of various factors on the development of atopic dermatitis

N = 459	Unadjusted OR	Adjusted OR	
Male gender	1.56 (0.90-2.70)	1.69 (0.95-3.04)	1.66 (0.92-2.99)
Gestational age	1.08 (0.90-1.29)	1.14 (0.89-1.45)	1.15 (0.90-1.47)
Birth weight	0.96 (0.54-1.70)	0.62 (0.30-1.29)	0.66 (0.31-1.40)
Maternal age	1.03 (0.98-1.08)	1.03 (0.98-1.09)	1.04 (0.98-1.10)
Parity	0.71 (0.41-1.21)	0.71 (0.39-1.31)	0.75 (0.44-1.44)
Smoking in pregnancy	1.08 (0.61-1.90)	1.09 (0.60-1.97)	1.14 (0.63-2.09)
Duration of membrane rupture	1.00 (0.98-1.02)	1.00 (0.98-1.03)	1.00 (0.98-1.03)
Delivery by cesarean section	1.52 (0.88-2.62)	1.35 (0.74-2.47)	1.30 (0.70-2.36)
Exclusive breast feeding*	1.09 (0.57-2.07)	0.97 (0.49-1.93)	0.95 (0.47-1.89)
Antibiotics exposure in pregnancy†,‡	0.53 (0.18-1.52)	0.48 (0.16-1.44)	0.47 (0.15-1.42)
Family history of atopy§	3.12 (1.72-5.67)	2.76 (1.46-5.21)	-
None	Reference	-	Reference
Atopic dermatitis	7.39 (2.70-20.2)	-	8.06 (2.66-24.5)
Other allergic disorders¶	2.31 (1.15-4.61)	-	1.91 (0.92-4.01)

Multivariable logistic regression models. Unadjusted OR refers to the crude effect of each factor separately. Adjusted OR refers to the effect of each factor adjusted for the effect of the others.

* exclusive breast feeding for at least 6 months; † exposure during the 3rd trimester of pregnancy;

‡ none of the children with atopic dermatitis had antibiotics exposure in early infancy; § any parent with atopy; ¶ allergic asthma, allergic rhinitis or food allergy