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ORIGINAL PAPER

Pre-natal folic acid and iron supplementation and atopic dermatitis in the first 6 years of life

Cristina Fortes[1] · Simona Mastroeni[1] · Thomas J. Mannooranparampil[1] · Domenico Di Lallo[2]

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Abstract

Exposure in utero has been suggested to influence health later in life. The aim of this study was to investigate, if the use of prenatal food supplements was associated with atopic dermatitis in the offspring. Mothers who gave birth in the hospital G. B. Grassi were invited to participate in the study ($n = 395$). Information on socio-demographic characteristics, clinical data of the mothers and babies, vegetables and fruit intake, food avoidance, and food supplements use during pregnancy, depression status, and environmental exposure was obtained for all subjects in the hospital at the time of delivery. Data on breastfeeding practice, introduction of weaning foods, day care attendance, and atopic dermatitis were collected in the postnatal follow-ups. Logistic regression was applied to estimate odds ratio (OR) and 95% confidence intervals (CI). Children in which mothers used both iron and folic acid supplementation had a fourfold decreased risk of developing atopic dermatitis [OR = 0.22; 95% confidence interval (CI) 0.06–0.79, $p = 0.02$], after adjusting for possible confounding factors. Findings suggest an independent and protective effect of prenatal folic acid and iron supplementation for atopic dermatitis in children.

Keywords Atopic dermatitis · Risk factors · Folic acid and iron supplementation

Introduction

According to the WHO Global Burden of Disease, dermatitis is the skin disease with the highest disability-adjusted life-years [11]. Atopic dermatitis (AD) is a common inflammatory skin disease characterized by a chronic relapsing remitting disease course. Clinical manifestations are dry skin, pruritus, and eczematous lesions, while flares is a major component of disease morbidity [19]. Atopic dermatitis mainly affects children, with the first manifestations in the first year of life (60%), although it also occurs in adults (10%). Atopic dermatitis comorbidities include food allergy, asthma, allergic rhinitis, and allergic conjunctivitis [19] which point out the involvement of both cutaneous and systemic immune activation. AD skin lesions are characterized by epidermal hyperplasia, large T-cell and dendritic cell infiltrates as well as augmented inflammatory production. Activation of blood T cells was seen in moderate-to-severe AD [2]. Many AD patients also (35–67%) present high concentration levels of allergen-specific serum IgE.

A worldwide continuous increase in the prevalence of AD has been suggested [19]. The prevalence varies according to geographic region (2.4–38.4%) and it is higher in more industrialized countries [6]. The only well-recognized risk factor for AD is family history and the most known genetic susceptibility gene to date for AD is the gene-encoding filaggrin (FLG) that is involved in skin barrier function. It has been suggested that subjects with null mutations in FLG have three times an increased risk of AD [10]. However, the majority of the AD subjects do not have mutations in FLG and the ones who have it do not necessarily develop AD [10]. It seems that AD only manifests if it is driven by environmental exposure. There is increasing interest in the possible role of prenatal [7] and postnatal environmental exposure on the development of AD. Environmental exposure in utero has been suggested to influence phenotype and transgenerational inheritance through epigenetic mechanisms [19]. Very few epidemiological studies investigated the role of food supplements in AD, but the results are controversial [8, 12, 14, 16]. Therefore, the aim of this study was to investigate whether food supplements intake during

✉ Cristina Fortes
c.fortes@idi.it

[1] Epidemiology Unit, Istituto Dermopatico dell'Immacolata (IDI-IRCCS), Via dei Monti di Creta, 104, 00167 Rome, Italy

[2] Lazio Regional Health Authority, Rome, Italy

pregnancy was associated with the risk of AD development in the first 6 years of life, controlling for all possible confounding factors.

Materials and methods

This study was conducted in 395 Italian women who delivered babies in the hospital G.B. Grassi in Rome, Italy. Among the 395 women, 51 refused to participate in the study. The response rate was 87%. The present study was approved by the Ethics Committee of the Local Health Authority and a total of 344 women gave a written consent and participated in the study.

The outcome of the study was atopic dermatitis at age 6. Atopic dermatitis was defined according to the UK Diagnostic Criteria for atopic dermatitis [9]. All women answered the validated questionnaire to identify atopic dermatitis [9]. In summary, the presence of AD was derived from the presence of the following conditions: itchy skin condition in the last 12 months (scratching or rubbing the skin) plus the presence of at least three or more of: history of flexural dermatitis (skin creases of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes); visible flexural dermatitis; history of generally dry skin; history of atopic disease in a first relative; onset before the age of 2 years. Day care attendance until the age of 2 years was assessed by a questionnaire in the same occasion.

At the time of delivery, clinical data were retrieved from hospital clinical records and a standardized questionnaire on pre-natal risk factors was administered by trained interviewers during the hospital stay to all women enrolled in the study. Information was collected and classified as: gestational age (early term: ≤ 38; full term: > 38 weeks), active and passive smoking during pregnancy, infants' sex, birth weight, siblings, diet of the mother during pregnancy, use of food supplements during pregnancy, type of supplements, commercial name, and trimester of intake. Food supplement use was classified in five categories according to the overall distribution of intake as following: no supplements use; iron only; folic acid only; both iron and folic acid; mixed use. Educational level was classified in two categories: low level (primary and/or middle school education) and high level (high school and/or university degree). Educational attainment was used as a proxy measure of social class. The presence of episodes of depression (pre-pregnancy) was assessed by asking the mothers whether they had episodes of depression diagnosed by a doctor before pregnancy and whether they followed a specific treatment (medication and/or psychological support). Psychological distress was a variable created and used in our previous study [13]. It was classified as none; the presence of at least one psychological distress condition (episodes of depression or insomnia or traumatic perception of birth) and the presence of two or more psychological distress conditions. Body mass index (BMI) was used to assess nutritional status. Exposure variables to environmental allergens were as following: living in a high traffic area (defined as the presence of at least two conditions: road traffic, bus lines, traffic lights in the street of residence), the presence of domestic animals in the home and homes with moulds and/or curtains and/or carpets. Data on maternal antigen avoidance (foods avoided during pregnancy) were categorized in two groups (no/yes). The food items avoided were as follows: eggs, cows' milk and cow's milk products, nuts, fish, and tomatoes. The intake of fruits and vegetables during pregnancy was considered a proxy of the mother's antioxidants intake. A food-frequency questionnaire was administrated in the hospital to the mothers to assess dietary habits and the intake of foods was defined on a five-point scale. The five-point scale was collapsed in two categories. Combination of categories was based on the overall distribution in the population studied.

Questionnaires administered by telephone every 2 weeks for 6 month postpartum (12 interval questionnaires) were used to assess breastfeeding practice and introduction of weaning foods. Early introduction of weaning foods was defined as any food given before 4 months of the baby. Data on day care attendance before the age of 2 were collected in the 6-year follow-up.

Statistical analysis

Unconditional logistic regression analysis was used to identify possible risk factors for atopic dermatitis. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated. Age and education of the mother and all variables with a p value < 0.05 (Wald test) in the bivariate analysis were included in the multivariable model. The following variables were included in the final model: age of the mother, educational level, passive smoking during pregnancy, family history of atopic dermatitis, and food supplement use. Active smoking was not considered because of the very small number of mothers who smoked during pregnancy. However, we assessed passive smoking. We also controlled, one at a time in the model, for other potential confounders such as breastfeeding, maternal psychological distress, BMI of the mother, maternal food antigen avoidance during pregnancy, passive smoking during pregnancy, maternal dietary intake of fruits and vegetables, birth weight, infant's sex, day care attendance, the presence of domestic animals, early introduction of weaning foods, the presence of indoor, and exposure to outdoor allergens. However, none of the variables contributed significantly to the model.

All the analyses were performed using STATA software package PC-STATA (Stata 11.0; StataCorp LP, College Station, TX, USA).

Results

A total of 344 women (mean age 31.6 years, SD = 4.7) participated in our study. Out of the 344 offspring, 27 developed atopic dermatitis (7.8%). Mean follow-up time was 5.77 years (SD = 0.57). In our population, 68.8% of women were taken both folic acid and iron supplements in the first and second trimesters.

Table 1 shows the characteristics of mothers participating in the study by the presence of atopic dermatitis in the offspring. In our population, the majority of mothers participating in the study (67.7%) had a high educational level (> 8 years), a BMI (< 25) (79.9%), and no family history of atopic dermatitis (77.0%). In our population, 89.2% used food supplements during pregnancy.

In the univariate analysis, a protective effect for atopic dermatitis in the offspring was found for intake of both folic acid and iron supplementation during pregnancy (OR: 0.19; 95% CI 0.06–0.68, p value = 0.01). No statistical significant effect was seen for the use of only iron (OR: 0.54; 95% CI 0.17–1.74, p value = 0.30); only folic acid (OR:0.57; 95% CI 0.15–2.22, p value = 0.57) and mixed use (OR:0.55; 95% CI 0.15–1.96, p value = 0.36).

Out of the 344 women, 138 women used both iron and folic acid during pregnancy. Out of the 138 women, who used both iron and folic acid supplementation, 68.8% of women used for two trimesters of pregnancy. The supplementation doses in our study varied from 0.4 to 5 mg of folic acid and from 37.5 to 105 mg of iron. An increased risk for atopic dermatitis in the offspring was also found for maternal passive smoking during pregnancy (OR: 2.39; 95% CI 1.07–5.32; p value = 0.03) and family history of atopic dermatitis (OR: 2.51; 95% CI 1.11–5.65; p value = 0.03). No association was found for age, BMI, psychological distress condition, maternal food antigen avoidance during pregnancy, and consumption of fruits and vegetables as an indicator of antioxidants intake.

Table 2 depicts the characteristics of the offspring by the presence of atopic dermatitis. No differences were found between infants' sex, birth weight, and the presence of atopic dermatitis. No association was found between postnatal exposure to breastfeeding for at least 4 months, early introduction of weaning foods (< 4 months), the presence of siblings, day care attendance, and the presence of indoor allergens (homes with moulds, curtains, and carpets) and outdoor allergens (living in a high traffic area).

Table 3 reports the results of the multivariate analysis. After adjusting for age, education, family history of atopic dermatitis, and passive smoking during pregnancy, children in which mothers used both iron and folic acid had a fourfold decreased risk of developing atopic dermatitis [OR = 0.22; 95% confidence interval (CI) 0.06–0.79, p = 0.02]. No effect was observed for the use of only iron, only folic acid, and for the use of multi-vitamins and minerals. The increased risk observed for maternal passive smoking exposure during pregnancy remained, although it was no longer statistically significant (OR: 2.13; 95% CI 0.93–4.89, p value = 0.07). The increased risk found for family history of atopic dermatitis (OR: 2.79; 95% CI 1.18–6.57) remained statistically significant. We also controlled, one at a time in the model, for other potential confounders such as breastfeeding, maternal psychological distress, gestational age, BMI of the mother, maternal food antigen avoidance during pregnancy, antioxidant intake, birth weight, infant's sex, the presence of siblings, day care attendance, the presence of domestic animals, early introduction of weaning foods, the presence of indoor allergens (homes with moulds, curtains and carpets) and the exposure to outdoor allergens, and the risk estimates did not change.

Discussion

There is increasing evidence, indicating that prenatal and early life exposure can influence the development of allergic disease. In our study, we investigated the role of food supplements on atopic dermatitis, and found, after adjusting for all possible confounding factors, that children in which mothers used both iron and folic acid supplementation during pregnancy had a fourfold decreased risk of developing atopic dermatitis.

Little is known about the benefits of prenatal folic acid supplementation beyond the role of folic acid and neural tube defects [4]. Very few epidemiological studies investigated the role of folic acid in atopic dermatitis and the findings are controversial [8, 12, 14, 16]. The controversial findings found in the studies could be explained by different study designs and/or different follow-up time and lack of control for important confounding factors. However, it could also be explained by different quantities of folic acid contained in supplementation capsules. In fact, Dustan et al. [8] showed that both low and high levels of cord blood folate were associated with greater allergic sensitization in comparison to medium levels, suggesting that there might exist an optimal folate level that decreases the risk of AD and also prevent neural tube defect. Only one epidemiological study, so far, investigated the role of folic acid and iron on atopic dermatitis [16] and the results are in agreement with our findings. Oh and colleagues [16] conducted a case–control study among children age 6 years, and showed that children with high dietary intake of iron (OR: 0.39, 95% CI

Table 1 Characteristics of women participating in the study and atopic dermatitis in offspring

Characteristics	All ($N=344$)	Atopic dermatitis		p value[c]
		Presence[a] ($N=27$)	Absence ($N=317$)	
	N (%)[b]	N (%)[b]	N (%)[b]	
Age group (years)				
< 30	112 (32.6)	11 (40.7)	101 (31.9)	
30–34	129 (37.5)	8 (29.6)	121 (38.2)	
≥ 35	103 (29.9)	8 (29.6)	95 (30.0)	0.57
Educational level (years)				
Low (≤ 8)	111 (32.3)	9 (33.3)	102 (32.2)	
High (> 8)	233 (67.7)	18 (66.7)	215 (67.8)	1.00
Body mass index (kg/m^2)				
< 25	270 (79.9)	19 (73.1)	251 (80.5)	
≥ 25	68 (20.1)	7 (26.9)	61 (19.5)	0.44
Psychological distress condition				
None	178 (51.7)	12 (44.4)	166 (52.4)	
At least one condition[d]	128 (37.2)	10 (37.0)	118 (37.2)	
Two or more conditions[e]	38 (11.1)	5 (18.5)	33 (10.4)	0.35
Family history of atopic dermatitis				
No	264 (77.0)	16 (59.3)	248 (78.5)	
Yes	79 (23.0)	11 (40.7)	68 (21.5)	0.03
Passive smoking exposure during pregnancy[f]				
No	208 (60.5)	11 (40.7)	197 (62.1)	
Yes	136 (39.5)	16 (59.3)	120 (37.9)	0.04
Maternal food antigen avoidance during pregnancy				
No	208 (60.5)	19 (70.4)	189 (56.6)	
Yes	136 (39.5)	8 (29.6)	128 (40.4)	0.31
Use of antibiotics during pregnancy				
No	309 (89.8)	23 (85.2)	286 (90.2)	
Yes	35 (10.2)	4 (14.8)	31 (9.8)	0.50
Weekly consumption of vegetables during pregnancy				
Low (≤ 2 times/week)	150 (43.6)	10 (37.0)	140 (44.2)	
High (≥ 3 times/week)	194 (56.4)	17 (63.0)	177 (55.8)	0.55
Weekly consumption of fruits during pregnancy				
Low (≤ 1 time/week)	144 (41.9)	12 (44.4)	132 (41.6)	
High (≥ 2 times/week)	200 (58.1)	15 (55.6)	185 (58.4)	0.84
Supplemention during pregnancy				
No	37 (10.8)	6 (22.2)	31 (9.8)	
Yes	307 (89.2)	21 (77.8)	286 (90.2)	0.06
Type of food supplements				
No supplements	37 (10.9)	6 (22.2)	31 (9.9)	
Iron only	74 (21.7)	7 (25.9)	67 (21.3)	
Folic acid only	40 (11.7)	4 (14.8)	36 (11.5)	
Both iron and folic acid	138 (40.5)	5 (18.5)	133 (42.4)	
Mixed use[g]	52 (15.2)	5 (18.5)	47 (15.0)	0.07

[a]An itchy skin condition in the last 12 months plus Nottingham score ≥ 3

[b]Totals may vary because of missing values

[c]p value for Fisher's exact test

[d]Insomnia and/or depression episodes in life or experienced birth as a traumatic event

[e]Insomnia and/or depression episodes in life and experienced birth as a traumatic event

[f]At home and/or work

[g]Multivitamins and minerals and/or iron and/or folic acid

Table 2 Characteristics of the offspring and atopic dermatitis

Characteristics	All ($N=344$)	Atopic dermatitis		p value[c]
		Presence[a] ($N=27$)	Absence ($N=317$)	
	N (%)[b]	N (%)[b]	N (%)[b]	
Infant's sex				
Males	179 (52.0)	15 (55.6)	164 (51.7)	
Females	165 (48.0)	12 (44.4)	153 (48.3)	0.84
Gestational age				
Early term (≤38 weeks)	59 (17.1)	4 (14.8)	55 (17.3)	
Full term (>38 weeks)	285 (82.9)	23 (85.2)	262 (82.7)	1.00
Birth weight (kg)				
High (≥3)	294 (85.5)	25 (92.6)	269 (84.9)	
Low (<3)	50 (14.5)	2 (7.4)	48 (15.1)	0.40
Breast feeding				
<4 months	216 (66.3)	19 (73.1)	197 (65.7)	
≥4 months	110 (33.7)	7 (26.9)	103 (34.3)	0.52
Early introduction of weaning foods (<4 months)				
No	136 (41.7)	10 (38.5)	126 (42.0)	
Yes	190 (58.3)	16 (61.5)	174 (58.0)	0.84
Siblings				
No	188 (54.7)	14 (51.9)	174 (54.9)	
Yes	156 (45.3)	13 (48.1)	143 (45.1)	0.84
Day care attendance				
No	184 (53.8)	15 (55.6)	169 (53.7)	
Yes	158 (46.2)	12 (44.4)	146 (46.3)	1.00
Living in a high traffic area[d]				
No	171 (49.7)	11 (40.7)	160 (50.5)	
Yes	173 (50.3)	16 (59.3)	157 (49.5)	0.42
Presence of domestic animals in the home				
No	275 (79.9)	23 (85.2)	252 (79.5)	
Yes	69 (20.1)	4 (14.8)	65 (20.5)	0.62
Presence of allergenes in the home[e]				
No	288 (83.7)	22 (81.5)	266 (83.9)	
Yes	56 (16.3)	5 (18.5)	51 (16.1)	0.79

[a]an itchy skin condition in the last 12 months plus Nottingham score ≥3

[b]Totals may vary because of missing values

[c]p value for Fisher's exact test

[d]At least two conditions between presence of road traffic and/or bus lines and/or traffic light in the street of residence

[e]Presence of moulds and/or curtains and/or presence of carpets

0.19–0.79) and high dietary intake of folic acid (OR: 0.37, 95% CI 0.18–0.73) had a decreased risk of AD.

The present study suggests that prenatal folic acid and iron supplement intake are protective factors for AD development in the first 6 years of life. Iron is a critical cofactor in immune function and iron deficiency impairs T-cell response [5]. At experimental level, high levels of iron in diet decreased secretion of INF-gamma, although T-lymphocyte proliferation remains unaffected [17].

A recent study suggests that maternal folic acid supplement (in utero exposure) is associated with changes in DNA methylation that continue for many years after exposure [18]. DNA methylation at genes regulating immune response may be a possible epigenetic mechanism to explain the effect of folic acid on AD. As folic acid is a methyl donor, we could hypothesized that prenatal supplementation of folic acid affects in the offspring, the expression [1] of immune regulatory cytokines that are involved in AD (e.g., interferon gamma, IFNγ). Lack of adequate iron and folate in a critical period such as gestation have been suggested to impair the development and differentiation of a normal immune system [3]. Moreover,

Table 3 Association between pre-natal exposures and atopic dermatitis–multivariate analysis

Variable	ORs (95% CI)[a]	*p* value
Age group (years)		
< 30	1	
30–34	0.70 (0.26–1.90)	0.49
≥ 35	0.78 (0.28–2.14)	0.63
Educational level (years)		
Low (≤ 8)	1	
High (> 8)	0.76 (0.31–1.87)	0.55
Passive smoking exposure during pregnancy[b]		
No	1	
Yes	2.13 (0.93–4.89)	0.07
Family history of atopic dermatitis		
No	1	
Yes	2.79 (1.18–6.57)	0.02
Type of food supplements		
No supplements	1	
Iron only	0.57 (0.17–1.91)	0.36
Folic acid only	0.61 (0.15–2.46)	0.49
Both iron and folic acid	0.22 (0.06–0.79)	0.02
Mixed use[c]	0.57 (0.15–2.12)	0.40

[a]Odds ratio adjusted for mother's age and education, passive smoking during pregnancy, family history of atopic dermatitis, and type of micronutrient

[b]At home and/or work

[c]Multi-vitamins and minerals and/or iron and/or folic acid

folic acid plays an important role on strengthening epithelial barriers [3, 15].

In our study, children with family history of AD had three times an increased risk for AD in relation to children without family history of AD confirming previous findings [19] and it was the only factor besides the protective effect of folic acid and iron supplementation that remained statistically significant in the multivariate model.

Our study has strengths and limitations. The major strength was the ability of assessing both prenatal and postnatal exposures before the onset of atopic dermatitis. Other factors are the good follow-up time, the high response rate, and the possibility of controlling for many possible confounding factors (e.g. allergens and breastfeeding practice). One of the limitations of our study is the relatively small sample size and the low number of AD subjects, since we examined a cohort up to 6 years of age. However, the prevalence observed in our study corresponds to the AD prevalence in similar age group reported elsewhere [6] and the sample size was sufficient to detect the difference observed. The minimum estimated sample size with an alpha (α) of 0.05 and a power (β) of 80% was 280 subjects.

In conclusion, we suggest a protective effect for the use of both folic acid and iron supplementation during pregnancy for AD development. Further epidemiological studies with larger sample sizes are envisaged to confirm the findings.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflicts of interest to disclose.

Informed consent Informed consensus was obtained from all participants of the study.

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