

## Original Article

# Relationship between duration of breastfeeding and development of atopic dermatitis

Saeedeh Farajzadeh\*, Armita Shahesmaeili\*\*, Nasrin Bazargan\*\*\*, Zahra Mohebbi Poorkani\*\*, Zakiyeh Karaminejad\*\*, Hamideh Aghaei†, Nasim Pourdamghan\*\*

\* Department of Dermatology & Pediatric Dermatology, Kerman University of Medical Sciences, Kerman, Iran

\*\* General Practitioner, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

\*\*\*Department of Pediatric Immunology & Allergy, Kerman University of Medical Sciences, Kerman, Iran

† Department of Dermatology, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

**Abstract** *Background* Earlier studies on breastfeeding (BF) and atopy in infants have yielded contradictory results.

*Objective* To evaluate the relationship between duration of BF and developing of AD.

*Patients and methods* Seven hundred fifty infants between 2 to 3 years old from kindergartens of Kerman, Iran were enrolled in this cross-sectional study. Data were obtained by questionnaires. Diagnosis of atopic dermatitis (AD) was made according to UK Working Party criteria.

*Results* There was a significant association between duration of BF and the risk of AD (OR=0.93, 95% CI=0.90-0.96). Early supplement feeding increased the risk of AD (OR=0.69, 95% CI=0.52-0.92). The adjusted odds ratios of variables show that a positive family history of atopy, contact with smoke during pregnancy, suffering from asthma and rhinoconjunctivitis increased the risk of AD in infants. On the other hand, having elder siblings and taking oral contraceptive pills by mother decreased the risk of AD.

*Conclusion* Our results suggest that duration of BF has a protective effect against developing AD in infants. We recommend prolonged BF in all infants for protection against AD.

### **Key words**

Atopic dermatitis, breastfeeding, infant.

## **Introduction**

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Its incidence in the developed world has increased dramatically over the past several decades.<sup>1</sup> A multifactorial etiology is postulated, with genetic,

immunological and environmental factors all thought to be relevant to the pathogenesis.<sup>2</sup>

The relationship between breastfeeding (BF) and the developing of AD is a controversial issue.<sup>3</sup> While some studies have supported an inverse relationship, others have failed to show this relationship.<sup>4</sup> Although most studies agree on the protective effects of BF,<sup>5,6</sup> exclusive breastfeeding (EBF) seems to have a protective effect on the early development of allergic diseases including asthma, AD and allergic rhinitis.<sup>7</sup> In a study on the association

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### **Address for correspondence**

Dr. Saeedeh Farajzadeh,  
Pediatric Dermatology Department,  
Afzalipour Hospital,  
Kerman University of Medical Sciences,  
Tel: 0341 3222250-60, Fax: 0341 3222763  
Email: safaderm@yahoo.com

between AD and breastfeeding, EBF during the first 3 months of life was observed to decrease the risk of AD just in children with positive family history of atopy.<sup>3</sup> The probable mechanism of protective effects of BF is high levels of soluble cluster of differentiation number 14 (sCD14) in breast milk which plays an important role in innate immunity.<sup>8</sup> Another protective factor is TGF- $\beta$  in colostrum which enhances specific IgA production.<sup>9</sup> Mother's milk contains IgA, TGF- $\beta$ -type cytokines and long-chain polyunsaturated fatty acids that may play an important role in the acquisition of tolerance to food and the prevention of AD.<sup>10</sup> Some studies found reverse relationship between AD and BF. A cohort study showed that each month of BF increased the risk of AD.<sup>11</sup> Breast milk fatty acids may have immunomodulatory properties related to the development of AD. Hoppu *et al.*<sup>12</sup> in 2005, found that breast milk rich in saturated and low in n-3 fatty acids can be a risk factor for AD in the infant.

These different outcomes may be due to the effect of confounding factors like contact with pet, cigarette smoking, birth weight and maternal delivery age. Other factors which may cause this controversy to occur are duration of BF, different definition of EBF, study design, sample size and different criteria used for diagnosis of AD. We did this cross-sectional study to investigate the relationship between duration of BF and AD in 2 to 3 year old infants in kindergartens of Kerman, Iran considering the confounding factors.

### Patients and methods

In this cross-sectional study, 750 infants between 2 to 3 years old were enrolled. All subjects were selected from 55 kindergartens in Kerman, Iran by stratified random sampling method. Clinical manifestations of AD were examined by two dermatology-oriented general practitioners and recorded in the

questionnaires. In order to validate the BF data in questionnaires, parents were asked if and at what age the infant had first been fed breast milk, formula and supplement. In order to adjust for potential confounding factors, parents were also asked about infant's sex, age, birth weight, older sibling, preterm birth, duration of BF, symptoms of asthma, AD, and rhinoconjunctivitis, family history of atopy (rhinoconjunctivitis, AD, asthma), history of contact with furred pets, plants, carpet and cigarette smoke, maternal contact with cigarette smoke and pets during pregnancy, delivery age and taking oral contraception pill. Diagnosis of AD was based on UK working party criteria.<sup>13</sup> Criteria for diagnosing asthma were obtained from Global Initiative of Asthma.<sup>14</sup> Diagnosing rhinoconjunctivitis was according to its definition (sneezing, rhinorrhea, nasal and eye itch and nasal congestion).<sup>15</sup> Exposure to furred pets was defined as presence of furry animals like cat, dog, sheep and cow at the infant's house. Preterm birth was defined as gestational age less than 37 completed weeks. Contact with smoke more than four days in a week was regarded as a case exposed to smoke. Age of beginning formula was divided into 3 groups: less than four months, four months, not formula fed.<sup>4,16</sup>

Data were entered and analyzed using SPSS version 15 soft ware. Categorical data were analyzed for significance with  $X^2$  test and numeric data were analyzed with independent sample t-test. We conducted logistic regression analysis (backward: LR method) to estimate the association between relevant predictor variables and the outcome. The predictor variables were identified from the literature as possible factor that may be associated with infantile AD including infant's sex, age, birth weight, older sibling, preterm birth, duration of BF, suffering from asthma and rhinoconjunctivitis, a family history of atopy, a history of contact with furred pets, plants,

carpet and cigarette smoke, age of starting supplement and formula, also maternal contact with cigarette smoke and pets during pregnancy, delivery age and taking oral contraception pill. Crude and adjusted odds ratios were reported for variables that met the 0.1 significance level in the model. A *p* value of less than 0.05 was considered significant.

## Results

Of 750 infants who have been studied, 140 (18.7%) suffered from AD and 610 (81.3%) were healthy. The mean age of infants with AD was significantly lower than healthy infants ( $29.76 \pm 5.04$  vs.  $31.04 \pm 4.98$  months,  $p=0.008$ ). Eighty one infants (57.9%) with AD and 313 healthy infants (51.3%) were male, whereas 59 AD infants (42.1%) and 297 healthy infants (48.7%) were female. This difference was not statistically significant. The characteristics of the atopic and non atopic subjects have been shown in **Table 1**. The mean duration of BF in AD and healthy infants was  $15.67 \pm 8.25$  and  $19.84 \pm 7.08$  months, respectively. There was a significant association between duration of BF and the risk of AD, so that with an increase in the BF duration the risk of AD was decreased (OR=0.93, 95% CI=0.90-0.96). Early supplement feeding increased the risk of AD (OR=0.69, 95% CI=0.52-0.92). The adjusted odds ratios of variables showed that a positive family history of atopy, contact with smoke during pregnancy, suffering from asthma and rhinoconjunctivitis increased the risk of AD in infants. Having older sibling and using oral contraception by mother decreased the risk of AD (**Table2**).

## Discussion

According to our results, with an increase in BF duration and delay in the beginning of supplement food, the risk of AD in infants decreased. As mentioned above, each month of

BF decreased the risk of AD (OR=0.9). History of asthma and rhinoconjunctivitis in infant, maternal passive smoking during pregnancy and a positive family history of atopy seem to be risk factors for AD, but having elder siblings and taking oral contraception pills by mother decreased the odds of AD in infants. Results of previous researches in this field can be classified into 3 categories:

1. BF increases the risk of AD.
2. BF decreases the risk of AD.
3. BF has no effect on developing AD.

Kull *et al.*<sup>17</sup> in 2005 in Sweden demonstrated that EBF for more than four months reduced the risk of AD at four years of age in those with or without a family history of allergy in comparison with infants who breast fed for a shorter period.<sup>4</sup> A meta-analysis of 18 prospective studies in 2001 in Israel that compared the incidence of AD in breastfed infants with infants who were fed cow's milk formula showed that EBF during the first 3 months of life is associated with lower incidence of AD during childhood in children with a family history of atopy.<sup>3</sup> The protective effect of BF can be due to some bioactive substances in breast milk. The IgA, TGF- $\beta$  cytokines and long-chain polyunsaturated fatty acids of the mother's milk may have an important role in the acquisition of tolerance to food and prevention of AD.<sup>10</sup> In addition, soluble CD14 is another substance in breast milk which plays an important role in innate immunity. The protective effects of breastfeeding on AD might be further supported by high levels of soluble CD14 in breast milk.<sup>8</sup> In contrast, Bergmann *et al.*<sup>11</sup> conducted a cohort study in Germany in 2002 which showed that each month of BF elevates the risk of developing AD in the first 7 years by 3%.

**Table1** The characteristics of atopic and non atopic subjects

Characteristic	AD	No AD
Duration of breastfeeding (month)	15.67 ± 8.25	19.84 ± 7.08
Age of beginning supplement (month)	5.76 ± 1.00	6.19 ± 2.08
Birth weight (gram)	3031.62 ± 521.36	3138.98 ± 459.31
Maternal delivery age (year)	25.72 ± 4.11	26.54 ± 4.79
Age (month)	29.76 ± 5.04	31.04 ± 4.98
Age of beginning formula (month)		
not formula fed	78 (55.7%)	403 (66.1%)
≥4 mo formula fed	27 (19.3%)	99 (15.1%)
<4mo formula fed	35 (25%)	115 (18.9%)
Older sibling	58 (41.4%)	287 (47%)
Using OCP by mother	56 (42.1%)	113 (19.2%)
Contact with pets during pregnancy	23 (16.4%)	72 (11.8%)
Sex (male)	81 (57.9%)	313 (51.3%)
Maternal contact with smoke during pregnancy	35 (25.0%)	95 (15.6%)
Contact with pets	21 (15.0%)	58 (9.5%)
Indoor smoking	37 (26.4%)	89 (14.6%)
Carpet in room	99 (70.7%)	421 (69.0%)
Contact with plants	52 (37.1%)	256 (43.4%)
Suffering from asthma	63 (45.0%)	64 (10.5%)
Suffering from rhinoconjunctivitis	64 (45.7%)	99 (16.2%)
Maturity (preterm)	21 (15.8%)	70 (11.8%)
Positive family history of atopy	109 (77.9%)	245 (40.2%)

AD=Atopic dermatitis, OCP=oral contraceptive pills.

**Table 2** Crude and adjusted odds ratios of evaluated variables

Characteristic	Crude OR (CI 95%)	P. value	Adjusted OR (CI95%)	P. value
Family history of atopy	5.23 (3.40-8.05)	0.00	3.74 (2.16-6.48)	0.00
Older sibling	0.79 (0.54-1.15)	0.22	0.50 (0.30-0.83)	0.00
Duration of breastfeeding	1.06 (1.04-1.09)	0.00	0.93 (0.90-0.96)	0.00
Age of beginning supplement	1.24 (1.03-1.49)	0.19	0.69 (0.52-0.92)	0.01
Contact with smoke during pregnancy	1.80 (1.16-2.80)	0.00	2.08 (1.15-3.77)	0.01
Using OCP by mother	3.06 (2.05-4.57)	0.00	0.41 (0.24-0.69)	0.00
Suffering from asthma	6.98 (4.57-10.64)	0.00	3.01 (1.73-5.21)	0.00
Suffering from rhinoconjunctivitis	4.34 (2.92-6.45)	0.00	2.81 (1.63-4.85)	0.00
Using carpet in room	1.08 (0.72-1.62)	0.69	1.58 (0.90-2.78)	0.10
Contact with pets during pregnancy	1.46 (0.88-2.44)	0.14	1.80 (0.91-3.53)	0.08

OCP=oral contraceptive pills.

Purvis *et al.*<sup>18</sup> in 2005 also found that duration of BF was associated with an increased risk of AD in New Zealand children at 3.5 years of age. In their retrospective study in Japan, Nakamura *et al.*<sup>19</sup> also demonstrated that breast milk would slightly elevate the risk of AD. Breast milk does contain small amounts of foreign proteins transferred from mothers and there are reports of AD improvement in breastfed infants when their mothers would start an exclusion diet or stop BF.<sup>20</sup>

Such differences in results can be due to infant's age; in Bergman *et al.*<sup>11</sup> and Purvis *et al.*<sup>18</sup> studies, infants were followed up to 7 years and 3.5 years, respectively whereas we performed our study only in 2 to 3 year old infants. We did not look at AD in later ages of childhood. Controversy in mentioned researches could be due to methodological differences for example prospective vs. retrospective studies, interventional vs. observational and self-selective vs. randomized studies. Moreover, different

diagnostic criteria for AD and varying accuracy in filling the questionnaires can also affect the results. Another reason is that observational studies might not be able to control biases such as genetic, environmental and behavioral factors. The main factor that may induce a bias is breastfeeding that ethically and naturally could not be randomized or blinded.

Another factor that decreased the risk of AD in our study was a delay in beginning the supplementary food. There is some evidence that early solid food diet could increase the risk of AD.<sup>21</sup> In a prospective birth cohort study of 1265 New Zealand neonates evaluated by chart reviewing the early introduction of solid foods on eczema by ages 2 and 10 years, solid food feeding patterns were associated with eczema but not asthma. A significant linear relationship was observed between the number of solid foods introduced from birth to four months and the incidence of eczema by 2 years and a recurrent chronic eczema by 10 years.<sup>22</sup> In another study on the relationship between early solid food introduction and asthma by 4 years of age, no such relationship could be found.<sup>23</sup> A prospective randomized study of high risk newborns found that eczema at 1 year of age decreased in infants exclusively breastfed for 6 months compared with a group of breastfed infants in whom solid foods were introduced at 3 months of age.<sup>24</sup> An increase in age and a development of gut integrity and intestinal mucosal barrier function would enhance the immune system function. So, delay in initiating supplements may associate with lower risk of AD.<sup>25</sup>

There are many perinatal risk factors associated with AD. There is a great body of evidence that siblings have a protective effect against atopic diseases such as hay fever, atopic eczema, allergic sensitization or asthma. In the present study, we found that having

elder sibling has a protective effect against AD. One hypothesis is that siblings would promote early infections in children, and repeated infections protect against atopic disorders. According to other hypothesis, the potential in utero programming has been neglected. In 2001, Karmaus *et al.*<sup>26</sup> found that umbilical cord IgE decreased with an increase in birth number; hence, this indicates that the sibling effect may have its origin in uterus. Our results also showed that a maternal history of oral contraceptive pills (OCP) consumption is associated with decreased risk of AD. The role of OCP, as a protective or risk factor for AD, is not yet clear. Peters and Golding, in 1987, reported an increased risk of eczema for children of mothers who had used oral contraceptives in the 18 months prior to the index pregnancy,<sup>27</sup> but in another study conducted in 2004, there were no increased odds of eczema in offsprings of mothers with a positive history of OCP consumption.<sup>28</sup> So, more studies in this field are needed. Maternal passive smoking during pregnancy was another risk factor that contributed to elevated odds of AD in infants. The role of passive/active maternal smoking in the past and during pregnancy was evaluated in some studies. In an animal study, environmental tobacco smoke exposure influenced the immune response toward a Th2 type and indicated that smoking may be a Th2 adjuvant.<sup>29</sup> Presence of IgE antibodies and abnormalities in cord blood interleukin-4 and interferon gamma levels have also been related to maternal smoking in pregnancy in some articles.<sup>30</sup> So, maternal exposure to smoke during pregnancy can be a risk factor for developing AD in infants by its effect on these immune factors. The high incidence of atopic disease in the family history of AD children in previous studies is in concordance with our results regarding the hereditary background of the disease.<sup>31-35</sup> We also found that AD is associated with asthma and allergic rhinoconjunctivitis. This may be explained by

the correlation between IgE levels, eczematous symptoms and bronchial hyperresponsiveness. Children with visible dermatitis have higher IgE concentrations<sup>36</sup> and children with high IgE concentrations have been shown to develop bronchial hyperresponsiveness.<sup>37</sup> Thus, this mechanism may involve IgE mediated events.

### Strengths and limitations

In this study, we have considered other risk factors of atopic dermatitis as confounders, but we are totally aware that those observational studies such as the present study are not able to control biases effectively, and the main factor is breastfeeding because it is the personal choice of mothers whether or not to breastfeed their infants; by the way, breastfeeding could not be randomized, ethically and naturally. Another factor is maternal recall of precise duration of breastfeeding which could lead to a recall bias.

### Conclusion

Our results suggest that duration of breastfeeding, having elder siblings, delay in the age of introducing supplements and a history of maternal OCP consumption are the most important risk factors that would protect against developing AD in infants, but family history of any atopic disease, maternal passive smoking during pregnancy and a history of asthma and rhinoconjunctivitis are associated with increased odds ratios of AD. Hence, due to many other benefits of BF, we would recommend prolonged breastfeeding in all infants for protection against AD.

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