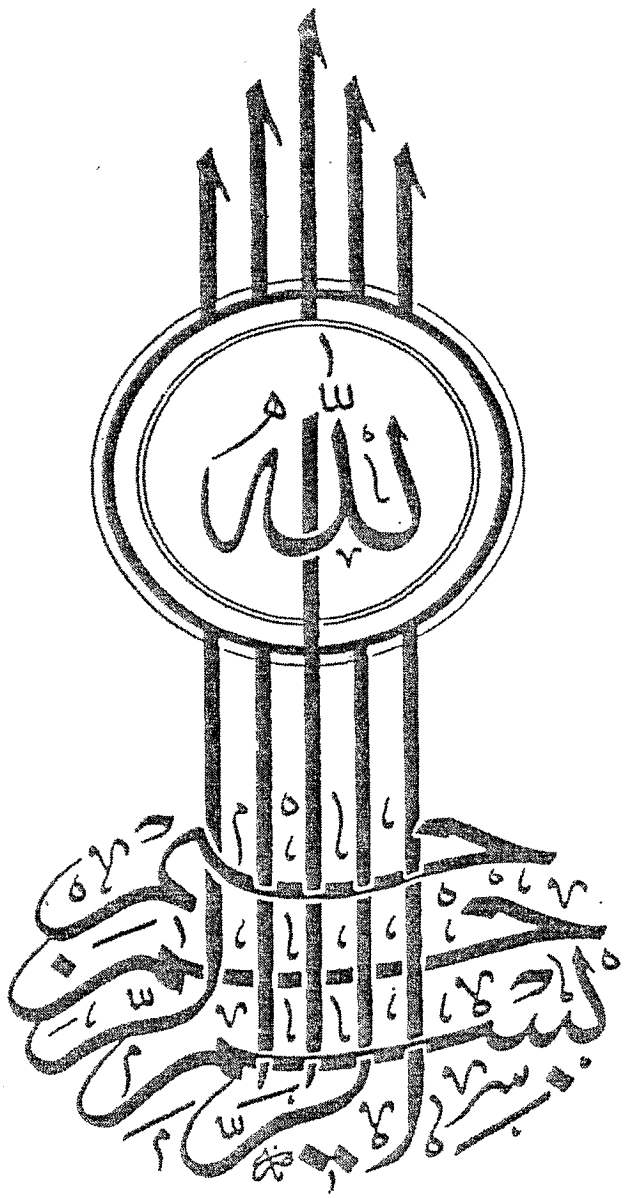

پروردگارا!

سپاست می گویم که به من منت نهاده، خلعت تحصیل علم بر من پوشاندی،

از درگاه پرالطافت خواستارم که بر قلبم ایمان، در بازوانم توان و بر قدمم استواری

بخشی تا غمگسار بندگانت باشم.

دانشگاه علوم پزشکی
و خدمات بهداشتی درمانی کرمان
دانشکده پـزشکی مهندس افضلی‌پور

پایان‌نامه:

برای دریافت درجه دکترای پـزشکی

عنـوان:

بررسی رابطه طول مدت تغذیه با شیر مادر با درماتیت آتوپیک در کودکان ۳-۲ ساله مهدکودکهای شهر کرمان در سالهای ۸۶-۱۳۸۵

۱۳۸۷/۹/۱۱

استـاد راهنما:
سرکار خانم دکتر سعیده فرج زاده

پژوهش و نگـارش:
زهرا محبی پورکانی
زکیه کرمی نژاد

بهـار ۱۳۸۷

با تقدیر و تشکر از:

استاد گرانقدر

سرکار خانم دکتر فرج زاده

به پاس راهنمایی های بی دریغشان

تقدیم به:

"پدر و مادر مهربان و صبورم"

عزیزانی که با اشکهایم می گریند و با لبخندی

جان می گیرند .

بر دستان پرمهر شان بوسه می زنم

و تقدیم به :

همسر مهربانم

[حسین عزیز]

زهرا

تقـدیم به:

خواهر و بـرادران عـزیزم که :

زندگیم با وجود آنها رنگین شد

چشم انتظار دیدن موفقیت هایشان هستم .

زهرا

تقدیم به:

پدر و مادر مهربانم

که وجودشان برایم همه عشق بود و وجودم برایشان همه رنج

توانشان رفت تا به توانایی برسم، مویشان سپیدی گرفت تا روی سپید بمانم

آنان که فروغ نگاهشان، گرمی کلامشان و روشنی رویشان سرمایه جاودانی زندگیم

است. در برابر وجود گرامیشان زانوی ادب بر زمین می‌نهم و با دلی مالامال از عشق و

محبت بر دستانشان بوسه می‌زنم. باشد که با این اندک، قطره‌ای از دریای

زحمات آنان را ارج نهاده باشم.

زکیه

تقدیم به : همسرم " عباس "

هدیه خوب خداوند و همدم صبور لحظه هایم .

تقدیم به خواهران و برادران عزیزم :

آنان که خاطره های قشنگ زندگیم با ایشان سپری شد

آنان که محبتشان همیشگی است و تجلی گاه آرزوهایم

آینده روشن آن است .

تقدیم به خواهر زاده دوست داشتنی ام : " جابر "

که وجودش در این سالها مایه دلگرمی ام بود .

زکیه

فهرست

Abstract:

Introduction: Earlier studies on breastfeeding (BF) and atopy in infants have yielded contradictory results.

Aim: The aim of this study was to evaluate the relationship between duration of BF and developing of AD.

Method: Seven hundred fifty infants between 2-3 years old from kindergartens of Kerman, Iran entered into this cross sectional study. Data were obtained by questionnaires. Diagnosis of 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 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 greater siblings and using OCP 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, formula, 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 (1). A multifactorial aetiology is postulated, with genetic, immunological and environmental factors all thought to be relevant to the pathogenesis (2). The relationship between breastfeeding (BF) and the developing of AD is a controversial issue (3). While some studies have supported an inverse relationship, others have failed to show this relationship (4). Although most studies agree on the protective effects of BF (5,6).

Exclusive breast feeding (EBF) seems to have a protective effect on the early development of allergic diseases including asthma, AD and allergic rhinitis (7). In a study on the association between AD and breastfeeding, EBF during the first 3 months of life decrease the risk of AD just in children with positive family history of atopy (3). The probable mechanism of protective effects of BF are high levels of soluble cluster of differentiation number 14 (sCD14) in breast milk which plays an important role in innate immunity (8). Other protective factor is TGF-β in colostrum which enhances specific IgA production (9). Mother's milk contain IgA, TGFb-type cytokines and long–chain polyinsaturated fatty acids that may play an important role in the acquisition of tolerance to food and the prevention of AD (10). Other studies found reverse relationship between AD and BF. A cohort study showed that each month of BF increased the risk of AD (11). Breast milk fatty acids may have immunomodulatory properties related to the development of AD Hoppu et al 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 (12).

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 considering for diagnosis of AD. We did this cross-sectional study to investigate the relationship between duration of BF and AD; in 2-3 years old infants in kindergartens of Kerman, Iran considering the confounding factors.

Methods

In this cross-sectional study 750 infants between 2-3 years old were enrolled to the study. All subjects were selected from 55 kindergartens in Kerman, Iran by stratified random sampling method. Clinical manifestations of AD were examined by two educated general practitioner 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 pet, plants, carpet and cigarette smoke; also maternal contact with cigarette smoke and pet during pregnancy, delivery age, using oral contraception pill. Diagnosis of AD was based on UK working party criteria (13). Criteria for diagnosing of asthma obtained from Global Initiative of Asthma (14). Diagnosing of rhinoconjunctivitis was according to its definition (sneezing, rhinorrhoea, nasal and eye itch and nasal congestion) (15). Exposure to furred pets was defined as presence of furry animals like cat, dog, sheep and cow at the infant's home. Preterm birth was defined as gestational age < 37 completed weeks. Contact with smoke > 4 days in a week was regarded as exposed to smoke. Age of beginning formula divided in to 3 groups ;< 4 months, ≥ 4 months, not formula fed (4, 16).

Data were entered and analyzed using SPSS version 15 soft ware. Categorical data were analyzed for significance with X2 test and numeric data were analyzed with independent sample t-test. We conducted logistic regression analysis (back ward: LR method) to estimate the association between relevant predictor variables and the out come. 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, family history of atopy, history of contact with furred pet, plants, carpet and cigarette smoke, age of beginning supplement and formula, also

maternal contact with cigarette smoke and pet during pregnancy, delivery age, using oral contraception pill". Crude and adjusted odds ratios were reported for variables that meet the 0.1 significance level in the model. $P<0.05$ was considered significant.

Results

Of 750 infants which 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 ± 5.04 v/s 31.04 ± 4.98 months, $p = 0.008$). Eighty one (57.9%) of infants with AD and 313 (51.3%) of healthy infants were male, whereas 59 (42.1%) of AD infants and 297 (48.7%) of healthy infants 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 ± 8.25, 19.84 ± 7.08 months respectively. There was a significant association between duration of BF and the risk of AD, so that with increasing of the BF duration the risk of AD has been 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 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 increasing of the BF duration and delay on the beginning of the supplement food, 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 rhinocojunctivits in infant, maternal passive smoke during pregnancy and positive family history of atopy seems to be risk factors for AD, but having greater sibling and using oral contraception by mother decreased the odds of AD in infants Results of previous researches in this field can be classified in to 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 in 2005 in Sweden demonstrated that EBF for more than 4 months reduces the risk of AD at 4 years of age in those with or without a family history of allergy in comparison to infants who breast fed for a shorter period (17, 4). 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 (3). The protective effect of BF can be due to some bioactive substances in breast milk. The IgA, TGF b cytokines and long-chain polyinsaturated fatty acids of the mother's milk may have an important role in the acquisition of tolerance to food and prevention of AD (10). In addition soluble CD14 is another substance in breast milk which plays an important part in innate immunity. The protective effects of breastfeeding on AD might be further supported by high levels of soluble CD 14 in breast milk (8). In contrast Bergmann et al in 2002 in a cohort study in Germany showed that each month of BF elevates the risk of developing AD in the first 7 years by 3% (11) Purvis et al in 2005 have also found that duration of BF was associated with an increased risk of AD in New Zealand children at 3.5 years of age (18). Nakamura e

al in their retrospective study in Japan also demonstrated that breast milk slightly elevates the risk of AD (19). Breast milk does contain small amounts of foreign proteins transferred from the mother and there are reports of AD improving in breastfed infants when their mothers started an exclusion diet or stopped BF (20). These differences in results can be due to infant's age; in Bergman et al. and Purvis et al. studies infants were followed up to 7 years and 3.5 years respectively whereas we performed our study only in 2-3 years old infants. We didn't look at AD in later ages of childhood. Controversy in mentioned researches can be resulted by the methodological differences for example prospective v/s retrospective studies, interventional v/s observational and self–selective v/s randomized studies. More over, different diagnostic criteria for AD, different accuracy in filling of the questionnaires can 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 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 delay in beginning of the supplementary food. There is some evidence that early solid food diet increase the rate of AD (21). In a prospective birth-cohort study of 1265 New Zealand neonates evaluated by chart review 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 seen between the number of solid foods introduced from birth to 4 months and the incidence of eczema by 2 years and recurrent chronic eczema by 10 years (22). In another study on the relationship between early solid food introduction and asthma by 4 years of age no such relationship could be found (23). In another prospective randomized study of high risk newborns found that eczema at 1 year was reduced 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 (24). By increasing age, gu

integrity and intestinal mucosal barrier function being more developed, on the other hand, the immune system function enhance. So delay on initiation of supplement may associate with lower risk of AD (25).

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 present study we found that having older sibling have a protective effect against AD. One hypothesis is that siblings promote early infections in children, and repeated infections protect against atopic disorders. According to other hypothesis, the potential in utero programming has been neglected. Karmaus et al in 2001 found that umbilical cord IgE reduces with increasing birth number so this indicating that the sibling effect may have its origin in utero (26).

Our results also shows that 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 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 (27), but in another study that was conducted in 2004, there was not any increased odds of eczema in off springs of mothers with positive history of OCP consumption (28). 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 adjuant (29). 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 (30). 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 supports our results that concerning the hereditary background of the disease (31, 32, 33, 34, 35). We also found that AD is associated with asthma and allergic rhinoconjunctivittes. This may be explained by the correlation between IgE levels, eczematous symptoms and bronchial hyperresponsiveness. Children with visible dermatitis have higher IgE concentrations (36) and children with high IgE concentrations have been shown to develop bronchial hyperresponsiveness (37). Thus, this mechanism may involve IgE mediated events.

Strength and limitations

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

Conclusion

Our results suggest that duration of breast feeding, having greater siblings, delay in the age of introduction of supplement and history of maternal OCP consumption are the most important risk factors that protect against developing AD in infants, but family history of any atopic disease, maternal passive smoking during pregnancy and history of asthma and rhinoconjunctivits are associated with increased odds ratios of AD. So, because of many other benefits of BF, we recommend prolonged breastfeeding in all infants for protection against AD.

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