Paediatrica Indonesiana

VOLUME 54 January • 2014 NUMBER 1

Original Article

Exposure to cow's milk as a prognostic factor for atopic dermatitis during the first three months of life

Putu Ayu Widyanti[1], Endy P. Prawirohartono[2], Ketut Dewi Kumara Wati[1]

Abstract

Background The incidence of atopic dermatitis has increased in the early life of children. Cow's milk, the first foreign protein to which infants are exposed, is predicted to be a prognostic factor of atopic dermatitis.

Objective To determine if exposure to cow's milk is a prognostic factor for atopic dermatitis during the first three months of life.

Methods We performed a cohort study involving 136 newborns from families with and without histories of atopy in Sanglah Hospital, Denpasar, between April to August 2012. Subjects were allocated into 2 groups, those who were exposed to cow's milk (n=68) and not exposed to cow's milk (n=68). We analyzed the impact of several possible prognostic variables on atopic dermatitis at 3 months of age including exposure to cow's milk, birth weight, sex, gestational age, exposure to cigarette smoke, early solid feeding, and history of atopy in the mother, the father, or both, as well as maternal consumption of chicken eggs when nursing. Data were analyzed with Cox's proportional hazard function. The cumulative incidence and incidence rate in each group were calculated.

Results Exposure to cow's milk in the first 3 months of life resulted in a cumulative incidence of atopic dermatitis of 17.6%, with an incidence rate of atopic dermatitis of 54.5%. However, multivariate analysis showed that cow's milk exposure was not a significant prognostic factor for atopic dermatitis (HR 1.37; 95%CI 0.22 to 8.43).

Conclusion Cow's milk exposure is not a prognostic factor of atopic dermatitis during the first three months of life. **[Paediatr Indones. 2014;54:28-34.]**

Keywords: *cow's milk, atopic dermatitis, prognostic*

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disease characterized by severe itching, and localized to certain parts of the body.[1-7] According to the International Study of Asthma and Allergies in Childhood, the prevalence of AD in children aged 6-7 years over a 1 year period varied from less than 2% in Iran and China, to about 20% in Australia, Britain, and Scandinavia.[4,8-12]

Many factors are thought to be prognostic for AD, such as genetics, age, birth weight, sex, food allergens, especially cow's milk (CM), as well as early introduction of solid food, aeroallergens, and other environmental factors including exposure to tobacco smoke.[13-20] The consumption of cow's milk has increased parallel to the increased incidence of AD. Although there have been many studies on AD and exposure to cow's milk in atopic families, relatively few have been done in non-atopic families.[10,12-14,17-21] In addition, those studies were mostly done in the first year of life.[13,17,18,20,21] We aimed to assess exposure to cow's milk in an earlier period of life, the first three months, as a prognostic factor for AD.

From the Departments of Child Health, Udayana University Medical School/Sanglah Hospital, Denpasar[1] and Gadjah Mada University, Sardjito Hospital, Yogyakarta.[2]

Reprint requests to: Putu Ayu Widyanti, Department of Child Health, Udayana University Medical School, Sanglah Hospital, Jl. Pulau Nias Denpasar Bali. Tel./Fax: +62361-244038. E-mail: dr.widyanti@gmail.com.

Methods

We performed a cohort study to assess the impact of exposure to cow's milk on the incidence of AD at 3 months of age in Sanglah Hospital, Denpasar, between April to August 2012.

Subjects' inclusion criteria were newborns who did not consume hypoallergenic milk formula, require incubator care, undergo phototherapy, and whose parents could be contacted by telephone, lived in Bali, did not plan to travel away from Bali for the 3 months of the study, and consented to participate by signing a proxy consent form. We excluded infants with severe illness, such as severe congenital abnormalities or severe infections, and those whose parents had no mobile phone. Newborn infants were allocated into two groups by consecutive sampling, with and without exposure to cow's milk. Sample size was calculated based on Z score for α at (0.05) and a power of 80%, P_1 61%, P_2 35%, and 10% lost to follow up, yielding a minimum required sample size of 120, with 60 infants in each group.

The outcome of this study was AD, whereas potential prognostic factors were history of atopy in mother, father, both parents, sex, gestational age, birth weight, exposure to cigarette smoke, early solid feeding, as well as parents' educational and socioeconomic level, along with consumption of cow's milk or chicken eggs by nursing mothers. Infants were considered to be exposed to cow's milk if they consumed cow's milk formula, pure cow's milk and/or foods containing cow's milk, at any frequency and amount. Atopic dermatitis was confirmed by Hanifin and Rajka's criteria.[7]

The independent variables in this study as well as prognostic factors were maternal, paternal, and both parents' history of atopy, infant gender, gestational age at birth, birth weight, exposure to cigarette smoke, early solid food, maternal educational level, and family socioeconomic level. Gestational age was calculated from the first day of the last menstrual period expressed in weeks, and classified into <37 weeks and ≥ 37 weeks. Birth weight was measured within 1 hour of birth, and divided into <2500 grams and ≥ 2500 grams. Early solid food was defined as subjects consuming solid food during the observation period.

Mothers or fathers were considered to have a history of atopy if they had either AD (characterized by recurrent itch, redness, dry skin, linear scratch marks, and/or fissures, in certain body parts such as the elbow crease or knee crease), asthma (characterized by recurrent shortness of breath and wheezing, usually occurring in cold air or early morning or induced by allergens) or allergic rhinitis (characterized by recurrent sneezing, itchy nose, runny nose, or nasal congestion during particular seasons or times of year or otherwise induced by allergens).

Subjects were considered to be exposed to cigarette smoke for those with a history of maternal smoking during pregnancy or after birth, with or without any other family members smoking in the house. Maternal educational level was divided into low and high education, below junior high school and high school or higher levels, respectively.

Socioeconomic level was determined by the total monthly family income in Indonesian rupiah (IDR), and divided into low and high socioeconomic levels, at $\leq$ IDR 2,500,000.00 and $>$ IDR 2,500,000.00, respectively.

History of exposure to cow's milk or egg was defined as maternal consumption of cow's milk or chicken egg during nursing.

Parents from eligible subjects were given an explanation on the signs and symptoms of AD using brochures containing pictures of infants with AD symptoms. We also gave parents a list of questions on the signs and symptoms of AD to help parents recognize them before reporting to the researchers through phone numbers listed on the brochure.

Every 2 weeks parents were contacted by phone to report on their child's AD symptoms. Subjects with AD symptoms were asked to visit Sanglah Outpatient Clinic for confirmation by the pediatrician or chief resident. For subjects unable to travel to the clinic, a researcher visited their home to take a photograph and report to the pediatrician for confirmation of the AD diagnosis. The inter-rater reliability among the pediatrician and chief residents was assessed before the study yielding a Kappa value of 72.2%. During the phone calls to parents, researchers also asked about exposure to cow's milk, solid food, cigarette smoke, and the diet of nursing mothers in the 2 weeks prior to the phone call.

Subjects who were originally in the not exposed to cow's milk group (non-CM group), but then exposed to cow's milk more than once, were considered

to be dropped out from the study, then moved into the exposed to cow's milk group (CM group). These subjects were followed up until the age of 3 months. Subjects unable to be contacted were considered as lost to follow-up.

The incidences of AD in the CM and non-CM groups were calculated as cumulative incidence and incidence rates. Inferential statistical analyses were conducted to test the prognostic value of the independent variables in two stages. The first stage was to construct a univariate Kaplan-Meier curve describing the relationship between each independent variable and the dependent variable. All variables that showed uncrossed Kaplan-Meier curves were analyzed by Cox's proportional hazard function. Significance was expressed by hazard ratio (HR) and 95% confidence interval (CI). Statistical analysis was performed with SPSS version 20 (SPSS Inc., IL, Chicago, USA). This study was approved by the Research Ethics Committee at the Udayana University Medical School, Sanglah Hospital, Denpasar.

Results

During the study period, 138 subjects met the eligibility criteria, with 63 subjects in the CM group and 75 subjects in the non-CM group. Seven subjects dropped out from the non-CM group, then entered the CM group. Two subjects in the CM group were

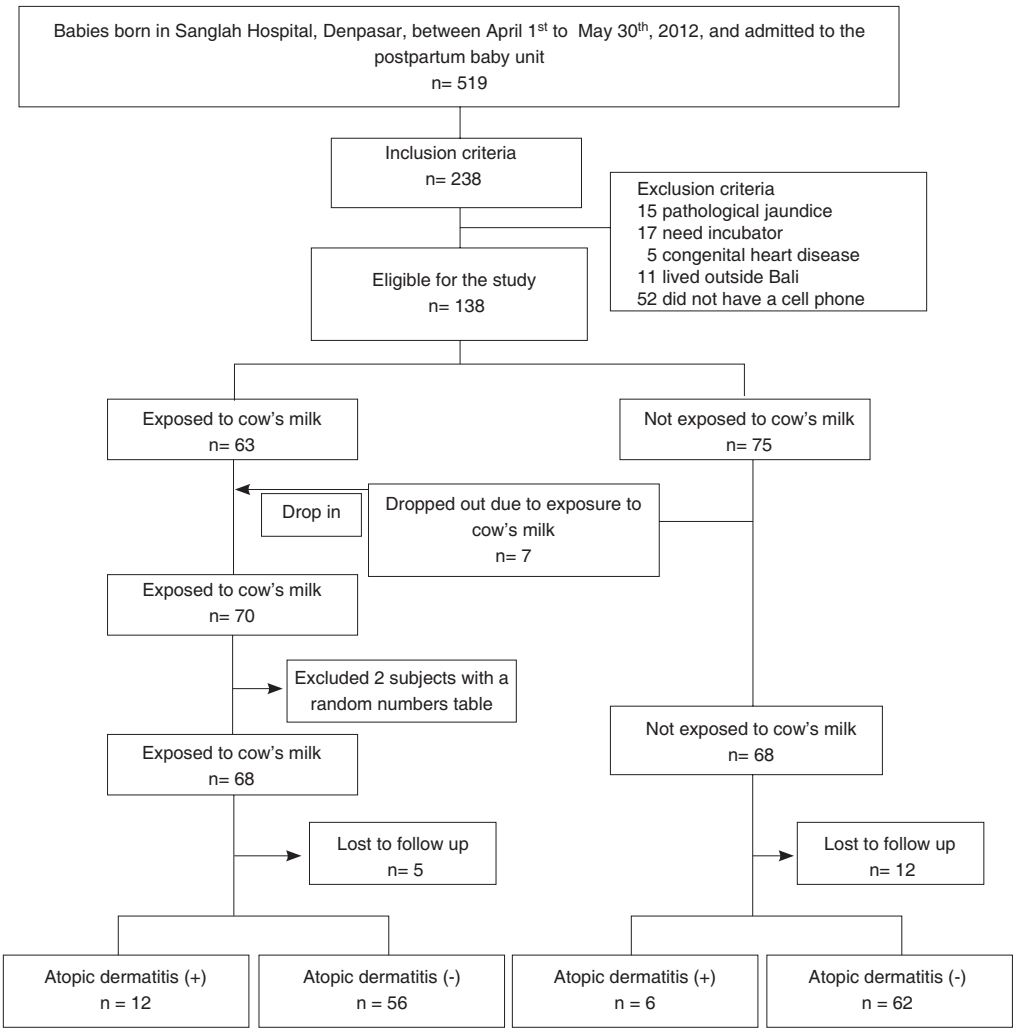

Figure 1. Research study outline

excluded by a random numbers table. At the final analysis, there were 68 subjects in each group. There were 17 subjects (13%) lost to follow-up, 5 (8%) in the CM group, and 12 (16%) in the non-CM group (**Figure 1**).

Characteristics of the study subjects are presented in **Table 1**. Most subjects were boys (60%), with birth weights ≥2500 grams (87%), full term (90%), from low-income families (78%), and had mothers with low education level (56%). Mother history of atopy and enviromental tobacco smoke exposure in the CM group were 19.2% and 51.5%, respectively, while those of the non-CM group were 19.2% and 54.4%, respectively. During breastfeeding, 54.4% of all mothers consumed chicken eggs and/or cow's milk, 24.3% did not consume these foods, while the remaining 21.3% were not nursing mothers.

The cumulative AD incidence for the three-month observation period were 13.2% for both groups, 17.6% for the CM group and 8.8% for the non-CM group. The incidence rate of AD for the CM group was 54.5%, while that of the non-CM group was 66.7%.

Table 1. Study subjects' characteristics

Characteristics	Cow's milk exposure	
	Yes (n = 68)	No (n = 68)
Gender, n (%)		
Boys	42 (61.8)	39 (57.4)
Girls	26 (38.2)	29 (42.6)
Birth weight, n (%)		
<2500 grams	9 (13.2)	9 (13.2)
≥2500 grams	59 (86.8)	59 (86.8)
Gestational age, n (%)		
<37 weeks	8 (11.8)	5 (7.4)
≥37 weeks	60 (88.2)	63 (92.6)
Mother's median age (range), years	28 (16-42)	26 (16-45)
Father's mean age (SD), years	31.8 (5.94)	32.3 (7.24)
Parents' occupation, n (%)		
Not working	5 (7.4)	2 (2.9)
Private employee	53 (77.9)	56 (82.4)
Government employee	3 (4.4)	2 (2.9)
Entrepreneur	7 (10.3)	8 (11.8)
Parents' history of atopy, n (%)		
Father only	7 (10.3)	2 (2.9)
Mother only	13 (19.2)	13 (19.2)
Both parents	1 (1.4)	2 (2.9)
No atopic history	47 (69.1)	51 (75.0)
Early solid feeding, n (%)		
Yes	1 (1.4)	1 (1.4)
No	67 (98.6)	67 (98.6)
Environmental tobacco smoke exposure, n (%)		
Yes	35 (51.5)	37 (54.4)
No	33 (48.8)	31 (45.6)
Maternal education level, n (%)		
Low	33 (48.5)	42 (61.8)
High	35 (51.5)	26 (38.2)
Socioeconomic level, n (%)		
Low	50 (73.5)	57 (83.8)
High	18 (26.5)	11 (16.2)
When nursing, maternal consumption of chicken eggs and/or cow's milk, n (%)		
Yes	26 (38.2)	48 (70.6)
No	13 (19.1)	20 (29.4)
Mother not nursing	29 (42.7)	0 (0)

Kaplan-Meier curves of all prognostic factors did not intersect (data not shown), so all prognostic factors were analyzed using Cox's proportional hazard analysis multivariate function.

Table 2 shows the three variables with P < 0.25, however, the confidence intervals were not significant. Subjects in the CM group had a cumulative AD incidence 8.8% higher and occurred earlier than in those the non-CM group in the first 3 months of life (HR 1.37; 95%CI 0.22 to 8.43). Another prognostic factors that also showed P < 0.25 were exposure to cigarette smoke and subjects with mothers who consumed chicken eggs and/or cow's milk when nursing with HR 2.58 (95%CI 0.91 to 7.29) and HR 2.56 (95%CI 0.22 to 29.93), respectively.

Table 2. Crude and adjusted analysis of atopic dermatitis as a prognostic factor in the first 3 months of life

Prognostic factors	Crude HR			Adjusted HR		
	HR	95% CI	P value	HR	95% CI	P value
Exposure to cow's milk	1.91	0.72 to 5.09	0.19	1.37	0.22 to 8.43	0.74
Gender	0.68	0.26 to 1.83	0.45			
Gestational age	1.99	0.27 to14.97	0.53			
Birth weight	0.82	0.24 to 2.84	0.75			
Maternal history of atopy	1.21	0.39 to 3.68	0.73			
Paternal history of atopy	0.94	0.12 to 7.03	0.94			
Both parents' history of atopy	0.05	0.00 to 4.67	0.66			
Maternal education level	1.58	0.63 to 4.01	0.33			
Socioeconomic level	1.35	0.48 to 3.79	0.56			
Environmental tobacco smoke exposure	2.46	0.88 to 6.90	0.08	2.58	0.91 to 7.29	0.08
Early solid feeding	0.05	0.00 to 1.00	0.72			
Maternal consumption of chicken eggs and/or cow's milk when nursing	3.66	0.48 to 28.16	0.21	2.56	0.22 to 29.93	0.46

Discussion

The AD incidence of our subjects was 13%. Other studies reported AD incidences of 17.1% in the first six months of life and 35.8% in the first year of life.[20-22] A study conducted in infants aged 0-24 months found the AD incidence to be 18%.[23] We found that subjects in the CM group had an 8.8% greater cumulative AD incidence than the non-CM group. Similarly, another study found that those exposed to cow's milk were at a 3.72 times greater risk for AD compared to infants who were exclusively breastfed.[19]

The incidence rates of AD were 54.5% in the CM group and 66.7% in the non-CM group, indicating that subjects exposed to cow's milk had AD earlier than those not exposed to cow's milk. Both results were not significant, with HR 1.37 and 95%CI 0.22 to 8.43. In our study, we found that the youngest child with AD was 1-month old. Several studies found that AD started to occur at 1 month of age, and later at 3 months of age.[10,18] These differences in the time of AD onset may be due to the low production and immature function of IgA in newborns.[17,21] Infants receive IgA antibodies from breast milk, forming a rejection antigen system, some of which may be directly against the protein foods in the mother's diet, as well as foreign proteins including cow's milk. Infants easily absorb macromolecules because of their immature intestinal mucosa, so the granting of foreign proteins, though in small amounts, may result in the activation of the immune system.[14, 24]

We found that gender was not a prognostic factor for AD in the first 3 months of life. In contrast, another study found that males had a 1.76 times greater risk of AD by the age of 12 months.[22] This effect may be due to higher IgE levels in males at birth.[25]

History of atopy (maternal, paternal or both parents) in our study was not a prognostic factor for AD. However, another study found that subjects with parental history of atopy had a 1.99 times greater risk of AD.[20]

The AD incidence rate in subjects exposed to cigarette smoke was earlier than those not exposed to cigarette smoke, and it had almost significant value (HR 2.58; 95%CI 0.91 to 7.29). This observation

may be due to air pollutants which generally have an irritating effect on skin and mucous membranes, facilitating the penetration of potential allergens into the body, causing AD symptoms and increasing the risk of sensitization.[15, 29]

Chicken eggs and/or cow's milk consumption by mothers when nursing was a prognostic factor for AD, but this result was not significant. Food allergens can be detected in breast milk, including peanuts, cow's milk protein, and eggs.[26] Avoidance of food allergens in the mother's diet while breastfeeding was reported to be a protective factor against the onset of AD.[27] However, no relationship has been found between peanuts in the maternal diet and peanut allergies.[28] One case report stated that food allergens in breast milk may interact with the mucosal immune system, inducing an allergic reaction in infants who were previously clinically suspected of having allergies against these antigens.[14]

A limitation of our study was that the AD symptoms were collected by phone interview of the mothers who live in distant places. If AD occurred before the researcher called the subjects' parents at a predetermined time, a measurement bias could be introduced since parents might forget about the symptoms.

Since we did not find a prognostic factor for AD in the first 3 months of life, the AD incidence may have been too low due to the small sample size. A larger sample size and longer observation time is needed to assess a more accurate incidence and prognostic factors of AD.

Acknowledgments

We extend our sincere gratitude to the physician and nurses in charge at the Perinatology Ward at Sanglah Hospital, and to I Gde Raka Widiana, MD for his help in methodology construction and statistical analysis.

References

1. Beck LA. Atopic dermatitis. In: Lichtenstein LM, editor. Current therapy in allergy, immunology and rheumatology. 6th ed. Philadelphia: Elsevier Inc; 2004. p. 88-94.
2. Sicherer SH, Sampson AH. Atopic dermatitis. In: Stiehm RE, editor. Immunologic disorders in infants and children. 5th ed. Philadelphia: Elsevier Inc; 2004. p. 980-1.
3. Leung DYM. Atopic dermatitis. In: Leung DYM, Sampson HA, editors. Pediatric allergy, principles and practice. Philadelphia: Mosby; 2003. p. 561-6.
4. Williams HC. Clinical practice: atopic dermatitis. N Engl J Med. 2005;352:2314-24.
5. Wolf RL. Atopic dermatitis. In: Shanahan J, editor. Essential pediatric allergy, asthma & immunology. New York: McGraw Hill; 2004. p. 38-40.
6. Yunginger JW. Outdoor allergen. In: Leung DYM, Sampson HA, editors. Pediatric allergy, principles and practice. Philadelphia: Mosby; 2003. p. 252-9.
7. Terr AI. The atopic diseases. In: Parslow GT, editor. Medical immunology. 10th ed. Singapore: McGraw-Hill; 2001. p. 349-66.
8. Finlay AY. The burden of atopic eczema. In: Ring J, editor. Handbook of atopic eczema. 2nd ed. New York: Springer; 2006. p. 31-3.
9. Warner JO. Allergy practice worldwide, a report by the world allergy organization specialty and training council. Allergy Clin Immunol Int. 2006;18:4-10.
10. Sugiyama M, Arakawa H, Ozawa K, Mizuno T, Mochizuki H, Tokuyama K, *et al*. Early life risk factors for occurrence of atopic dermatitis during the first year. Pediatrics. 2007;119:716-23.
11. Scafer T. Epidemiology of atopic eczema. In: Ring J, editor. Handbook of atopic eczema. 2nd ed. New York: Springer; 2006. p. 21-7.
12. Host A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Pediatr Allergy Immunnol. 2002;13:23-8.
13. Laubereau B. Effects of breast feeding of the development of atopic dermatitis during the first 3 years of life-results from the GINI birth cohort study. J Pediatr. 2004;144:602-7.
14. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition. Effects of early nutritional interventions on the development of atopic disease in infants and children: The role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics. 2008;121:183-91.
15. Shinohara M, Saito H, Matsumoto K. Different timings of prenatal or postnatal tobacco smoke exposure have different effects on the development of atopic eczema/dermatitis syndrome (AEDS) during infancy. J Allergy Clin Immunol. 2011;12:813-7.
16. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-

feeding and the onset of atopic dermatitis in childhood : a systematic review and meta-analysis of prospective studies. J Am Acad Dermatol. 2001;45:520-7.

17. Gustafsson D, Lowhagen T, Andersson K. Risk of developing atopic diseases after early feeding with cow's milk based formula. Arch Dis Child. 1992;67:1008-10.
18. Liu AH, Martinez FD, Taussig LM. Natural history of allergic diseases and asthma. In: Leung DYM, Sampson HA, editors. Pediatric allergy, principles and practice. Philadelphia: Mosby; 2003. p.10-1.
19. Budiastuti M. Hubungan antara pemberian ASI eksklusif dengan kejadian dermatitis atopi pada bayi risiko tinggi alergi [master's thesis]. [Yogyakarta]: Bagian Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Gadjah Mada; 2008.
20. Moore MM, Rifas-Shiman SL, Rich-Edwards JW, Kleinman KP, Camargo CA, Gold DR, *et al*. Perinatal predictors of atopic dermatitis occurring in the first six months of life. Pediatrics. 2004;113:468-74.
21. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort study. Pediatrics. 2008;122:115-22.
22. Morgan J, Williams P, Norris F, Williams CM, Larkin M, Hampton S. Eczema and early solid feeding in preterm infants. Arch Dis Child. 2004;89:309-14.
23. Zutavern A, Brockow I, Schaaf B, Bolte G, von Berg A, Diez U, *et al*. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from the prospective birth cohort study. Pediatrics. 2006;117:401-11.
24. Trahms CM. Nutrition during infancy. In: Mahan LK, editor. Krause's food, nutrition, & diet therapy. 11th ed. Philadelphia: Saunders; 2004. p. 220-2.
25. Lopez N, de Barros-Mazon S, Vilela MM, Silva CM, Ribeiro JD. Genetic and environmental influences on atopic immune responses in early life. J Investig Allergol Clin Immunol. 1999;9:392–8.
26. Vadas P, Wai Y, Burks W, Perelman B. Detection of peanut allergens in breast milk of lactating women. JAMA. 2001;285:1746-8.
27. Lovegrove JA, Hampton SM, Morgan JB. The immunologic and long-term atopic outcome of infants born to women following a milk-free diet during pregnancy and lactation: a pilot study. Br J Nutr. 1994;71:223–38.
28. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. N Engl J Med. 2003;348:977- 85.
29. Yi O, Kwona HJ, Kim H, Ha M, Hong SJ,Leem JH, *et al*. Effect of environmental tobacco smoke on atopic dermatitis among children in Korea. Environ Res. 2012;113:40–5.