Ann Dermatol Vol. 22, No. 2, 2010 DOI: 10.5021/ad.2010.22.2.180

ORIGINAL ARTICLE

The Influence of Pregnancy and Menstruation on the Deterioration of Atopic Dermatitis Symptoms

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Background: Female patients with atopic dermatitis (AD) often experience cutaneous deterioration associated with their pregnancy or menstrual cycle. **Objective:** We wanted to determine the prevalence of symptom aggravation as related to pregnancy and the menstrual cycle in female patients with AD. **Methods:** One hundred female patients with AD were included in the study and interviews were performed. The total IgE level and the Eczema Area and Severity Index score of the patients were retrospectively reviewed. **Results:** Ninety seven patients replied the questionnaire, and among them, 23 patients had completed at least 1 pregnancy. Among the 23 women who experienced pregnancy, 14 (61%) had noticed deterioration of their clinical symptoms during pregnancy. Of the 97 females, 31 (32%) patients had noticed deterioration of their AD as related to their menstrual cycle. For the patients who were sub-grouped as the intrinsic type of AD, the prevalence of symptom aggravation as related to pregnancy was significantly higher as compared to that of the extrinsic type of AD patients ($p=0.048$). **Conclusion:** Of the 97 patients, 45 (46%) females answered that they have experienced deterioration of AD during pregnancy or in relation to their menstrual cycle, and this suggests the relation of a hormonal influence on the clinical manifestations of AD. **(Ann Dermatol 22(2) 180～185, 2010)**

-Keywords-
Atopic dermatitis, Hormone, Intrinsic, Menstruation, Pregnancy

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory disease with the lifetime prevalence of 8～17% in adults under 60 years old and it has a number of subtypes[1]. Intrinsic AD (IAD) is differentiated from the much more common extrinsic type (EAD) by a total serum immunoglobulin E (IgE) level that is within the normal range, by the lack of specific IgE positivities and by the fact that no immediate skin reaction to environmental allergens or respiratory involvement can be observed[2-4]. In several previous studies, the disease activity of several dermatoses was shown to be influenced by hormonal factors in women, and AD had a higher prevalence in adult females[5,6]. According to previous studies, approximately 25% of females who have AD experience improvement during pregnancy, and more than 50% of the AD female patients experience deterioration during pregnancy[7,8]. Moreover, female patients with AD often show a deterioration of cutaneous symptoms in relation to the menstrual cycle[9]. We have experienced that a number of female patients with AD in our clinic have reported their symptoms worsened during pregnancy and even in relation to their menstrual cycle. However, the influence of pregnancy and the menstrual cycle on AD has not been discussed in the Korean dermatologic literature. The purpose of this study is to investigate the influence of pregnancy and the menstrual cycle on the symptoms of AD, which would reflect a hormonal influence on AD, and to compare the results between the intrinsic and extrinsic types of AD.

Received January 12, 2010, Revised February 10, 2010, Accepted for publication February 19, 2010
*This study was supported by a grant of the Korea Health 21 R&D Project (Ministry of Health & Welfare and Family Affairs, Republic of Korea, A080892).

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MATERIALS AND METHODS

Patients

One hundred female patients with AD who visited the Department of Dermatology at Yonsei University Health System in Seoul, Korea during January, 2007 to December, 2008 were included in the study. The diagnosis of AD was based on the criteria of Hanifin and Rajka[10]. The inclusion criteria were female AD patients over the age of 20 years old who had no other systemic diseases and who had the ability to understand and give appropriate answers to the questionnaire.

Assessment of the influence of pregnancy and the menstrual cycle on AD symptoms

An interview was performed for the 100 female patients. The questionnaire included questions about whether the patients have experienced deterioration or improvement of AD during pregnancy or as related to their menstrual cycle, and if they have experienced any changes, which period did the change appear during pregnancy or during the menstrual cycle was asked.

The degree of aggravation each patient experienced in relation to pregnancy or their menstrual cycle was also assessed using a mild-moderate-severe 3 scale grading system: mild (<33% worsening as compared to the average cutaneous signs and symptoms before pregnancy), moderate (33~66% worsening) or severe (>66% worsening). The total IgE levels and the Eczema Area and Severity Index (EASI) score were examined on the hospital visit and the average values were compared between the patient groups (those who have experienced deterioration and those who have not experienced any noticeable changes). In addition, we classified the patients into those who showed low total serum IgE levels (<200 kU/l), with the absence of associated respiratory diseases, a lack of allergen specific serum IgE antibodies and negative skin prick tests into the intrinsic AD (IAD) group[11]. We compared the difference in the prevalence of symptom aggravation in association to pregnancy or menstruation between the IAD patients and the extrinsic AD (EAD) patients.

Statistical analysis

All the analyses were performed with the SPSS statistical package (SPSS Inc., Chicago, IL, USA). The differences in the levels of total IgE and the EASI score between the patient groups (those who experienced deterioration and those who did not experience any noticeable changes) were analyzed with Student's t-test. The chi-square test and Fisher's exact test were performed in order to determine the difference of the prevalence of symptom aggravation in association with pregnancy or menstruation between the IAD and EAD patients. A p-value <0.05 was accepted as statistically significant.

RESULTS

Demographic and clinical characteristics of the AD patients

Ninety seven of the 100 enrolled patients replied the questionnaire. The mean age of the patients was 26.3±5.8 years (range: 20~50 years old). Seventy one (73.2%) of patients were in their twenties, 23 (23.7%) were in their thirties and 3 (3.1%) were over 40 years old. The mean EASI score of the 97 patients was 12.3±10.1 and 51 patients had EASI scores from 0~9, 29 had scores from 10~19, 9 had scores from 20~29, and 8 had EASI scores higher than 30. Twenty three females had experienced at least 1 pregnancy and their mean age was 35.1 years (range: 29~50 years). There were 34 patients who were sub-grouped as IAD, and 63 were sub-grouped as EAD (Table 1).

Association between pregnancy and aggravation of AD symptoms

Among the 23 patients who experienced pregnancy, 15 (65%) females described a clinical change of their AD during pregnancy, with 14 (61%) females who experienced deterioration of AD during their pregnancies and 1 (4%) who had improvement of symptoms during pregnancy. The remaining 8 patients answered that they did not

Table 1. The demographics and clinical manifestations of the enrolled AD patients

Characteristics	AD patients (n=97) (%)
Age [years, mean±SD (range)]	26.3±5.8 (20~50)
20~30	71 (73.2)
30~40	23 (23.7)
40~50	3 (3.1)
Total IgE [kU/l, mean±SD (range)]	1,007.3±1,295.5 (4.1~5,000)
Log total IgE	2.5±0.8
EASI score [value, mean±SD (range)]	12.3±10.1 (0.8~41.7)
<10	51 (52.6)
10~20	29 (29.9)
20~30	9 (9.3)
>30	8 (8.2)
Subtype	
IAD	34 (35.1)
EAD	63 (64.9)
Experienced at least 1 pregnancy	23 (23.7)

AD: atopic dermatitis, EASI: Eczema Area and Severity Index, IAD: intrinsic AD, EAD: extrinsic AD.

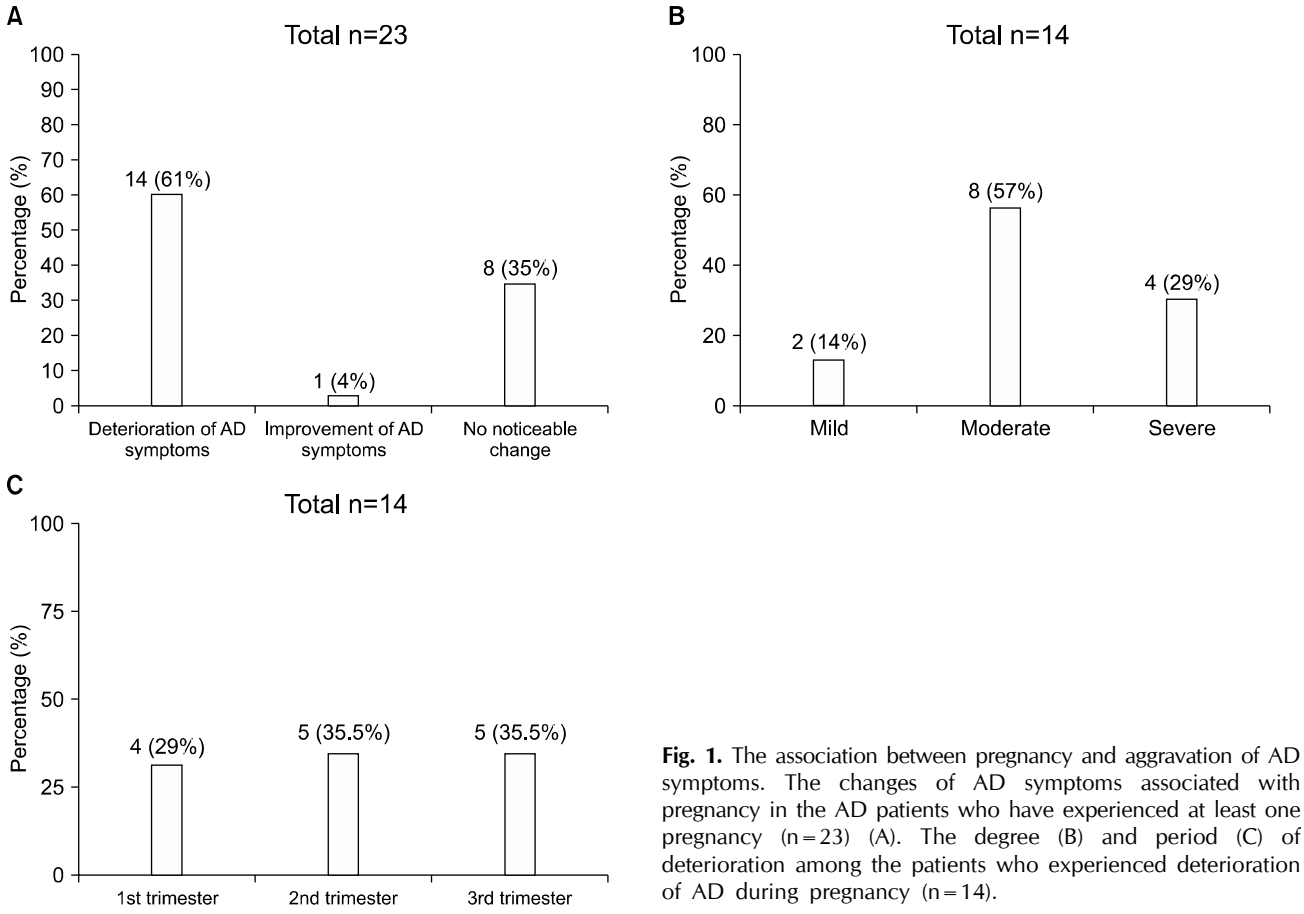

Fig. 1. The association between pregnancy and aggravation of AD symptoms. The changes of AD symptoms associated with pregnancy in the AD patients who have experienced at least one pregnancy (n=23) (A). The degree (B) and period (C) of deterioration among the patients who experienced deterioration of AD during pregnancy (n=14).

notice any change during pregnancy (Fig. 1A). Of the 14 patients who experienced deterioration during pregnancy, 2 (14%) experienced a mild degree, 8 (57%) experienced a moderate degree and 4 (29%) experienced a severe degree of deterioration (Fig. 1B). Ten patients (71%) experienced deterioration during the 2nd or 3rd trimester of pregnancy (Fig. 1C). Of the 14 patients who experienced symptom aggravation during pregnancy, 6 (42.9%) patients were sub-grouped as IAD and 8 (57.1%) were sub-grouped as EAD. The patients who did not experience any clinical changes of AD during pregnancy and the 1 female who experienced improvement were all EAD. The prevalence of AD symptom aggravation associated with pregnancy was significantly higher for the IAD patients as compared to that of the EAD patients (6/6, 100% vs 8/17, 47.1%, $p=0.048$) (Fig. 2).

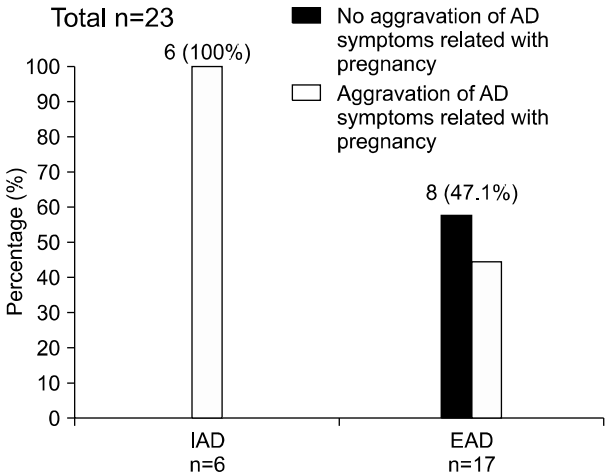

Fig. 2. The influence of pregnancy on the aggravation of AD symptoms between the IAD (n=6) and EAD groups (n=17).

Association between menstruation and the aggravation of AD symptoms

A question asking whether the patients have experienced any changes of AD as related to their menstrual cycle was asked of all 97 females. Thirty one (32%) females experienced deterioration of AD as related to the menstrual cycle, and 66 (68%) answered that they have not felt any noticeable changes (Fig. 3A). Twenty (64.5%) of the patients who experienced deterioration related to the menstrual cycle experienced mild worsening (Fig. 3B), and 18 (64%) females experienced premenstrual deterioration

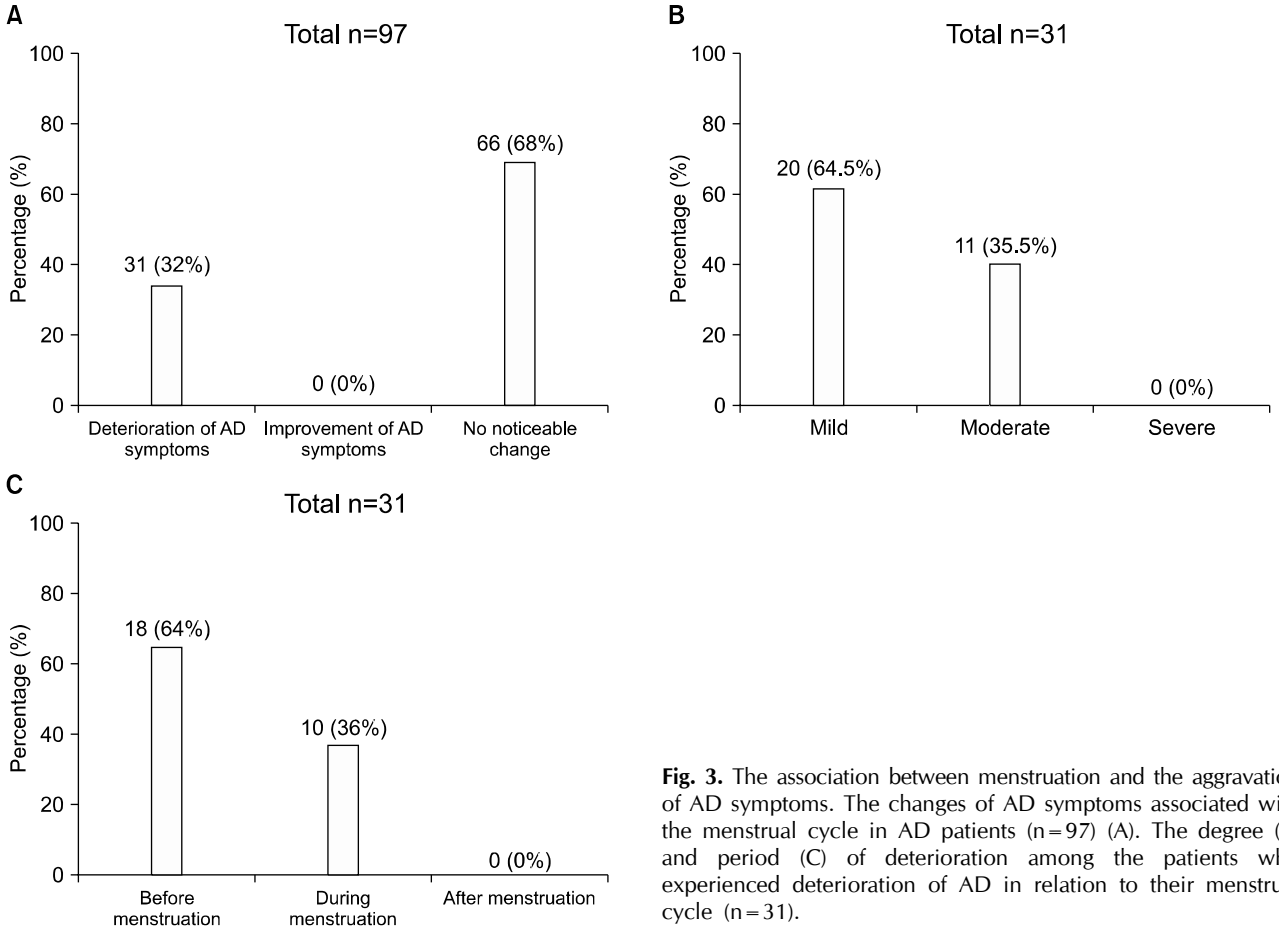

Fig. 3. The association between menstruation and the aggravation of AD symptoms. The changes of AD symptoms associated with the menstrual cycle in AD patients (n=97) (A). The degree (B) and period (C) of deterioration among the patients who experienced deterioration of AD in relation to their menstrual cycle (n=31).

within about 10 days before menstruation (Fig. 3C). Between the patient groups who experienced deterioration related to their menstrual cycle and those who did not, any statistical difference of the prevalence of symptom aggravation was not noticed between the IAD and EAD patients. Among the 23 females with AD and who experienced at least 1 pregnancy, 7 females (30.4%) were affected by both pregnancy and the menstrual cycle (30.4%), and 45 (46%) out of the 97 patients were affected by pregnancy or menstruation.

Comparison of the differences in the total IgE levels and the EASI score between the patient group who experienced deterioration of symptoms related to pregnancy or menstruation, and the patient group who did not

The total IgE levels and EASI score was compared between the patient group who experienced deterioration during pregnancy or as related to the menstrual cycle and the patient group who have not experienced any changes. The total IgE level and EASI score were measured when the questionnaire was filled in. The patients who experienced deterioration of AD during pregnancy had a mean lower level of total IgE and a mean higher EASI score as compared to those values of the patients who showed no relationship between pregnancy and AD symptoms ($904\pm1,351$ vs $1,810.6\pm1,577.4$ and 15.6 ± 10.9 vs 11 ± 11.2, respectively). The patients who experienced deterioration of AD as related to the menstrual cycle had a slightly higher mean total IgE level and mean EASI score as compared to those values of the patients who have not experienced any changes as related to the menstrual cycle ($1,185.6\pm1,499.7$ vs $923.5\pm1,191$ and 13.4 ± 9.9 vs 11.7 ± 10.3, respectively). However, the statistical analysis did not reveal significant differences.

DISCUSSION

Although it has long been recognized that female patients with AD often show a deterioration of cutaneous symptoms in relation to the menstrual cycle, the information about this subject is insufficient[12,13]. A review of the literature has revealed great variance in the prevalence of the menstrual-cycle-associated worsening of AD skin lesions,

ranging from 9% to 100%[7,14-18]. Yet in the previous studies that have examined a comparatively large number of patients, the frequency of menstrual cycle-associated aggravation of AD skin lesions was estimated to be around 50～70%[15,18].

In our study, we found out that 46% of the female AD patients have experienced deterioration of symptoms during pregnancy or in relation to the menstrual cycle. Among the patients who experienced aggravation related to the menstrual cycle, 64% experienced deterioration before the menstruation and generally within 10 days before menstrual initiation. The results suggest that there exists a relation between hormonal influences and the clinical manifestations of AD. As Kemmett and Tidman[7] reported previously, there might be some association between the premenstrual worsening of AD and the presence of symptoms of premenstrual syndrome. According to a study of Kiriyama et al.[9], the physical and psychological symptoms of premenstrual syndrome were present in all the AD patients who showed premenstrual worsening of skin lesions, but these were absent in the group of patients who did not show premenstrual skin aggravation. Systemic evaluations and further interviews of AD patients regarding premenstrual syndrome are required to reveal the definite relation.

Most pregnant women are unwilling to use topical and systemic treatments, and so discontinuation of medications might be a leading cause of aggravation of AD. In our study, among the 14 patients who experienced aggravation during pregnancy, 10 patients experienced aggravation during the 2nd or 3rd trimester, and the 4 patients who experienced aggravation during the 1st trimester did not use any oral medications for several months prior to pregnancy. Therefore, the cessation of medication itself independent to pregnancy did not seem to be the major cause of AD aggravation. The use of medication by AD patients before and after pregnancy should be consistent to firmly determine if pregnancy is a deteriorating factor of AD. Nevertheless, as the continuation of AD symptoms into adulthood, which is when most of females experience pregnancy, is not very common, we included all the AD patients who experienced pregnancy in our study for the purpose of obtaining a large cohort. Therefore, further studies are needed with controlled distributable factors to clarify the relationship between pregnancy and the deterioration of AD symptoms.

The total IgE levels and EASI score did not show statistically significant differences between the patients who noticed some deterioration during pregnancy or in relation to the menstrual period and the patients who were without deterioration of AD symptoms during pregnancy and menstruation. This infers that that worsening during pregnancy or in relation to the menstrual cycle is not related to the severity of the disease. The degree of the premenstrual skin deterioration was different from patient to patient, suggesting there are individual differences in the susceptibility to the aggravation of AD. These results are equivalent with those of the previous studies[9]. The patient group who experienced deterioration during pregnancy or as related to the menstrual cycle had a larger portion of patients sub-grouped as IAD, as compared to that of the patient group who did not experience any changes. This result suggests that, for IAD, the disease can be more susceptible to hormonal influences as compared to the extrinsic type. In our study, the deterioration of AD as related to pregnancy tended to appear at higher rates for the IAD patients as compared to that of the EAD patients, but the relationship between menstruation and symptom aggravation of AD in the IAD or EAD patients did not reveal statistically significant differences. These results suggest that although IAD patients lack sensitization by allergens and they do not show aggravation by specific allergens, other factors such as hormones or stress may have more impact on the clinical manifestations of IAD. Further studies are required to investigate the susceptibility of hormonal influences in patients with IAD and EAD.

It is now known that pregnancy shifts the T cell immunity towards a type 2 T helper response, and this is thought to be important for continuation of a normal pregnancy[19]. Ikeno and Takahashi[20] described that the Dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEA-S) levels, which apparently show the immunomodulatory effects probably by enhancing Th1 activity[21,22], decrease during pregnancy[20], and this can be one factor that contributes to the shift of the immune response to the type 2 helper response during pregnancy. As the type 2 T helper response is also associated with AD, this shift may explain why AD can deteriorate during pregnancy. There is also some experimental data suggesting sex hormones have an influence on the symptoms of AD, as estrogens were shown to affect mast cell activation, while progesterone was shown to suppress histamine release, but potentiate IgE induction in rodent models[6]. However, as any actual data from human studies is lacking, further investigations are required.

The mechanisms still remain obscure for the case of deterioration of AD as related to the menstrual cycle. It is reported that for females, skin reactivity to irritants and antigenic substances increases during the premenstrual phase[23,24]. It is then possible that female patients with AD show an exaggerated inflammatory skin response to

various aggravating substances in the week prior to menstruation, leading to the premenstrual deterioration of the disease[9].

In conclusion, although this study is limited by the small number of patients and its retrospective and subjective nature, it is valuable because such a study is rare in the Korean literature. Our results suggest that there exist a relation between hormonal influences and the clinical manifestations of AD, and further investigations with larger cohorts are needed to clarify the relationship between sex hormones and AD.

REFERENCES

1. Montnemery P, Nihlen U, Goran Lofdahl C, Nyberg P, Svensson A. Prevalence of self-reported eczema in relation to living environment, socio-economic status and respiratory symptoms assessed in a questionnaire study. BMC Dermatol 2003;3:4.
2. Folster-Holst R, Pape M, Buss YL, Christophers E, Weichenthal M. Low prevalence of the intrinsic form of atopic dermatitis among adult patients. Allergy 2006;61:629-632.
3. Ingordo V, D'Andria G, D'Andria C, Tortora A. Results of atopy patch tests with house dust mites in adults with 'intrinsic' and 'extrinsic' atopic dermatitis. J Eur Acad Dermatol Venereol 2002;16:450-454.
4. Wuthrich B, Schmid-Grendelmeier P. The atopic eczema/dermatitis syndrome. Epidemiology, natural course, and immunology of the IgE-associated ("extrinsic") and the nonallergic ("intrinsic") AEDS. J Investig Allergol Clin Immunol 2003;13:1-5.
5. Kornizky Y, Topilsky M, Fireman E, Kivity S. Specific IgE antibodies to aeroallergens and food among Israelis. Ann Allergy Asthma Immunol 1999;83:149-152.
6. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy 2008;63:1418-1427.
7. Kemmett D, Tidman MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. Br J Dermatol 1991;125:59-61.
8. Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. BMJ 2007;335:152-154.
9. Kiriyama K, Sugiura H, Uehara M. Premenstrual deterioration of skin symptoms in female patients with atopic dermatitis. Dermatology 2003;206:110-112.
10. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venerol 1980;92:44-47.
11. Ott H, Stanzel S, Ocklenburg C, Merk HF, Baron JM, Lehmann S. Total serum IgE as a parameter to differentiate between intrinsic and extrinsic atopic dermatitis in children. Acta Derm Venereol 2009;89:257-261.
12. Brunsting LA. Atopic dermatitis (disseminated neurodermatitis) of young adults. Analysis of precipitating factors in one hundred and one cases and report of ten cases with associated juvenile cataract. Arch Derm Syphilol 1936;34:935-957.
13. Rajka G. Essential aspects of atopic dermatitis. Berlin: Springer-Verlag, 1989.
14. Hellerstrom S, Lidman H. Studies of Besnier's prurigo (atopic dermatitis). Acta Derm Venereol 1956;36:11-22.
15. Rajka G. Prurigo Besnier (atopic dermatitis) with special reference to the role of allergic factors. III. The role of some factors in the course of the prurigo Besnier. Acta Derm Venereol 1961;41:363-395.
16. Garell DC. Atopic dermatitis in females during adolescence. Am J Dis Child 1964;107:350-355.
17. Roth HL, Kierland RR. The natural history of atopic dermatitis. A 20-year follow-up study. Arch Dermatol 1964;89:209-214.
18. Wuthrich B. Zur Immunopathologie der Neurodermatitis constitutionalis. Bern: Huber, 1975.
19. Saito S, Sakai M, Sasaki Y, Tanebe K, Tsuda H, Michimata T. Quantitative analysis of peripheral blood Th0, Th1, Th2 and the Th1:Th2 cell ratio during normal human pregnancy and preeclampsia. Clin Exp Immunol 1999;117:550-555.
20. Ikeno N, Takahashi K. Studies on changes in serum estrone, estradiol, estriol, DHA-S, and cortisol and urinary estriol excretion. Nippon Sanka Fujinka Gakkai Zasshi 1985;37:99-106.
21. Daynes RA, Dudley DJ, Araneo BA. Regulation of murine lymphokine production in vivo. II. Dehydroepiandrosterone is a natural enhancer of interleukin 2 synthesis by helper T cells. Eur J Immunol 1990;20:793-802.
22. Suzuki T, Suzuki N, Daynes RA, Engleman EG. Dehydroepiandrosterone enhances IL2 production and cytotoxic effector function of human T cells. Clin Immunol Immunopathol 1991;61:202-211.
23. Agner T, Damm P, Skouby SO. Menstrual cycle and skin reactivity. J Am Acad Dermatol 1991;24:566-570.
24. Alexander S. Patch testing and menstruation. Lancet 1988;2:751.