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Research Article

The Impact of Pregnancy and Phases of the Menstrual Cycle on Atopic Dermatitis

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Abstract

Objective: To investigate the impact of pregnancy and phases of the menstrual cycle on the symptoms of atopic dermatitis.

Patients and Methods: Eighty female patients with atopic dermatitis 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 prospectively reviewed.

Results: Eighty patients replied the questionnaire, and among them, 18 patients had completed at least 1 pregnancy. Among the 18 women who experienced pregnancy, 12 (66.7%) had noticed deterioration of their clinical symptoms during pregnancy. Of the 80 females, 30 (37.5%) 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 ($p < 0.05$).

Conclusion: This suggests the relation of a hormonal negative influence on the clinical manifestations of AD.

Keywords: Atopic dermatitis; Hormone; 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 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.

Patients and Methods

Patients: One hundred female patients with AD who visited the Department of Dermatology at Al Azhar University in Cairo 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

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Table 1: Demographic and clinical characteristics of the AD patients.

Age	
< 30 30-40 >40	10 45 25
Total IgE (KU/L)	1067.87 ± 854.56
EASI score	
<10 10-20 20-30 >30	39 19 12 20
Subtype	
IAD EAD	37 43
Experienced ≥ 1 pregnancy	18 (22.5%)

Table 2: Association between pregnancy and aggravation of AD symptoms.

Deterioration of symptoms	12
Mild	3
Moderate	7
Severe	2
No effect	5
Improvement of symptoms	1
IAD	5
EAD	7

between the IAD patients and the extrinsic AD (EAD) patients.

Statistical analysis

All statistical calculations were performed using the statistical software package SAS, Release 9.3 (SAS Institute Inc., Cary, NC, USA). Absolute and relative frequency was given for quality characteristics; mean, standard deviation, minimum and maximum values were determined for quantitative variables. To detect group differences, a variance analysis with repeated measurements was performed using the SAS procedure, SAS MIXED. This approach permits to observe concurrently whether there is a distinction between groups (treatment *vs*. control group), whether changes occur over time (beginning *vs*. end) and if interactions can be confirmed. The P-value of the interaction indicates whether temporal changes in both groups have a significant difference. Furthermore, t-tests for two independent samples were taken to compare groups at a particular point in time (beginning *vs*. end). The Wilcoxon test for paired samples was used to determine the severity between the points 'beginning' and 'end'. The outcome of the statistical analysis was deemed significant when the P-value was below 0.05. Findings with P-values between 0.05 and 0.10 were considered 'slightly significant'.

Results

Demographic and clinical characteristics of the AD patients

Eighty enrolled patients replied the questionnaire. The mean age of the patients was 39.6±7.4 years (range: 20~50 years old). Ten (12.5%) of patients were in their twenties, 45 (56.3%) were in their thirties and 25 (31.3%) were over 40 years old. The mean EASI score of the 80 patients was 14.8±14.1 and 39 patients had EASI scores from 0~9, 19 had scores from 10~19, 12 had scores from 20~29, and 20 had

Table 3: Relationship between pregnancy and AD symptoms.

	deterioration	No effect	P-value
Ig E	823 ± 723	1.645 ±1.342	< 0.05
EASI scores	16.8 ± 9.6	12.6 ± 6.2	< 0.05

Table 4: The statistical analysis did not reveal significant differences.

	deterioration	No effect	P-value
Ig E	1.013 ± 1.014	948 ± 822	> 0.05
EASI scores	13.7 ± 9.5	12.8 ± 7.1	> 0.05

EASI scores higher than 30. Eighteen females had experienced at least 1 pregnancy and their mean age was 38.2 years (range: 29~50 years). There were 37 patients who were sub-grouped as IAD, and 43 were sub-grouped as EAD (Table 1).

Among the 18 patients who experienced pregnancy, 13 (72.2%) females described a clinical change of their AD during pregnancy, with 12 (66.7%) females who experienced deterioration of AD during their pregnancies and 1 (5.6%) who had improvement of symptoms during pregnancy. The remaining 5 patients answered that they did not notice any change during pregnancy. Of the 12 patients who experienced deterioration during pregnancy, 3 (25%) experienced a mild degree, 7 (58.3%) experienced a moderate degree and 2 (16.7%) experienced a severe degree of deterioration. Of the 12 patients who experienced symptom aggravation during pregnancy, 5 (41.6%) patients were sub-grouped as IAD and 7 (58.4%) were sub-grouped as EAD (5/8 *vs* 7/10, p > 0.05) (Table 2).

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 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 (823 ± 723 *vs* 1.645 ± 1.342 and 16.8 ± 9.6 *vs* 12.6 ± 6.2 respectively, P< 0.05) (Table 3).

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 (1.013 ± 1.014 *vs* 948 ± 822 and 13.7 ± 9.5 *vs* 12.8 ± 7.1, respectively). However, the statistical analysis did not reveal significant differences (Table 4).

Discussion

Existing data on changes in skin reactivity to irritants are few. In one study, 29 healthy women were exposed to Sodium Lauryl Sulfate (SLS) (0.5%) through an irritant patch test at day and at days 9-11 of the menstrual cycle, with reactivity assessed by visual scoring, Trans Epidermal Water Loss (TEWL), superficial blood flow, and skin thickness. Skin response to the irritant was shown to be significantly stronger at day 1 than at days 9-11 by TEWL $p < 0.05$, skin thickness $p < 0.005$, and visual scoring of erythema $p < 0.05$, and non-

significantly stronger by blood flow measurements. No significant correlation between serum oestradiol and the magnitude of skin response was reported (31). As no cyclical variations in TEWL were observed, it is believed that increases in irritant sensitivity during menstruation represent increased inflammatory capacity rather than any compromise of barrier function.

The same authors later evaluated reaction to different quantities of SLS with TEWL, cutaneous blood flow, colorimeter and measurement of skin thickness by ultrasound-A, and confirmed the earlier finding that irritation was more pronounced during menstruation than immediately in mid-follicular phase (7).

Another study evaluated irritant susceptibility by measuring vasodilatation induced by topical application of methyl nicotinate. Doppler velocimetry blood flow and TEWL were both assessed at three time points as follows: day of (putative) maximal oestrogen secretion, day of (putative) minimal oestrogen/progesterone secretion, and day of (putative) maximal progesterone secretion. No significant differences in irritant response were observed across the three time points, although baseline TEWL was higher on the day of minimal oestrogen/progesterone secretion than on the day of maximal oestrogen secretion, and baseline blood flow was higher on the day of maximal oestrogen secretion than on the day of maximal progesterone secretion (33). As these studies utilized different irritants with different mechanistic actions as well as different sampling times, it is difficult to draw meaningful conclusions from the available data. All of the time points sampled in the latter study, however, occur in the period starting shortly before ovulation to about mid-luteal phase and therefore relatively distant in time from day 1, the point at which a significant increase in irritant susceptibility was found by the first two studies.

The incidence of monthly worsening of atopic dermatitis ranged, in published studies, from 4% to 100% (9, 40). The broad variation observed may be due to the limited number of patients studied or the patients' response rate to the questionnaires (40). In a study of 286 women with atopic dermatitis, 47% reported a cyclic exacerbation of the disorder, while the other 53% of patients did not. Of those who reported cyclic worsening of symptoms, 96% reported a deterioration of symptoms during the week preceding menses with rapid improvement after the onset of menstrual flow (40).

In contrast, attempts to correlate the hormone fluctuations of the menstrual cycle with results of patch testing with nickel have yielded more equivocal results.

Rohold et al. (1994) performed patch tests using various concentrations of nickel sulfate in 20 healthy women with nickel allergy, comparing days 7-10 with day's 20-24. No difference in reactivity between the two time periods was observed, although the study did find a booster effect when results from the second set of results was compared to the first (41).

Tamer et al. (2003) tested 30 healthy women with nickel allergy and also compared days 7-10 with day's 20-24. No significant differences were found, although it was reported that reactions observed were more intense during days 20–24 (3).

Bonamonte et al. (2005) also tested 30 healthy women with nickel allergy, in serial dilution with nickel concentrations ranging from 5% to 0.0013%. Women were tested in the ovulatory phase (verified by transvaginal ultrasound) and the progestinic phase. The authors observed that significantly less intense responses were elicited during the ovulatory phase as compared to the progestinic phase, and concluded that the hormone profile characteristic of the ovulatory phase acts to suppress delayed hypersensitivity-type reactions (8).

Hindsén et al. (1999) patch tested 30 women with nickel contact allergy (in serial dilutions with concentrations ranging from 0.0032 to 12.5%) and also observed heightened test reactivity later in the menstrual cycle (42). Their results, however, which spanned a 7-month period, demonstrated tremendous intrapersonal variability in patch test results, with as much as a 250-fold individual difference in reactivity between test periods (42).

Kirmaz et al. (2004) performed skin prick tests in 42 women with demonstrated seasonal allergic rhino conjunctivitis with both a panel of relevant allergens and histamine (21). Levels of serum oestradiol and LH were also evaluated; days 3-4, days 14-15, and days 27-28 were compared. Significantly decreased reactivity to allergens was observed in the middle of the menstrual cycle, with a strong correlation to levels of LH and oestradiol. Histamine levels, however, showed no fluctuation over the time points measured.

Available data suggest that the elevated levels of oestrogen and progesterone characteristic of the periovulatory period, in agreement with earlier experiments (2,18,19), appear to produce substantial inhibition of cellular immunity, particularly the delayed hypersensitivity-type reaction (21), while lower levels of both hormones (both preceding and immediately following the onset of menstruation) allow for the exacerbation of symptoms seen fairly consistently in atopic patients (9,30,31,37,39,40). The lack of agreement in patch testing so far may relate to differences in methodology or both high levels of interpersonal and intrapersonal variability as observed earlier (42).

Allergies to autologous sex hormones have been also been recently documented in the published literature. Autoimmune progesterone dermatitis is an autoimmune reaction believed to be caused by an allergic response to one's own progesterone secretion (11,15). Morphological features include dermatitis, erythema multiforme, urticaria, pompholyx, stomatitis, dermatitis herpetiformis, and nonspecific popular erythema (11). Similarly, oestrogen dermatitis is an autoimmune reaction postulated to be caused by an allergic response to one's own oestrogen secretion (10,43).

There is some debate as to whether patients who are diagnosed with autoimmune progesterone dermatitis in fact suffer from a menstrual cycle-related exacerbation of atopic dermatitis (9).

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].

Among the 18 patients who experienced pregnancy, 13 (72.2%) females described a clinical change of their AD during pregnancy, with 12 (66.7%) females who experienced deterioration of AD during their pregnancies and 1 (5.6%) who had improvement of symptoms during pregnancy. The remaining 5 patients answered that they did not notice any change during pregnancy. Of the 12 patients who experienced deterioration during pregnancy, 3 (25%) experienced a mild degree, 7 (58.3%) experienced a moderate degree and 2 (16.7%) experienced a severe degree of deterioration. Of the 12 patients who experienced symptom aggravation during pregnancy, 5 (41.6%) patients were sub-grouped as IAD and 7 (58.4%) were sub-grouped as EAD (5/8 *vs* 7/10, $p > 0.05$).

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. 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 Dehydro Epiandrosterone (DHEA) and DHEA-sulphate (DHEA-S) levels, which apparently show the immune modulatory 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 models6. 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].

Conclusion

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 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.

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