

Review Article

The possible relevance of sex hormones on irritant and allergic responses: their importance for skin testing

MIRANDA A. FARAGE¹, ENZO BERARDESCA² AND HOWARD MAIBACH³

¹Procter and Gamble, Cincinnati, OH,

²San Gallicano Dermatologic Institute, Rome, Italy and

³University of California, School of Medicine, Department of Dermatology, San Francisco, CA

Dermatological responses are affected by the menstrual cycle phase in female patients, an unsurprising observation as oestrogen and progesterone affect the skin and immunological function, with oestrogen suppression of cellular immunity in particular. Exacerbation of dermatological symptoms is typically observed in either the latter phase of the menstrual cycle or during menstruation. The allergic response is diminished in the ovulatory phase and heightened in the progestinic phase. Definitive conclusions with regard to the effect of reproductive hormones on skin disorders have been somewhat hampered by a body of research that has employed diverse research parameters, such as dosage, testing sites, concentration, vehicle of irritant delivery, and method of assessment, however, individual patient sensitivity varies widely. Standardization of measurement techniques is necessary to provide reproducible results as much as individual patient variation and technique will allow.

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The cyclical variations of progesterone and oestrogen that define the menstrual cycle constitute a significant physiological influence on the reproductive female. The menstrual cycle begins with the onset of menstruation (1). The follicular phase which follows is characterized by increasing levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which peak at ovulation. Oestradiol reaches its highest level immediately before the ovum is released. Progesterone peaks in luteal phase: both progesterone and oestrogen begin to drop at about day 26, with falling levels inducing onset of menstruation (1).

These cyclic fluctuations of oestrogen and progesterone levels over the course of the menstrual cycle influence numerous medical conditions, including various dermatological disorders. Asthma (2–6), migraines (2, 5), epilepsy (2, 5) diabetes (5), porphyria (2), catamenial pneumothorax (5), acute appendicitis (5), myasthenia gravis (2), and allergic rhinitis (7) are all influenced by levels

of oestrogen or progesterone. Many dermatological conditions are affected by fluctuating levels of oestrogen and progesterone, the most widely recognized being acne vulgaris (8). Other dermatological conditions influenced by changing levels of sex hormones are presented in Table 1. Some studies have associated a worsening of dermatological conditions with the pathological and psychological manifestations of premenstrual syndrome (2, 9). Recent research has implicated an autoimmune response to endogenous sex hormones as a possible aetiology for the constellation of complaints that comprise premenstrual syndrome (10). The association between the dermatological response and the menstrual cycle will be reviewed here. The need for standardization of testing measures is demonstrated.

This manuscript is a retrospective review of the available published literature identified through a search of Medline, Scopus and Biosis databases for the years 1950 to the present, as well as cross-references to publications that were cited in this manuscript. The literature review protocol employed

Table 1. Dermatological clinical conditions with reported exacerbation of symptoms in association with female sex hormones

Condition	References
Acne vulgaris	(2, 3, 8, 10–12, 58)
Apthous ulcerations	(2)
Cyclical vulvovaginitis	(2, 10)
Dermatitis herpetiformis	(2, 11)
Erythema multiforme	(8, 11)
Hereditary angioedema	(2)
Herpes gestationis	(2)
Herpes simplex	(2, 3, 8)
Hyperpigmentation	(2, 10)
Keratosis follicularis (Darier's disease)	(2)
Lupus erythematosus	(2, 3, 10, 11, 13)
Pompholyx	(11)
Porphyria cutanea tarda	(2)
Pruritus vulvae	(2, 10)
Psoriasis	(8, 11)
Pruritic papules	(10)
Rosacea	(8, 11)
Urticaria	(2, 3, 8, 11, 14, 15)

the search terms: menstruation, menses, or menstrual with skin, prick, or patch, and with dermatitis, dermal, or dermatological. A representative article of nickel contact allergy and menstruation was searched through Scopus to find affiliated articles. The cut-off year of 1950 was selected on the basis that allergy tests have not significantly changed in the past 50 years, and that an association of allergy with the menstrual cycle had been cited in early literature. Finally, electronic searches were supplemented by references cited in the articles included in this review.

Effect of sex hormones on skin

The skin has highly sensitive receptors for oestrogen and progesterone, which facilitate numerous hormone-driven interactions (2). Oestrogens are instrumental in maintaining the structural integrity of the skin (primarily the collagen component) as well as the water-binding capacity of the stratum corneum (16). Oestrogens also promote skin elasticity, and improve wound healing (16).

Progesterone also influences skin structure and function. Progesterone as well as oestrogen stimulate keratinocyte production and inhibit the degradation of collagen (17). Increased vascularity and sebaceous gland activity have been attributed to progesterone (11).

Effect of oestrogen and progesterone on immune function

Oestrogen is postulated to be a 'natural modulator' of the immune system. Although some facets of immunity appear to be enhanced by oestrogen exposure (18), oestrogen has been demonstrated to decrease cellular immune response in the skin (2).

Females have less cellular immunity than males, a deficiency at least partially credited to oestradiol levels (18, 19). Progesterone, although less understood, also exhibits an immunosuppressive effect (2).

The hormonal fluctuations of the menstrual cycle, therefore, may influence the susceptibility of the skin to both irritant and allergic sensitization. Oestradiol is known to induce inhibition of delayed hypersensitivity reactions (8). In general, susceptibility to contact sensitization seems to increase in late luteal phase, shortly before menstruation, while the follicular phase appears to suppress contact sensitization (8). T-cell depletion and B-cell proliferation coincide with ovulation (20). Mast cell degranulation has also been reported during the midcycle ovulatory period (21). It is postulated that the decrease in T-cells which reaches its nadir during ovulation leads to a suppression of cellular immune response (22).

An active role of oestrogen on immune function is implied by the presence of oestrogen receptors on peripheral lymphocytes of a 'suppressor-cytotoxic' phenotype (23). Oestrogen is known to produce thymic atrophy (24), as well as decreased numbers and suppressed function of thymocytes (25).

An evaluation of menstrual midcycle rashes identified a progesterin-binding component with properties of immunoglobulin antibody G (IgG), implying antibodies to an endogenous steroid (26). Another found increased eosinophil counts during episodes of urticaria, which decreased with increased progesterone levels later during the menstrual cycle. The hormone inhibited antihuman immunoglobulin E (IgE)-induced histamine release from the peripheral basophils of the patient (14). A decreased IgE concentration was found midcycle in another study by Vellutini et al. (27) Additionally, oestradiol acted directly on B-cells, increasing synthesis of the immunoglobulin M (IgM) class of antibodies (28).

As postulated by Kemmett and Tidman, the premenstrual syndrome may be due to abnormal neurotransmitters, which may be related to a hyporesponsive reaction to intradermally injected neurotransmitter substance P in atopic dermatitis. Additionally, this neurotransmitter may cause vascular and mast cell changes in atopic dermatitis patients (9).

Evidence of the major role that sex hormones play in the regulation of immune function in the human female carries implications for a woman's intake of additional oestrogen in the form of oral contraceptives or hormone replacement therapy. The role that oral estrogens may play in the treatment of autoimmune diseases, particularly, is an area of much interest (29). Satisfactory consideration of this topic, however, is beyond the scope of this discussion.

The Menstrual Cycle And Dermatitis

Allergic contact dermatitis is a dermatological condition resulting from exposure to an allergen, whereas *irritant contact dermatitis* is a dermatological condition caused by single to repetitive exposure to irritant substances over time (7). *Atopic dermatitis*, or *eczema*, is a chronic dermatologic manifestation with symptoms starting as early as infancy, with exacerbations throughout later years (2, 4, 8, 30, 31). In a report by Meding and Swanbeck, the epidemiology of hand eczema cases were as follows: 35% irritant contact dermatitis, 19% allergic contact dermatitis, and 22% atopic hand eczema (7, 32).

Irritant contact dermatitis

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, transepidermal 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.

Allergic contact dermatitis

The changes in endogenous hormone levels characteristic of the menstrual cycle appear to affect allergic responses as well as clinical expression of atopic disease (8, 15, 21, 34, 35). Correlating various time points in the menstrual cycle to specific onset of symptoms helps to define the particular sex hormone, specifically oestrogen (and oestradiol) and progesterone, that influences the expression or inhibition of response (8, 31).

The first published study of the effect of menstrual cycle fluctuations of female hormones on atopic dermatitis was in 1929 by Müller, who reported that 23% of patients experienced a premenstrual exacerbation of symptoms (9, 36). A premenstrual exacerbation of atopic dermatitis was also observed in another earlier study, which evaluated 492 patients at the Mayo Clinic (37).

More recent studies also support increased reactivity to antigens in the premenstrual phase (31, 38). In a study of 143 patients who responded to a questionnaire, 28.7% of female atopic dermatitis patients reported worsened symptoms of eczema the week before menstruation as compared with 9.1% who reported exacerbations at other times (30). Similarly, in a 1991 study by Kemmett and Tidman, 33% of 150 atopic dermatitis patients who were surveyed reported a decline in their condition immediately before or during menstruation (9). Seven percent of the patients reported a cyclic variation at another time in the menstrual cycle, but did not define a specific time point (9). In Garrell's study (1964) of 14 atopic dermatitis patients, 80% showed a deterioration of skin condition immediately prior to or during menstruation (39).

Another study of patients with atopic dermatitis found exacerbation of symptoms during the week preceding menstruation or even during menstruation but not in the ovulatory phase (40), although premenstrual syndrome was not found to be associated with the premenstrual deterioration of symptoms.

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 days 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 days 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 rhinoconjunctivitis 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).

Analysis of methodologies employed in reviewed literature

Skin testing for irritant or allergic responses, including those that have evaluated reactivity in conjunction with the menstrual phase, involves multiple variable factors and have employed various approaches, a fact which has complicated comparative analysis.

The concentration of irritant solutions, as well as anatomical site to which they are applied, directly affects the intensity of dermatological response, although the extent of irritancy of SLS is also due to the action of the substance on surface tension. Furthermore, the preservative 0.1% formaldehyde can also cause contact sensitization. Environmental conditions also varied and should be considered as a factor into the variation of skin response.

Numerous variations in study design have been employed; endpoints have included TEWL, skin hydration, cutaneous blood flow, skin colour and temperature, and more. Various patch test units and vehicles for the irritant have also been used. Most significantly, for skin testing related to the

Table 2. Parameters and approaches in skin testing

Test variables	References
Irritants	
Parietaria	(44)
Sodium lauryl sulfate	(31)
Cantharidin	(7)
Croton oil	(7)
Dithranol	(7)
Phenol	(7)
Hydrochloric acid	(7)
Kerosene	(7)
Benzalkonium chloride	(7)
Sapo kalinus (an alkali)	(7)
Nonanoic acid	(7)
Propylene glycol	(45, 46)
Allergens	
Mercuric chloride	(7)
Nickel sulfate	(8)
Thymoquinone	(7)
Sites	
Upper Arm	(31)
Lower Arm	(7)
Upper Back	(3, 8, 44)
Lower Back	(42)
Test concentrations	
Sodium lauryl sulfate concentrations 0.10–5%	(31)
Nickel Sulfate concentrations:	
0.0013–5%	(8)
0.0032–12.5%	(42)
Environmental conditions	
Relative humidity, drafts, water vapour gradient	(7, 31)
Endpoints measured	
TEWL	(7, 31)
Skin hydration	(7, 31)
Cutaneous blood flow	(31, 33)
Light refraction colorimetry	(7)
Skin temperature	(7)
Visual scoring	(3, 8)
Skin thickness	(7, 31)
Subjective patient self-evaluation	(8, 40)
Sampling approaches	
Sampling at specific day of cycle	(3, 8)
Sampling at specific hormone level	(21, 31)
Methodology	
Finn chamber® (variable sizes)	(7)
Duhring chamber	(7)
A1-test®	(7)
Silver patch	(7)
Van der Bend® chamber	(7)
Plastic chamber	(7)

menstrual cycle it is critical to determine accurately the specific stage of the menstrual cycle at which testing is performed (3, 8). Some researchers have established time of testing as number of days into cycle. Others have verified the circulating hormone levels, typically serum oestradiol, simultaneous with skin testing, as a more rigorous approach (21, 31). A list of various approaches to skin testing in the current literature appears in Table 2.

The fact that the methodology used to assess dermatological response has varying degrees of efficacy also creates difficulty in assessing the affects of sex hormones on response (7, 10, 47). In general, objective assessment is preferred over subjective evaluation (7, 48). However, patient subjective

assessment should be complimented to objective results. In a recently published study by Farage, subclinical visual scoring of skin response to SLS was enhanced through the use of cross-polarized light (49). Furthermore, subclinical skin reactions were able to be correlated to subjective sensory complaints (50).

Discussion

Although the majority of studies reviewed indicate suppression of the allergic response at the time of ovulation (8, 31, 38), as well as increased sensitivity of allergic reaction in the latter phase of the menstrual cycle (3, 30, 42, 44, 51), some studies show no significant influence of the menstrual cycle (8, 41, 52). There are numerous factors with regard to experimental design and execution that may have contributed to the current inconsistency in experimental results, as shown in Table 3.

When evaluating the effect of menstrual cycle on the specific symptoms of a dermatological disorder, an accurate differential diagnosis must be obtained, for example, in studies which evaluated autoimmune progesterone dermatitis, it was postulated that some of the subjects would be more accurately reported as a premenstrual flare of atopic dermatitis (9). Multiple factors may contribute to dermatological response (barrier function, inflammatory mechanisms, skin status, test conditions, etc.) and each one must be controlled to arrive at meaningful conclusions.

Table 3. Confounding factors in skin sensitivity testing

Confounding factors	Reference
Menstrual cycle	(8, 44)
Concentration of test substance	(7, 8, 42)
Dose of test substance	(7, 42)
Batch volume	(7, 50)
Purity of test substance	(7, 42)
Test substance vehicle	(7)
Length of exposure	(7)
Time of occlusion	(7)
Release of test substance from chamber	(7)
Enhancement of penetration	(7)
Method of evaluation	(3, 7, 8, 30, 31, 33, 40, 49, 51, 53)
Time of evaluation after exposure	(3, 7, 8, 21, 31)
Humidity	(7, 31, 42)
Water vapour gradient	(7)
Impairment of skin barrier	(7)
Anatomical site	(7)
Intrinsic level of skin sensitivity	(7)
Booster effect	(41, 54)
Individual variation	(38, 41, 42, 55–57)
Skin temperature	(7)
UV light exposure	(7)
Age	(7)
Sex	(7)
Race	(7)
Circadian rhythms	(42, 44)
Concomitant medications	(42, 44)

Physicians may need to also consider whether a booster effect of added allergen is possible in the event of a second negative patch test result, particularly when clinical symptoms indicate an allergic response upon presentation (41). In a study of 20 patients by Rohold et al., heightened skin reactivity was exhibited in patients at their second nickel sulfate patch test despite, a 6-week interval between tests ($0.02 < p < 0.05$) (41). Therefore, this effect can be observed even after a reasonable amount of time for recovery. Similarly, Friedmann et al. also produced a lowered sensitization threshold to allergens administered by patch test on repeat exposure (55). However, the lack of a booster effect is evident in other studies (3, 8, 42). Furthermore, in the study by Hindsén et al., no downgrading of effect was observed (42). Nevertheless, as noted in other studies, the varying response to allergens at different endpoints in the menstrual cycle should be viewed in the context of the reproducibility of the patch tests.

Individual variations that are dependent on the particular allergen or menstrual cycle phase must be considered as well (38, 41, 42, 52, 54, 56). In a study of individual variation of nickel contact allergy by Hindsén et al., intra-individual samplings revealed 250-fold variation in repeated patch testing carried out four times (42). Furthermore, none of the 30 women studied showed the same patch reactivity on all four occasions tested during a period of 9 months (42). Freeman and Maibach also documented considerable variation in skin responses to identical patch tests in the same individual (7, 12).

The reproducibility of test results would appear to be influenced by not only hormonal and intrapersonal variation, but also standardization of test procedures. Best practices in evaluation of allergic and irritant response would provide for the standardization of protocol to include choice of irritant, test site, environmental controls, batch volume, batch concentration, delivery vehicle, use (or no use) of occlusive dressing, time to evaluation, assessment tool used, and, in females, a consistent time within the menstrual cycle to assess dermatological response based on circulating oestradiol.

Most research supports the hypothesis that oestradiol suppresses cellular immunity (3, 8). As false-negative results can result in the ovulatory phase of the menstrual cycle, patch testing may need to be repeated in the progestinic phase of the cycle (8).

The effectiveness of skin barrier function is also challenged in those patients with sensitive skin or irritant contact dermatitis (7). Although some studies have reported no association between the response to one particular irritant and the response

to another, other studies have shown that 'hyper-reactors' have an increased susceptibility to skin tests (7). However, further study may reveal differences in the skin response due to dosage or depth of penetration of the irritant (7). Similarly, irritant contact dermatitis is caused by cumulative barrier function injury (7).

Although the bulk of available research supports anecdotal reports that dermatological conditions in women of reproductive age follow a cyclic pattern of symptom severity that is associated with fluctuating levels of female sex hormones, the wide variety of both intrinsic and extrinsic factors, combined with a prior lack of standardization of research methods by those who have investigated this topic, has contributed to a body of somewhat contradictory literature. The wide range of intrapersonal variation in skin sensitivity further clouds the available literature. Additional research, with strict attention to standardizing experimental parameters and minimizing other compounding factors will help to elucidate the biological and immunological basis for the observed effects of progesterone and oestrogen levels on skin health. Future studies may produce supporting evidence for an allergen of unknown origin in females who experience exacerbation of allergic and irritant response in conjunction with the menstrual cycle. In conclusion, dermatologists should be aware that the menstrual cycle can affect the sensitivity of women to primary irritants and can affect their dermatological response.

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Address:

Miranda A. Farage, PhD
Feminine Clinical Sciences
The Procter & Gamble Company
Winton Hill Business Centre
6110 Centre Hill Rd.
P.O. Box 136
Cincinnati, OH 45224 USA
Tel: (513) 634-5594
Fax: (513) 634-7364
e-mail: farage.m@pg.com