

Correspondence

The effect of sex hormones on irritant and allergic response: possible relevance for skin testing

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SIR, The cyclical variations of progesterone and oestrogen that define the menstrual cycle represent a major biological influence on the female body. The skin has highly sensitive receptors for oestrogen and progesterone, and many dermatological conditions are affected by oestrogen and progesterone levels (Table 1). Rare autoimmune disorders known as oestrogen dermatitis and autoimmune progesterone dermatitis, believed to be cutaneous reactions to endogenous sex hormones, are also reported in the literature.¹

Oestrogen is also postulated to be a 'natural modulator' of the immune system, with high oestrogen levels acting to inhibit allergic response. Ovulation occurs in conjunction with peak oestrogen levels in a woman of reproductive age. Mast cell degranulation has been reported during this phase,² as well as decreases in T-cell numbers,³ leading to depression of cellular immune response. B-cell numbers have been observed to increase in coincidence with ovulation.³

Sex hormones influence the dermatological expression of allergic response.⁴ Correlation of menstrual cycle timepoints with symptom onset helps to define the particular sex

hormone associated with cutaneous symptoms.⁴ Numerous studies demonstrate increased reactivity to antigens in the premenstrual phase as well as deterioration of atopic skin conditions immediately prior to or during menstruation. In a study of 143 women with eczema, 28.7% reported worsening of symptoms the week before menstruation. In a study of 286 women with atopic dermatitis, 96% of those who reported cyclic variations in symptoms reported deterioration of symptoms during the week preceding menses with rapid improvement after the onset of menstrual flow.⁵ The prevalence of premenstrual worsening of atopic dermatitis symptoms, in published reports, was as high as 100%.⁵

The follicular phase of the menstrual cycle, in contrast, seems to inhibit manifestation of allergic contact dermatitis.⁴ Although most studies indicate a suppressed allergic response at the time of ovulation,^{4,6} others show an increased sensitivity in the latter phase of the menstrual cycle⁷ or no association of allergic response with the menstrual cycle at all.⁸

Skin testing with the objective of evaluating the influence of sex hormones on allergies has yielded interesting results. Kirmaz *et al.* found that while skin prick test (SPT) reactivity to histamine did not vary throughout the menstrual cycle, serum estradiol was positively correlated with SPT reactivity to allergens in the middle of the menstrual cycle.² Likewise, Kemmett and Tidman observed that, despite constant histamine levels, maximal erythema in women with atopic dermatitis occurred at onset of menstruation.⁹

Numerous factors can influence skin testing results⁶ (Table 2). Best practice in skin testing of allergic or irritant response would ensure standardization of protocols with regard to the choice of irritant, test site, environmental controls, batch volume and concentration, delivery vehicle, use of occlusive dressing, time to evaluation, assessment tools and (in women) menstrual cycle phase. Individual variations, including the possibility of a booster effect, must be considered as well.⁸ In a study of 20 patients by Rohold *et al.*, heightened skin reactivity was exhibited in patients at a second nickel sulphate patch test despite a 6-week interval between tests ($0.02 < P < 0.05$), confirming the possibility of a booster effect after a putatively reasonable amount of time for recovery.⁸ Intraindividual variations, over four repeated patch testings, were also observed to vary as much as 100-fold.¹⁰

In conclusion, 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, with most authors observing a heightened allergic response in the

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

Acne vulgaris ^{4,7,11}
Aphthous ulcerations ¹¹
Cyclic vulvovaginitis ^{1,11}
Dermatitis herpetiformis ¹¹
Hereditary angio-oedema ¹¹
Herpes gestationis ¹¹
Herpes simplex ^{4,7,11}
Hyperpigmentation ^{1,11}
Keratosis follicularis (Darier disease) ¹¹
Lupus erythematosus ^{1,7,11}
Polymorphous erythema multiforme ⁴
Porphyria cutanea tarda ¹¹
Pruritus vulvae ^{1,11}
Psoriasis ⁴
Pruritic papules ¹
Rosacea ⁴
Urticaria ^{4,7,11}

Table 2 Confounding factors in skin sensitivity testing

Menstrual cycle ⁴
Concentration of test substance ^{4,6,10}
Dose of test substance ^{6,10}
Batch volume ⁶
Purity of test substance ^{6,10}
Test substance vehicle ⁶
Length of exposure ⁶
Time of occlusion ⁶
Release of test substance from chamber ⁶
Enhancement of penetration ⁶
Method of evaluation ⁴⁻⁷
Time of evaluation after exposure ^{2,4,6,7}
Humidity ^{6,10}
Water vapour gradient ⁶
Impairment of skin barrier ⁶
Anatomical site ⁶
Intrinsic level of skin sensitivity ⁶
Booster effect ⁸
Individual variation ^{8,10}
Skin temperature ⁶
Ultraviolet exposure ⁶
Age ⁶
Sex ⁶
Race ⁶
Circadian rhythms ¹⁰
Concomitant medications ¹⁰

progestinic phase. Definitive conclusions with regard to the effect of reproductive hormones on skin disorders have been somewhat hampered, however, by the fact that individual patient sensitivity varies widely and 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. Further research, with strict attention to standardizing experimental parameters and limiting compounding factors, will help to elucidate the biochemical basis for the observed effects of progesterone and oestrogen levels on skin health. Dermatologists should be aware that the menstrual cycle can affect the sensitivity of women to primary irritants and can affect their allergic response.

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