

Nickel contact allergy and menstrual cycle

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According to some reports in the literature, the hormonal fluctuations which occur during the menstrual cycle may affect the clinical expression of contact allergy to a greater or lesser degree. In clinical practice, too, patient history often shows exacerbation of the contact dermatitis during the days immediately preceding menstruation. On the contrary, the follicular phase of the cycle seems to have a temporary protective role in inhibiting the eliciting phase of allergic contact dermatitis. One possible explanation for this phenomenon is of immunological type: it has been demonstrated that oestradiol induces inhibition of delayed hypersensitivity type reactions, probably by acting indirectly on cells having a regulatory function in cell-mediated immunity. To investigate any inhibitory effect of the ovulatory phase of the menstrual cycle on contact sensitization, 30 selected fertile women, allergic to nickel sulfate and with a regular menstrual cycle lasting between 25 and 32 days, were enrolled. Patch tests were performed with a series of 10 serial aqueous dilutions of nickel sulfate, from 5% to 0.0013%. The 30 women were tested at 2 different times, in the ovulatory phase (demonstrated by transvaginal ultrasound) and the progestinic phase; they were subdivided into 2 groups of 15 women: in one group, the tests were made first in the ovulatory phase, and in the other, first in the progestinic phase of the menstrual cycle. There was a minimum interval of 5 weeks between the 2 test phases. The study shows that during ovulation the patch tests elicited significantly less intense responses than in the progestinic phase. These data therefore suggest that the ovulatory phase of the cycle has a significant inhibitory role on delayed hypersensitivity type reactions. For this reason, negative responses to patch tests executed in this phase could likely be false-negatives, and after careful evaluation of the phenomenon and of the clinical condition and patient history, it may be considered advisable to repeat the tests during the progestinic phase of the menstrual cycle.

Key words: allergic contact dermatitis; menstrual cycle; nickel sulfate; ovulation; progestinic phase.

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The menstrual cycle seems to affect both some physiological skin parameters and some dermatological complaints. In the first case, the skin seems to be more prone to contact irritation during the premenstrual phase, as shown by a more intense response to patch tests with sodium lauryl sulfate in this phase as compared with the follicular phase of the cycle; this greater irritability could be partly due to a lower efficacy of the skin barrier (1–4). Secondly, the negative effects of the menstrual cycle on some dermatological complaints, such as herpes simplex and acne vulgaris, are well known. Other less classic examples include chronic urticaria and polymorphous erythema (5, 6); even atopic dermatitis seems to deteriorate or to recur in the premenstrual phase, although the percentage of cases varies considerably in the different series (7, 8).

Only few studies have been reported in the literature on the role of the menstrual cycle in patients suffering from contact allergy, and the results obtained are contradictory (9–14). The first report in the literature was that of a woman who was patch tested by accident twice, at different times of the menstrual cycle. The first test, performed in the premenstrual phase, elicited a positive reaction to fragrance mix, whereas the second, in the follicular phase, did not confirm these findings. Moreover, the patient referred that she could not use scent during the days before menstruation. Another case was reported in the same article that of a woman whose allergic contact dermatitis to her watchcase was only clinically evident during the premenstrual phase. Patch test to nickel was positive in this phase, but was negative when performed at about the 10th day of the cycle (9).

Hindsén et al. (11) applied patch tests with 10 serial dilutions of nickel sulfate in 30 women with nickel allergy; the tests were repeated 4 times in each patient, at intervals ranging from 2 to 2.5 months. At each of the 4 patch test applications, the women gave information about the regularity of the cycle and the exact day it started; the results of the research showed a significant increase in the reactions to nickel (expressed as a reduction in the concentration required to elicit a reaction) during the days immediately before menstruation.

However, not all authors have found a significant difference in the responses to patch tests in the 2 different phases of the menstrual cycle. In one study of 20 women with nickel allergy, no change was found in their reaction to the tests during the 2 periods (12). In another investigation aiming to assess the reproducibility of patch tests with nickel sulfate at 5% in the follicular and luteinic phases, the cases of non-reproducibility of the findings were not statistically correlated with the different phases of the cycle (13).

Some experimental data indicate that, *in vitro*, oestrogens can affect the immune system, by inhibiting cell-mediated hypersensitivity reactions (15–18). On this assumption, it can be hypothesized that the clinical studies made up to now were limited by the fact that the testing during the oestrogenic period was carried out too early in the follicular phase (7th to 10th day), in other words before the oestrogen peak that occurs during ovulation.

In this study, we assessed the role of the menstrual cycle on contact allergy, focusing particularly on the possibility that ovulation could inhibit contact sensitization mechanisms.

Patients and Methods

30 women with contact dermatitis to jewellery and/or jeans buttons, glass frames and belt buckles, of ages ranging from 20 to 48 years (mean age: 30.7 years), with a regular menstrual cycle lasting between 25 and 32 days, were selected. The women, recruited from the outpatient clinic, yielded a positive response to patch tests with nickel sulfate at 5% in petroleum of the standard series. Patient history was recorded, including the age of onset of menarche, the duration of the menstrual cycle and its regularity, any pregnancies and spontaneous or provoked abortions. Women taking oral contraceptives or any drug which could interfere with the endocrine-sexual sphere were excluded from the study.

The 30 women, subdivided in atopic and non-atopic subjects, answered questions regarding

the contact allergy to nickel: when it appeared, what skin zones it involved and the progression over time of the clinical manifestations. Particular attention was paid to any recurrence or worsening of the symptoms during the premenstrual phase and to any exacerbation during previous pregnancies. Finally, the circumstances of contact with sources of nickel were enquired about, as well as whether any preventive measures had subsequently been adopted.

After the preliminary enrolment phase had been concluded, including establishment of the precise day of the current menstrual cycle, the study was carried out in 2 phases. To individuate the exact period of the ovulatory and progestinic phases, the subjects were asked to present to our dermatology section during the presumed days of the menstrual cycle for 2 successive cycles. Ovulation (defined as the presence of an ovarian follicle of at least 20 mm Φ ready to undergo ovulation) was confirmed by transvaginal ultrasound. The progestinic phase, between the 21st and 23rd day of the same cycle or the successive one, was defined on the basis of ultrasound measurement of the thickness of the endometrium and of the presence of the corpus luteum. Ultrasound examination of the uterus and the ovaries was conducted using a sonograph (Aloka 5000; Aloka, Tokyo, Japan) equipped with a 5-MHz vaginal probe (19, 20).

Patch testing

In all the selected women, patch tests with nickel sulfate were performed in the 2 different phases, ovulatory and progestinic, of the menstrual cycle. There was an interval of at least 5 weeks between the 2 phases. The patients were subdivided into 2 groups: in one group of 15 women, the patch tests were applied first in the ovulatory phase and in the other group, in the progestinic phase.

The patch tests were conducted with a series of 10 serial aqueous dilutions (5%, 2%, 0.80%, 0.32%, 0.13%, 0.051%, 0.020%, 0.0081%, 0.0032% and 0.0013% w/v) of nickel sulfate (NiSO₄, 6H₂O; Sigma Chemicals, St Louis, MO, USA). The standard technique was adopted, using Finn Chambers[®] on Scanpor tape (Epitest, Tuusula, Finland), with 3 days of occlusion according SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) guidelines (21). On the Finn Chambers[®], 15 μ l of each nickel sulfate dilution was applied with a micropipette. The tests were applied symmetrically, 5 per side, on the upper part of the back.

Patch test reactions were evaluated 0.5–3 hr after removal and scored according to ICDRG criteria, with 2 classifications added to the 3 usual positive gradings: strong + and ++ reactions were graded as $+\pm$ and $++\pm$, respectively. The different steps, including the intermediate steps, are defined as follows:

+	erythema and infiltration
$+\pm$	erythema, infiltration and few papules
++	erythema, infiltration and papules
$++\pm$	erythema, infiltration, papules and few vesicles
+++	intense erythema and infiltration and coalescing vesicles

The same person, Domenico Bonamonte, tested the patients, and all the tests were read by the same reader, Gianni Angelini, who did not know the patients, neither to which group they belonged nor the results of previous tests.

This study was performed in accordance with the Helsinki declaration, and informed written consent was obtained from all patients before patch tests.

Statistical evaluation

To enable statistical calculations, the various scores were given values as follows: $- = 0$; $\pm = 0.5$; $+ = 1$; $+\pm = 1.5$; $++ = 2$; $++\pm = 2.5$; and $+++ = 3$.

The lowest concentration of nickel sulfate eliciting at least a + reaction was ascertained for each patient and registered as the minimal eliciting concentration (MEC). The scores for all reactions were summed to obtain a variable denominated as the summarized test score (STS).

The values for the variables under study (MEC and STS) observed in the 2 menstrual phases were compared with the signed rank test for paired samples.

The influence of the order of execution of the test in the 2 study groups was assessed by comparing variations in the 2 variables (MEC and STS) with the Wilcoxon test for paired samples. This test was also used to assess any differences due to the presence of atopy, the adoption of preventive measures and a positive history of premenstrual recurrence or exacerbation of the dermatitis.

Results

Of the 30 subjects, only one had a response to the lowest concentration of nickel sulfate (0.0013%).

Comparison of the MEC in the 2 test phases yielded significantly lower values in the progestinic phase than in the ovulatory phase of the menstrual cycle (signed rank test = -142 ; $P \leq 0.0001$): the MEC was lower in the progestinic phase in 23 of the 30 subjects, the same in 4 patients and increased in 3 subjects (Fig. 1). The variations in the MEC were not affected by the order of execution of the patch tests (Wilcoxon test = 223; $P = 0.7$), nor by the presence of atopy (Wilcoxon test = 127.5; $P = 0.88$), and preventive measures also had no effect (Wilcoxon test = 158.5; $P = 0.61$). A positive history of premenstrual recurrence or exacerbation of the contact dermatitis was not correlated with the variations in the MEC (Wilcoxon test = 177.5; $P = 0.72$).

As regards the STS, in 29 of the 30 subjects tested, the values were significantly higher during the progestinic phase than the ovulatory phase (signed rank test = 222; $P < 0.0001$) (Fig. 2). It should be noted that this applies also to the four cases who did not show differences in the MEC between the 2 study phases, as well as to 2 of the 3 cases who had a higher MEC in the progestinic

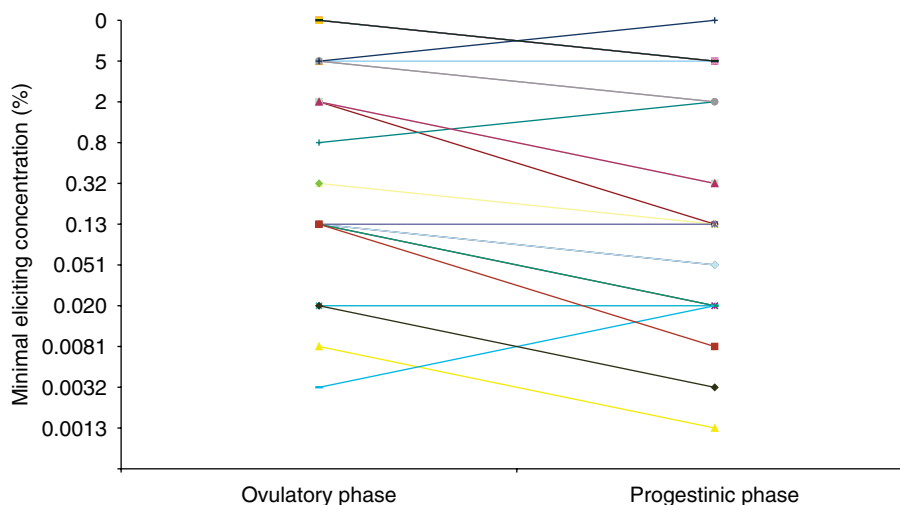


Fig. 1. Minimal eliciting concentration in the 2 phases of the menstrual cycle.

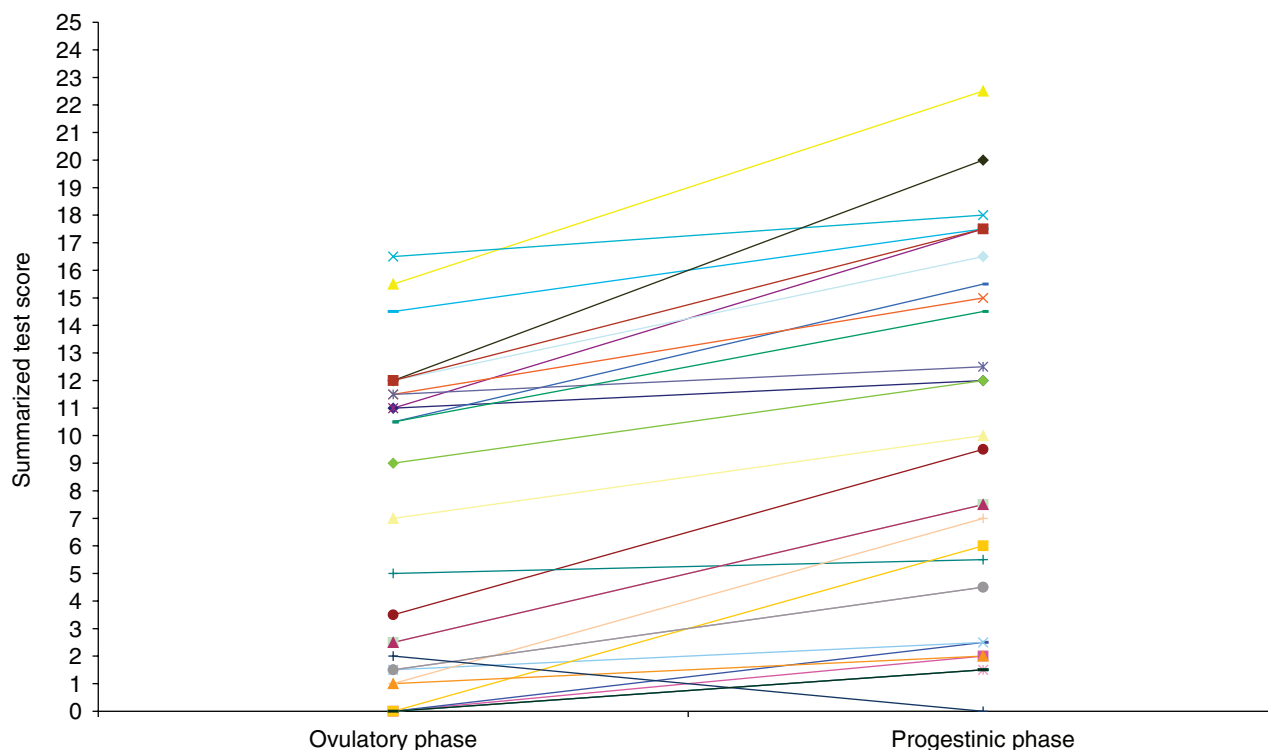


Fig. 2. Summarized test score in the 2 phases of the menstrual cycle.

phase. Only in one woman did the patch tests yield negative results to the various dilutions of nickel in the progestinic phase and positive results in the ovulatory phase. The variations in STS were not affected by the order of execution of the patch tests (Wilcoxon test = 232; $P = 1$), nor by the variables atopy (Wilcoxon test = 138; $P = 0.52$), preventive measures (Wilcoxon test = 150; $P = 0.39$) or a positive history of premenstrual recurrence or exacerbation of the contact dermatitis (Wilcoxon test = 166; $P = 0.41$).

Discussion

It seems from some clinical observations that the menstrual cycle can affect not only some physiological skin parameters (evaporation, hydration and skin barrier) (1–4), but also the inflammatory and immunological mechanisms underlying various dermatological complaints (herpes simplex, acne vulgaris, chronic urticaria, polymorphous erythema and atopic dermatitis) (5–8).

Only few studies in the literature have reported on the role of the menstrual cycle in contact allergy, and even in these, discordant results were obtained (9–14). Some authors support a possible exacerbation or recurrence of allergic contact dermatitis during the days immediately before menstruation, and also hypothesize that the follicular phase could have a 'protective' effect, reducing or masking the sensitized state

(9–11). One possible explanation for this phenomenon is of immunological type. In fact, experimental studies have demonstrated *in vitro* that oestradiol induces inhibition of cell-mediated hypersensitivity, probably due to an action on the cells regulating type IV immunity (15, 16). The presence of oestrogen receptors on the peripheral lymphocytes of OKT8 (+) type (with a cytotoxic and suppressor function) lends further weight to an active role of these hormones in the immune function (17). Barr et al. (18) examined the effect of the sex hormones on thymus subpopulations in the mouse and demonstrated that oestrogens reduce the number of cortical thymus cells.

Not all studies of this phenomenon have recorded a significant difference in the response to patch tests in the 2 different phases of the menstrual cycle (12–14). However, in view of the above experimental findings, it can be hypothesized that the studies were limited by execution of the patch tests too early in the follicular phase (7th to 10th day), when the peak production of oestrogens by the ovary has not yet been attained. It is known, in fact, that the peak plasma concentrations of oestrogens are present during the ovulation stage itself.

In our study, patch tests were performed both during ovulation (confirmed by transvaginal ultrasound) and in the progestinic phase. The results obtained show a significantly reduced

response to the patch tests during ovulation regardless of the order of performance of the tests. Further studies are needed in which serum hormone levels should be monitored.

Some authors believe that if patch tests are repeated at brief intervals, a higher intensity response in the later test could be attributed to a lowering of the sensitization threshold due to hyperstimulation of the immune system (a 'booster effect') (12, 22). Nevertheless, in our study, we obtained a higher response in the progestinic phase regardless of whether it was the first or the second arm of the study.

On the basis of our findings, it can be concluded that

- (1) In fertile women, in clinical practice it is possible to observe recurrence or exacerbation of allergic contact dermatitis during the premenstrual phase.
- (2) As also reported in other studies, delayed type immunological responses are lower or temporarily absent during the ovulatory phase. For this reason, negative responses to patch tests executed in this phase could likely be false-negatives and after careful evaluation of the phenomenon and of the clinical condition and patient's history, it may be considered advisable to repeat the tests during the progestinic phase of the menstrual cycle.

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