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Short communication

The influence of female sex hormones on nasal reactivity in seasonal allergic rhinitis

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Key words: grass pollen; hormonal influence; menstrual cycle;
nasal reactivity; seasonal allergic rhinitis.

Background: This study aimed to investigate whether the hormone peaks of estrogen and progesterone could influence the extent of the allergic reaction in grass-pollen-allergic women.

Methods: Twenty-three allergic women with seasonal allergic rhinitis due to grass pollen were included in this trial. Twelve were taking oral contraceptives (OC) (control group), and 11 were taking no pill (target group). The subjects were challenged with grass pollen by nasal provocation test around day 14 of their menstrual cycle (ovulation day) and again at the end of the cycle (day 27). The primary criteria were the subjective nasal symptoms rhinorrhea, nasal blockage, itching, and sneezing. A further criterion was the objectively measured nasal mucosal swelling, assessed by active anterior rhinomanometry. All criteria were evaluated before and 15 min after provocation, and the hormone status was determined on each investigation day.

Results: Comparisons of symptoms between the groups resulted in *P* values of >0.05 for all symptoms at both visits except the symptom blocked nose, which was significantly lower ($P=0.03$) in the patients with OC intake at visit 2, and the symptom sneezing, which showed a significantly ($P=0.02$) higher increase in patients taking OC at the end of the cycle. The flow decrease reached a greater extent in the target group than in the controls.

Conclusions: These results indicate a correlation of the hormonal situation and the nasal allergic reactivity. OC intake led to an intensifying of neurogenic symptoms near the end of pill intake, a result which could be due to a protective effect of the endogenous progesterone, in contrast to the orally administered hormones.

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A clear correlation exists between the endocrine system and the immune system. Hormone secretion is influenced by immunologic factors, and vice versa (1–6). Recently, the presence of estrogen- and progesterone-sensitive receptors in the nasal mucosa has been detected (7,8). Electron microscopic and histochemical changes in this area caused by female sex hormones have been observed in pregnant women suffering from allergic rhinitis (9). Konno et al. (10) demonstrated that there is an increase of cholinergic muscarinic receptors after nasal application of estradiol in guinea pigs, leading to nasal secretion and mucosal swelling. In their study, the application of progesterone resulted in a decrease of α_1 -adrenergic receptors and subsequently in nasal swelling. In guinea pigs, hormonal changes due to pregnancy induced an overall decrease of α -adrenergic receptors with the same consequences of increased nasal secretion and mucosal swelling.

Clinical observations in women indicate that there is an increased allergic reactivity in the midcycle (11) and during pregnancy (12), an effect traced back to immunomodulation caused by an altered hormonal state. On the other hand, dysmenorrhea and other cycle-dependent maladies occasionally occur in cases of allergic reaction (13).

An increasing concentration of female sex hormones, as in pregnancy, induces upregulation of estrogen and progesterone receptors in the nasal mucosal tissue (7). It is suspected that the immune system becomes more sensitive to allergic reactivity.

Still, it is unknown whether the physiologic hormonal fluctuation during the menstrual cycle can induce changes in allergic sensitivity and the clinical manifestations which result.

This study aimed to investigate whether the midcycle peak of estrogen and the luteal phase peak of progesterone could influence the sensitivity of the nasal mucosa and, subsequently, the extent of the allergic reaction in grass-pollen-allergic women.

Material and methods

Subjects

Twenty-three allergic women with seasonal allergic rhinitis due to grass pollen were included in this trial. Eleven of them had regular menstrual cycles lasting 28–30 days (target group), and 12 were taking a combined oral contraceptive (OC) containing 0.03 mg ethinylestradiol and a gestagen component of 0.075–0.1 mg per tablet (control group).

Pollinosis was proven by a case history of at least 2 years, and positive RAST and skin prick test, both performed within the last 12 months. There was no other sensitization of clinical relevance in these patients. Subjects with chronic diseases of the upper respiratory tract, asthma bronchiale, systemic illness requiring treatment, or gynecologic problems including hormonal disorders (e.g., luteal insufficiency) were excluded. No medication – especially glucocorticoids – except OC (for control group only) was allowed to be taken within the last 2 weeks. All women had to be without symptoms at the time of investigation. The patients of the target group were aged 22–37 years (mean age 27.2 years), and the patients of the control group were aged 22–38 years (mean age 27.5 years).

Oral and written informed consent according to Good Clinical Practice guidelines was obtained from each subject. The study was reviewed by the ethics committee of the University of Vienna.

Study design

The trial was carried out as an open study with two parallel groups. Subjects taking no contraceptive pill represented the normal biphasic type with a midcycle estrogen peak and a luteal progesterone peak. Subjects taking OC represented the control group with no endogenous hormonal fluctuations. The trial was carried out in symptom-free patients during the winter outside the pollen period.

For each patient, two visits were planned – at the day of ovulation (day 14 ± 1.5) and again near the end of the cycle (day 26) (Fig. 1).

For determination of the day of ovulation in the target group, each of the volunteers performed an ovulation test. This test can predict ovulation by the luteinizing hormone (LH) peak in the urine (Epignost[®], provided by Unipath Ltd, Bedford, UK). The LH peak occurs 24–36 h before follicle rupture. On the day when the test was positive, the first investigation visit took place. The second visit was arranged 12 days later. In the control group, visits were scheduled on days 14 and 26 of the cycle.

To establish a normal biphasic cycle in the target group and the effect of the contraception treatment in the control group, at each visit in all patients, the hormonal parameters 17- β -estradiol, LH, follicle-stimulating hormone (FSH), testosterone (T), androstendione, prolactin, and dihydroepiandrosterone (DHEA) – as well as progesterone at the second visit – were determined by commercially available enzyme immunoassay kits. Serum progesterone was determined additionally at the second visit to confirm a

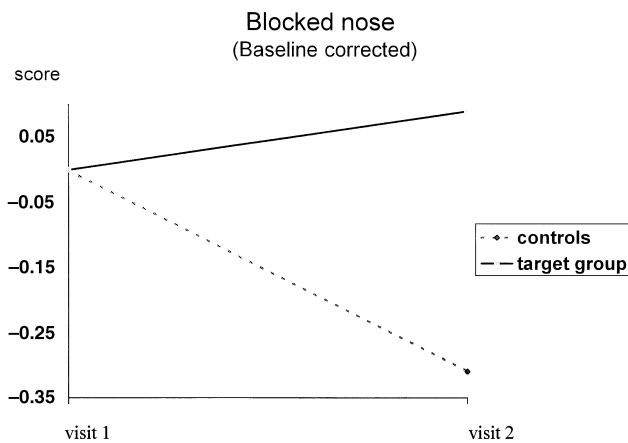


Figure 1. Score sum of vascular nasal symptom nasal blockage at visits 1 and 2, evaluated 15 min after allergen challenge on four-point scale, in patients with and without OC.

physiologic progesterone increase after ovulation in the target group.

To measure the extent of allergic reaction, a nasal provocation test (NPT) was carried out with a 5000-IE/ml grass-pollen allergen solution (*Dactylis glomerata*) provided by Allergopharma Joachim Ganzer KG, Hamburg, Germany. NPT was done at the first visit (ovulation time) and at the second visit 12 days later. A single puff of the allergen solution was applied via a pump spray in each nostril.

Evaluation of the NPT

The primary criteria were as follows:

- 1) the neurogenic nasal symptoms of itching and sneezing
- 2) the vascular nasal symptoms of rhinorrhea and nasal blockage in both groups.

A further criterion was the change of the objectively evaluated nasal mucosal swelling after nasal challenge, which was assessed by active anterior rhinomanometry.

Criteria were first obtained as baseline levels ahead of the allergen provocation and 15 min after allergen challenge in both visits.

Subjective symptoms

The subjective symptoms were scored before the challenge and 15 min after the challenge on a five-point scale (from 0 [no discomfort] to 4 [severe discomfort]).

Active anterior rhinomanometry

In this trial, the nasal airflow of the right and the left nostril was measured by active anterior rhinomanometry, a very sensitive method to assess objectively clinical parameters of

nasal obstruction (nasal flow, nasal resistance, and nasal flow decrease). Nasal flow and nasal resistance are observed at pressures of 75, 150, and 300 Pa.

During active anterior rhinomanometry, the patient had to put on an airtight face mask and not breathe through the mouth. Instead, breathing was possible only through one nostril to evaluate the nasal flow, while a sensor in the other nostril measured the difference in prenasal and choanal pressure. The device (RhinoTest MP 441, Allergopharma Joachim Ganzer KG, Germany) used is connected to a DOS-based PC System. Transducer signals of transnasal airflow and pressure are amplified and digitized, allowing on-screen control, and immediate printing and saving of data for statistical purposes with the Gupta database.

After evaluation of baseline data, the patients' nostrils were washed with 0.9% NaCl solution. A possible change in nasal airflow was controlled by consecutive rhinomanometry before NPT was started: one puff of the allergen solution was applied in the nostril with the higher airflow via a nasal pump spray. Fifteen minutes later, the extent of the nasal allergic reaction was measured by further rhinomanometry.

Statistics

Comparisons between groups were done by means of *t*-tests or (if parametric testing was not applicable) the Mann-Whitney *U*-test. For comparisons within groups, the dependent *t*-test or the Wilcoxon matched pairs sign rank test was used.

With regard to the pilot character of the study, the comparisons and the resulting *P* values have a descriptive character and do not represent hypothesis testing.

Results

There was no significant difference between the baseline data in either of the groups. All patients were comparable in pollen sensitivity (the mean grass-pollen RAST class was 4.4 in the target group and 3.5 in the control group, the mean diameter in SPT was 6.55 mm in the target group and 5.92 mm in the control group, and the mean IgE level was 247 kU/l [standard deviation 209 kU/l] in the target group and 137 kU/l [standard deviation 95 kU/l] in the controls) and duration of illness (mean duration of 17.5 years in the target group and 16.1 years in the control group).

With the exception of OC usage – and thus the hormonal parameters – all demographic and baseline data were comparable within the groups.

Table 1. Descriptive data of symptoms and nasal flow

Itching nose		Midcycle		Late progesterone phase	
		Baseline	Provocation	Baseline	Provocation
OC yes	Mean	0.00	2.33	0.00	2.91
	SD	0.00	0.89	0.00	0.70
	Median	0.00	2.00	0.00	3.00
OC no	Mean	0.00	2.36	0.00	2.91
	SD	0.00	1.36	0.00	1.04
	Median	0.00	2.00	0.00	3.00
Sneezing					
OC yes	Mean	0.00	2.75	0.08	3.55
	SD	0.00	1.14	0.29	0.69
	Median	0.00	3.00	0.00	4.00
OC no	Mean	0.09	3.27	0.09	3.36
	SD	0.30	0.90	0.30	0.92
	Median	0.00	4.00	0.00	4.00
Rhinorrhea					
OC yes	Mean	0.08	2.75	0.25	2.91
	SD	0.29	0.97	0.45	0.70
	Median	0.00	3.00	0.00	3.00
OC no	Mean	0.09	2.45	0.18	3.00
	SD	0.30	1.29	0.40	0.63
	Median	0.00	2.00	0.00	3.00
Blocked nose					
OC yes	Mean	0.17	2.58	0.33	2.27
	SD	0.39	1.00	0.49	0.65
	Median	0.00	2.00	0.00	2.00
OC no	Mean	0.45	2.91	0.09	3.00
	SD	0.69	0.83	0.30	0.77
	Median	0.00	3.00	0.00	3.00
Nasal flow sum					
OC yes	Mean	786	514	765	460
	SD	228	262	237	205
	Median	792	534	844	472
OC no	Mean	798	485	846	453
	SD	159	219	196	199
	Median	760	569	864	533

The hormonal parameters were within the physiologic range in the regularly menstruating women; i.e., a mean value of 17- β -estradiol of 92.9 pg/ml in the midcycle and 45.3 pg/ml at the end cycle, LH 6 and 2.8 mU/ml, FSH 6.8 and 4.1 mU/ml, testosterone (T) 0.3 and 0.23 ng/ml, androstendione 2.34 and 1.66 ng/ml, prolactin 13.4 and 15.5 ng/ml, DHEA 1.74 and 1.82 μ g/ml, and progesterone 2.03 ng/ml. In the control group, hormonal parameters were according to OC use; i.e., a mean value of 17- β -

estradiol of 18.11 pg/ml in the midcycle and 12 pg/ml at the end cycle, LH 0.8 and 0.1 mU/ml, FSH 1.8 and 0.4 mU/ml, testosterone (T) 0.14 and 0.11 ng/ml, androstendione 1.07 and 1.11 ng/ml, prolactin 14 and 12.9 ng/ml, DHEA 1.49 and 1.33 μ g/ml, and progesterone 0.23 ng/ml. The whole sample were able to complete challenges 1 and 2.

The descriptive statistical parameters of symptoms and nasal flow are summarized in Table 1.

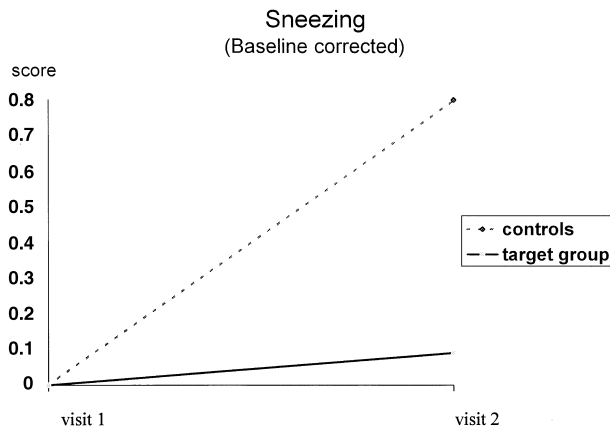


Figure 2. Score sum of neurogenic nasal symptom sneezing at visits 1 and 2, evaluated 15 min after allergen challenge on four-point scale, in patients with and without OC.

Comparisons between the groups

All comparisons of symptoms assessed in the midcycle resulted in $P > 0.2$ between the groups. In the late progesterone phase, all comparisons of symptoms assessed resulted in $P > 0.1$ between the groups with the exception of the symptom blocked nose ($P = 0.03$). This can be interpreted as lower severity of this symptom in the OC (control) group in the late progesterone phase (Fig. 1).

For additional comparisons, individual differences between midcycle assessment and the late progesterone phase were calculated. A statistical analysis of these differences resulted in $P < 0.05$ for the symptom sneezing ($P = 0.02$) (Fig. 2). This result can be interpreted as stable symptom score for the target group, and an increase in symptom severity for the control group. For all other differences, $P > 0.1$ was found.

Comparison within the groups

Additionally, the symptoms assessed in the midcycle and the symptoms assessed in the late progesterone phase were analyzed within each group.

In the target group, the symptom sneezing remained stable with a mean score of 3.27 in the midcycle and a mean score of 3.55 in the late progesterone phase ($P = 0.589$). The symptom itching increased from 2.36 to 2.91 on average ($P = 0.238$). The rhinorrhea on average increased from 2.45 at visit 1 to a value of 3 at visit 2 in the target group ($P = 0.258$). Nasal blockage remained stable with a mean of 2.91 in the midcycle and a mean of 3 at the end of the cycle ($P = 0.676$). On average, nasal flow was reduced by 331 ml/s at visit 1, and by 393 ml/s on average at visit 2 ($P = 0.278$).

In the control group, the symptom sneezing increased significantly from 2.73 on average in the midcycle to 3.55 on average in the late progesterone phase ($P = 0.005$). The symptom itching rose from 2.36 to 2.91 ($P = 0.238$). The vascular symptom rhinorrhea increased slightly from 2.64 at visit 1 to 2.91 at visit 2 ($P = 0.391$). Nasal blockage dropped from 2.45 in the midcycle to 2.27 at the end of the cycle ($P = 0.64$). Nasal flow was reduced by 255 ml/s at visit 1 and by 306 ml/s at visit 2 ($P = 0.36$).

Both neurogenic symptoms itching and sneezing remained stable in the target group, while an increase was observed in the control group. The vascular symptom rhinorrhea increased in both groups. Nasal blockage increased in the target group, but decreased in the controls. The flow decrease reached a greater extent in the target group than in the controls.

Discussion

The relation between hormonal changes and allergic reactivity is well documented for asthma in pregnancy (14–17). In pregnant asthmatics, the disease improves in one-third, worsens in another third, and remains stable in the rest. However, these facts do not suggest a conclusive connection between hormonal state and allergy in general. Moreover, no clinical data are available on the influence of physiologic hormonal fluctuation on nasal reactivity in healthy volunteers. A trial focused on nasal patency during the menstrual cycle in healthy women could not find evidence of the existence of steroid hormone receptors in the nasal mucosa (18). The existence of progesterone and estrogen-sensitive receptors in the mucosal tissue of the nose is indeed proven (7, 19), but it is unknown whether there is a hormonal modification of the nasal reactivity of individuals suffering from allergic rhinitis.

The results of our investigation show a clear correlation of hormonal fluctuation and nasal allergic reactivity in women: in our target group, the progesterone peak led to an increase of the vascular nasal symptoms, neurogenic symptoms remaining stable. In the controls, the neurogenic symptoms intensified toward the end of pill intake, possibly because a protective effect of the endogenously produced progesterone, in contrast to the orally administered hormones in nonvascular reaction mechanisms. The vascularly mediated allergic reaction showed a distinct behavior in the controls: the course of the symptom rhinorrhea was enlarged in the late progesterone phase, as in the target group, but nasal blockage was reduced compared to the midcycle

reaction and took an adverse course compared to the target group. This finding is in contrast to the results of the objective parameter nasal flow, which showed an increasing flow reduction at the end of the cycle in both groups. The cause of this phenomenon might be found in the estimation by the patients: the nasal patency could hardly be judged by patients due to their individual nasal cycle and the daily varying state of mucosal swelling; i.e., an identical extent of nasal blockage may be judged completely differently on two different days. The overall increase of the vascularly mediated nasal symptoms suggests that orally administered gestagens reach sufficient concentrations in the nose to mediate the vascularly mediated allergic reactions. For influencing the neurogenic nasal symptoms, higher hormone concentrations are apparently necessary than those achieved after administration of OC.

Collection of nasal secretions to quantify inflammatory mediators would seem to provide interesting objective data, but this was omitted, since Wang et al. (20) could not find any correlation between mediator release and nasal symptoms in the early phase of allergic reaction.

Konno et al. (10) reported that nasal swelling can be induced by application of progesterone, leading to receptor modulation, a finding which is in accordance with our results. Piccinni et al. (3) demonstrated that progesterone favors the development of T-helper cells producing Th2-type cytokines which are responsible for the IgE-mediated

immediate allergic reaction. In contrast, Holdstock et al. (21) found that in the presence of progesterone T-suppressor cells are increased, and Mittmann et al. (22) showed that IgE-mediated histamine release from basophils is suppressed by progesterone. The results of our investigation agree with the findings of Piccinni et al. suggesting an increased Th2-mediated reaction due to the influence of progesterone, but only in view of the vascularly mediated allergic reactions.

It remains unclear whether the mediation of vascular and neurogenic regulation mechanisms in the nasal mucosal tissue is the result of a direct effect of estrogen and progesterone on the nasal mucosa via the nasal steroid hormone receptors or a negative feedback mechanism to the hypophysis. For example, Krötsch & Riederer (19) could localize progesterone receptors in the nuclei of cells in the subepithelial region and connective tissue of seromucous glands, and further estrogen receptors in the cytoplasm of cells of the serous glands, and sometimes nerve bundles. They concluded that symptoms may be influenced by a change in the concentration of transmitters and receptors.

It also remains unclear whether the effect is caused by the hormones themselves or by an altered balance of estrogen and progesterone or related steroid hormone levels. Our results are encouraging for further studies on the menstrual cycle-dependent allergic constitution of women.

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