

Does hormone therapy increase allergic reactions and upper gastrointestinal problems?

Results from a population-based study of Swedish woman.

The women's health in the Lund area (WHILA) study

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Abstract

Objectives: To delineate the use of various drugs particularly pertaining to allergy and upper gastrointestinal problems in relation to hormone status in middle aged women. **Methods:** An analysis from a population-based study on women born between 1935 and 1945 and lived in the Lund area southern Sweden. Of 10766 women, 6917 provided complete data sets; in turn 5673 were assessed for the use of medication in this study. Among the cohort, 9% of women were premenopausal (PM), 54% were postmenopausal without hormone replacement therapy (PM0) and 37% were current hormone replacement therapy users (PMT). **Results:** There were 7 (1.3%) women in PM, 11 (0.4%) in PM0 and 21 (1.0%) in PMT group who used loratadine regularly. There was a significant difference between the PM and PM0 groups and also between the PM0 and PMT groups in the use of loratadine ($P < 0.05$). Among 21 loratadine users in PMT group 4 (19%) used transdermal patches and 17 (81%) used oral HRT. The result for omeprazole use was as follows: 4 (0.8%) of PM group, 39 (1.3%) of PM0 group and 42 (2.0%) of PMT group. The use of omeprazole was significantly higher in the PMT group than in the PM ($P = 0.05$) and PM0 group ($P < 0.05$). There was no relation between the use of omeprazole and smoking or alcohol consumption. **Conclusions:** Use of hormone replacement therapy seems to be related to a higher frequency of omeprazole and loratadine use, which implies that hormone replacement therapy, may be associated with more upper gastrointestinal symptoms as well as allergy.

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1. Introduction

Middle-age women experience a number of symptoms during the climacteric period. Many of these

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symptoms are related to the hormonal milieu others are not [1,2].

There are case reports on allergic reactions by hormone replacement therapy (HRT). The Women's Health Initiative Observational Study [3] showed that HRT increased C-reactive protein (CRP) levels among healthy postmenopausal women. The perceived inflammatory response seems to increase problems when HRT is used in healthy postmenopausal women. In a prospective study, Decensi et al. [4], comparing transdermal estradiol and oral conjugated estrogen effects on C-reactive protein in healthy women, concluded that, in contrast to oral conjugated equine estrogens, transdermal estradiol did not elevate C-reactive protein levels for up to 12 month of treatment. Corazza et al. [5] reported a case in which they found an allergic contact dermatitis probably caused by transdermal estradiol and the patient experienced a systemic pruritic rash when she was switched to an oral estrogen and it is mentioned that estrogen must be prescribed cautiously to avoid a systemic reaction. Siepmann and Kirch [6] reported a case in which a 51-year-old female complained about a marked pruritus of her whole integument while she was using an oral combination therapy (estrogen and gestagen) for climacteric symptoms for seven years. When stopping hormonal therapy, a complete cessation of pruritus occurred. The authors concluded that this combination therapy could have side effects such as pruritus and jaundice.

Autoimmune progesterone dermatitis is also a rare clinical condition associated with variable cutaneous and mucosal eruptions such as urticaria, erythema multiforme, and eczema. This condition improves with the use of an antiestrogen drug: Tamoxifen. This medication suppresses ovulation and the postovulation rise in endogenous progesterone levels [7].

Furthermore, hormone replacement therapy can have an unfavorable effect on the incidence of asthma during peri- and postmenopausal period [8].

There is likewise very limited information on gastrointestinal (GI) problems and menopause in the literature. Eliakim et al. [9], in their review mentioned that estrogen and progesterone have, both beneficial and detrimental effects on the esophagus and stomach. Fisher et al. [10] suggested that the female sex hormones can alter the lower oesophageal sphincter function and potentially may be of importance for

the pathogenesis of heartburn of pregnancy but they did not discuss it as a possibility for perimenopausal woman using hormone replacement therapy. Richter in a study on gastroesophageal reflux during pregnancy showed that approximately two-thirds of pregnant patients develop heartburn. The origin is multifactorial, but the predominant factor is a decrease in LES pressure caused by female sex hormones, especially progesterone. Mechanical factors play a small role.

Hormone replacement therapy may have side effects and those concerning the gastrointestinal system are mentioned as nausea, flatulence, heartburn and abdominal pains. HRT may also have adverse effect on skin such as allergic contact dermatitis, reversible postinflammatory pigmentations, erythema, rash and acne [11].

Every drug has some positive effects and also negative or side effect at the time or maybe later on the patient who uses it. The side effect of a drug may only affect one of the body systems or may involve two or more systems at the same time.

Given the scarce information on allergy and upper gastrointestinal problems in relation to the hormonal situation in middle-aged women it could be of general interest to delineate the prevalence of these complaints in a population-based cohort and to evaluate the potential influence by female hormones.

2. Material and methods

This is an analysis from the project Women's Health in the Lund Area (WHILA) [2,12,13].

The Lund area is located in southern Sweden and composed of a university town with approximately 100,000 inhabitants, and its surrounding rural areas, mainly farmland with a population of approximately 50,000 inhabitants. The WHILA project covered all women ($n = 10870$) who were born between 2 December 1935 and 1 December 1945, and living in the Lund area by 1 December 1995. The primary objectives of this project were to survey pre-, peri- and postmenopausal women in this area and to evaluate their health status, lifestyle, as well as social and medical risk factors for future disease.

The study was approved by the Local Ethics Committee of Lund University, Sweden and by the data registry inspection in Stockholm.

In 1996, all women in the WHILA study were offered a health assessment program that included a mailed generic self-administered questionnaire tied to laboratory examinations performed at a screening center. All women who had findings indicative of disease received medical attention.

The generic questionnaire contained 104 questions. Most of the questions had been used and validated previously [2,12,13]. After the subjects filled out the questionnaire, a personal interview was carried out by a specially trained nurse-midwife to endorse and correct questionnaire replies. This resulted in one or more corrections in 19% of the questionnaire due to sheer mistakes rather than to misunderstanding of the text.

2.1. Composition of the generic questionnaire

There were four sections of questions in this questionnaire based on:

- I. general background,
- II. climacteric problems,
- III. somatic symptoms, and
- IV. psychological symptoms.

One of the questions in the general background section was about drug use other than for hormone replacement therapy and if the answer was yes women should write the name of that drug. The names of the drugs used by the participants were grouped according to Anatomical Chemical Classification system (ATC-Code). They were then categorized by their corresponding code classification. The groups used for this study were (R06A) and (A02B).

There were also 19 questions for somatic symptoms and 10 for psychosomatic symptoms and if present for the preceding 3 months they should answer it by “Yes”.

2.2. Participants and groups

2.2.1. Participants

Six thousand nine hundred and seventeen women completed the questionnaire yielding a response rate of 65%. Those who responded were invited to undergo a physical and laboratory examination. Moving out from the community, foreign nationality, refusal and death were the main reasons for non-response to the

questionnaire. Ignorance of the name of medication use disqualified another 1244 women yielding 5673 subject eligible for this analyze.

2.2.2. Group

The participants were divided into three groups according to their menopause status and HRT use and were named as: premenopausal (PM) which were those who had still menstruations; postmenopausal (PM0) which were those with no menstruations in more than 12 month and peri- or postmenopausal women with current HRT use (PMT) were those who used systemic hormone therapy.

2.2.3. Statistical approach

The baseline characteristics and the prevalence of symptoms between the groups were compared by chi-square test and Student's *t*-test.

A *P*-value ≤ 0.05 was considered as statistically significant. Statistical analyses were carried out by a computer software program (SPSS version 11.0).

3. Results

Of the 5673 women, 9% were premenopausal (PM), 54% were postmenopausal without hormone replacement therapy (PM0) and 37% were current hormone replacement therapy users (PMT).

3.1. Anti allergic drug use during climacteric period

We found differences for the use of loratadine (Claritin®) and cetirizine (Zyrlex®) between the three groups. These two drugs were the most commonly used among the antihistaminic drugs in this population (Table 1).

There were 7 (1.3%) women in PM, 11 (0.4%) in PM0 and 21 (1.0%) in PMT group who used loratadine regularly. There was a significant difference between the PM (1.3%) and PM0 (0.4%) groups and also between the PM0 (0.4%) and PMT (1.0%) groups in using loratadine ($P < 0.05$), but between PM and PMT groups (1.3% versus 1.0%) no significant difference was found.

For cetirizine the use was 5 (1.0%), 11 (0.4%) and 18 (0.9%) for PM, PM0 and PMT, respectively; in

Table 1

Relationships for the use of loratadine, cetirizine, omeprazole and ranitidine among the three groups

Drug use (%)	PM	P-value	PM0	P-value	PMT	P-value
Loratadine	1.3	0.003	0.4	0.004	1.0	NS
Cetirizine	1.0	0.05	0.4	0.02	0.9	NS
Omeprazole	0.8	NS	1.3	0.04	2.0	0.05
Ranitidine	0.8	NS	0.4	NS	0.5	NS

Notes: PM: premenopausal; PM0: postmenopausal without therapy; PMT: pre- or postmenopausal with hormone replacement therapy; and NS: no significant difference.

which a significant difference persisted between the PM0 and PMT group ($P < 0.05$).

Among 21 loratadin users in the PMT group 4 (19%) used combined transdermal patches and 17 (81%) used oral HRT.

3.2. Drug used for GI problems during climacteric period

The most common drugs for upper GI problems were omeprazole (Losec®) and ranitidine (Artonil®). The results for omeprazole use were as follows: 4 (0.8%) of PM, 39 (1.3%) of PM0 and 42 (2.0%) of PMT groups. The use of omeprazole was significantly higher in the PMT group than in the PM ($P = 0.05$) and PM0 groups ($P < 0.05$). Omeprazole was used more in PM0 group than in PM group (1.3% versus 0.8%) but the difference was not significant.

The use of ranitidine in PM group was more than PM0 and PMT group (0.8% versus 0.4% and 0.5%) but no statistically difference was found (Table 1).

Acetylsalicylic acid (ASA) was the most prevalent non steroidal anti-inflammatory drug (NSAID) among all the women who participated in this study (29 of 6917 (0.4%)). In PM0 group, there were 14 of 3043 (0.5%) and in PMT group 9 of 2087 (0.4%) women who used ASA without any significant difference, of them there were only 2 (1.8%) women who used ASA at the same time with omeprazole among all omeprazole users.

There was a strong relationship between stomach ache and the use of omeprazole ($P < 0.001$). There were also statistical associations between psychosomatic symptoms such as irritability, nervousness, bad appetite and to be over stressed and omeprazole use in the PMT group. ($P \leq 0.05$) (Table 2).

Table 2

Relationship between the use of omeprazole and somatic and psychosomatic symptoms in the three groups

Symptoms	Groups		
	PM	PM0	PMT
Irritability	a	a	**
Stomach ache	a	**	**
Nervousness	*	a	*
Bad appetite	a	a	*
Over stressed	a	**	*
Crying spells	a	*	a

Notes: PM: premenopausal; PM0: postmenopausal without therapy; and PMT: postmenopausal with hormone replacement therapy.

^a $P > 0.05$.

* $P \leq 0.05$.

** $P \leq 0.001$.

Ranitidine (a H2-blocker) consumption was 0.8, 0.4 and 0.5% for PM, PM0 and PMT groups, respectively. The use of ranitidine was less common in the PM0 group but the difference did not reach a statistical significance.

In the PMT group, there was no relation between the use of omeprazole and smoking or alcohol consumption neither in the PM and PM0 groups.

3.3. Somatic and psychosomatic problems during climacteric period

Comparisons were made between the three groups also for somatic and psychosomatic symptoms. It was found that women in the PMT group had more concentration problems and more cry spells than women in the PM and PM0 groups (Table 3).

General tiredness was somewhat more prevalent in PMT women (83.3%) than in PM (75%) and PM0 (76.9%) but not statistically significant. For other symptoms like sleeping disorders (PM (75%), PM0 (64.1%) and PMT (64.3%)), nervousness (PM (50%), PM0 (38.5%) and PMT (31.0%)), coughing (PM (25%), PM0 (28.2%) and PMT (23.8%)), feeling stressed (PM (50%), PM0 (59%) and PMT (59.5%)), restlessness (PM (25%), PM0 (30.8%) and PMT (42.9%)), relaxing problems (PM (75%), PM0 (56.4%) and PMT (71.4%)) and stomach ache (PM (50%), PM0 (61.5%) and PMT (71.4%)) the prevalence were similar without any significant difference between groups.

Table 3

Frequency of somatic and psychosomatic symptoms according to omeprazole use in the three groups

Symptoms (%)	Groups		
	PM (n = 4)	PM0 (n = 39)	PMT (n = 42)
General tiredness	75	76.9	83.3
Sleeping problems	75	64.1	64.3
Nervous problems	50	38.5	31.0
Coughing	25	28.2	23.8
Easily irritated	25	48.7	64.3
Stressed	50	59.0	59.5
Concentration problems*	50	28.2	54.8
Restlessness	25	30.8	42.9
Crying spells**	0	43.6	61.9
Relaxing problem	75	56.4	71.4
Stomach ache	50	61.5	71.4

Notes: PM: premenopausal; PM0: postmenopausal without therapy; and PMT: postmenopausal with hormone replacement therapy.

* Significant difference between PM0 and PMT groups, $P \leq 0.05$.

** Significant difference between PM and PMT groups, $P \leq 0.05$.

The prevalence of irritability in the PMT (64.3%) group was higher than PM (25%) and PM0 (48.7%) groups but not statistically significant. Concentration difficulties were more prevalent in the PMT (54.8%) than PM0 (28.2%) group, which was statistically significant. ($P \leq 0.05$) Crying spells were also more prevalent in the PMT (61.9%) than the PM (0%) group ($P \leq 0.05$).

4. Discussion

We searched the Pub Med data base but found very limited information in the literature about menopause and allergic reactions or upper GI problems. There was also limited information about the prevalence of using anti-allergic and drugs for upper gastrointestinal problems during perimenopausal period.

4.1. Hormone therapy and anti-allergic medication

Among the risks that have been associated with estrogen replacement therapy endometrial disease, breast cancer and side effects such as vaginal bleeding,

somatic complains, idiosyncratic reactions, including hypertension and thrombosis are of great concern.

Idiosyncratic reactions including hypertension, thrombosis, and allergic manifestations have also been observed in estrogen users, particularly oral estrogen [14].

Loratadine is an antihistaminic H1-antagonist drug that is commonly used for allergic rhinitis, pruritus and urticaria.

Siepmann and Kirch [6] and Corazza et al. [5] stressed that there are women who are sensitive to female sex hormones so when physicians prescribe hormone replacement therapy, they should alert their patients for allergic side effects.

In a study on exogenous estrogen as an alternative to food allergy in the etiology of angioneurotic oedema, Andre et al. [15] mentioned that exogenous estrogens, such as those contained in most oral contraceptives, might play an iatrogenic role in the etiology of chronic angioneurotic oedema or urticaria.

Some case reports was found in the literature about autoimmune progesterone dermatitis (APD): Bolaji and O'Dwyer [16] presented two cases of autoimmune progesterone dermatitis in that the patients developed a recurrent eruption, primarily on the extremities after receiving oral oestrogen/progesterone replacement for the treatment of climacteric symptoms. The diagnosis was confirmed in one of the cases that had intradermal progesterone injection producing an early positive reaction. One case required transient prednisolone therapy and both eventually resolved completely.

Kumar and Georgouras [17] mentioned that sensitivity to estrogen and progesterone is rare in women and the clinical presentation may be similar. Positive intradermal testing is diagnostic.

It was found that high-level estradiol may facilitate the development of nasal hypersensitive reaction, and drop of the estrogen level resulted from ovariectomies may postpone it with improvement of the nasal symptoms. It is suggested that the estrogen plays an important role in the pathogenesis of nasal hypersensitive reactions [18].

The results from a study by Stubner et al. [19] indicates a correlation of the hormonal situation and the nasal allergic reactivity. Oral contraceptive intake led to an intensifying of neurogenic symptoms near the end of pill intake, a result that could be due to a

Table 4
Direct and indirect costs using these drugs for 1-year duration

Drugs costs (US\$)	Loratadine	Omeperazole	Cetirizine	Ranitidine
Direct	150	300	150	240
Drug				
Physicians visit	200	400	200	400
Indirect				
Loss of production	100	200	100	200
Sum	450	900	450	840

The costs in this table were accounted as minimum for a year for each patient.

protective effect of the endogenous progesterone, in contrast to the orally administered hormones.

Lange et al. [20] in their study about HRT and asthma or asthma-like symptoms concluded that an association had been observed between HRT and asthma and asthma-like symptoms; this had been relatively weak but there is no necessity to change present prescription practice.

The reason for using loratadine in this study was allergic symptoms like urticaria and pruritus. There is a 2.5-fold higher use of antihistaminic drugs in the postmenopausal women with hormone replacement therapy so it would be about 60 more women per 10,000 who need to take this drug and it must be taken everyday and the daily minimum dose for this drug is 10 mg.

A 30-tablet pack costs about US\$ 12, 1-year costs will be about US\$ 150 and the costs are the same for cetirizine. Personal costs like discomfort and allergic symptoms are the more important part of the bulk of costs for most patients (Table 4).

As an example for each 10,000 postmenopausal women an additional annual cost of US\$ 27,000 is incurred.

4.2. Hormone therapy and upper gastrointestinal problems

Antacids or sucralfate are considered the first-line medical therapy for upper gastrointestinal problems. If symptoms persist, histamine (H₂) receptors antagonists should be used. Histamine (H₂) receptor antagonists (e.g., ranitidine, cimetidine, famotidine, and nizatidine) act on gastric parietal cells to inhibit basal and stimulated gastric-acid production for 6–24 h. Ranitidine is probably preferred because of its documented efficacy and safety profile. Proton-pump

inhibitors like omeprazole and lansoprazole are reserved for the woman with severe symptoms or complicated reflux disease [21]. Omeprazole is a proton pump inhibitor drug that has an anti acidic effect and is mostly used for peptic ulcers and esophagitis due to gastroesophageal reflux disorder. Severe gastroesophageal reflux disorder rarely responds to antacid alone. Often patients with refractory symptoms or complications such as esophageal ulcers or strictures requires stronger therapeutic agents that act as inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole) provide more potent and prolonged acid suppression than H₂ receptor antagonists [22].

Progesterone, at physiological concentrations, does not predispose to gastroesophageal reflux in healthy menstruating women. The fluctuations in progesterone levels across the normal menstrual cycle have no significant impact on lower oesophageal sphincter pressure and 24-h ambulatory pH parameters [23].

Female sex hormones can alter the function of the lower oesophageal sphincter from which heartburn can follow [9].

Various lifestyle events such as diet and stress can also provoke symptoms from the upper GI tract too [24].

Allergic reactions to progestins and estrogens could be one explanation for these undesired effects. Also all women were given a standard dose, which in certain women may be too high or too low to influence pharmacokinetically and/or pharmacodynamically different.

In this study, the PM and PMT groups used significantly more omeprazole than PM0 group. This difference may be due to the sex hormones still present in the PM group or replaced in the PMT group or to women's psychosomatic conditions and lifestyle or other rare reasons.

4.3. Hormone therapy and somatic and psychosomatic problems

As shown in Table 3 middle-aged women experience many somatic as well as psychosomatic problems at this age and almost all problems are more frequent in the PMT group than in the PMO group. This might be due to the aging or possibly due to the hormonal changes during this period of life. So, whatever the reason might be, these symptoms are common and further studies are needed to delineate perceived relationships between these complains.

5. Conclusion

Use of hormone replacement therapy seems to be related to a high frequency of omeprazole and loratadine use, which implies that hormone replacement therapy, may provoke upper gastrointestinal symptoms as well as allergy.

Allergic and upper gastrointestinal problems are common symptoms among women; not only the postmenopausal women but also in the premenopausal subjects (Table 1).

Hormone replacement therapy does not seem to be the only reason for these complains.

Further studies and investigations are warranted.

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