The Effects of Estrogen Replacement Therapy on Airway Function in Postmenopausal, Asthmatic Women

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Background: Data from multiple clinical, epidemiologic, and in vitro studies are conflicting regarding the effect of estrogen replacement therapy (ERT) on airway function in postmenopausal women with asthma.

Objective: To determine the impact of withdrawal of estrogen administration in postmenopausal, asthmatic women.

Methods: Twenty asthmatic women who were postmenopausal for at least 2 years and undergoing ERT were recruited for this prospective crossover study. Subjects continued taking baseline estrogen for 28 days, stopped taking estrogen for 28 days, and then resumed taking the medication for 14 days. Objective measurements were obtained by recording daily peak flows in the morning and evening and formal spirometry at days 14, 28, 42, 56, and 70. Compliance was measured by evaluating serum estradiol levels at days 28 and 56. Daily use of short-acting β-agonist bronchodilators was also recorded.

Results: Differences in estradiol levels indicated compliance with the medication regimen. The combined day 14 and 28 (taking estrogen) mean percent predicted forced expiratory volume in 1 second (FEV1) was 77% compared with the combined day 42 and 56 (not taking estrogen) mean FEV1 of 78% and the day 70 (taking estrogen again) FEV1 of 76% (P > .05). Average peak flow measurements were 295.5 L/min for the duration of ERT, 293.9 L/min while not undergoing ERT, and 291.8 L/min when ERT was restarted for the final 2 weeks of the study (P > .05). Use of short-acting β-agonist bronchodilators did not differ between study periods.

Conclusion: These data indicate that neither the discontinuation nor reinitiation of ERT in postmenopausal, asthmatic women has any effect on objective measures of airway obstruction.

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The relationship between sex hormones and asthma is complex. Women are more commonly admitted to the hospital for asthma compared with men of similar age. A particular subset of asthmatic women experience premenstrual asthma, with symptoms of wheezing and dyspnea that worsen corresponding to different phases of the menstrual cycle. Some studies suggest that emergency department visits for asthma exacerbations may be more common during the premenstrual phase, whereas other studies indicate that the preovulatory phase (days 5-11) is the most common time of presentation.

The relationship between exogenously administered estrogen (as in oral contraceptives or postmenopausal replacement therapy) and asthma is also inadequately characterized. In a large cohort study, Troisi et al demonstrated an increased incidence of adult-onset asthma among postmenopausal women undergoing hormone replacement therapy compared with women who did not receive hormone supplementation. A prospective study of 15 postmenopausal women noted subclinical deterioration of peak expiratory flow rates (PEFRs) after estrogen replacement therapy (ERT) was initiated, but no change in symptoms was noted. Variant observations include a case series of 3 patients, 2 of whom were postmenopausal, whose asthma improved with hormone replacement therapy. These patients were steroid dependent before initiating ERT and were able to be weaned from steroids after beginning hormone therapy.

To provide more objective data on the relationship of ERT and asthma, we designed a prospective crossover study to measure pulmonary function test (PFT) results and daily PEFRs in postmenopausal, asthmatic women taking and not taking estrogen.
Subjects and Methods

Subjects were recruited from the Internal Medicine, Allergy, and Pulmonary Clinics at Brooke Army Medical Center, Fort Sam Houston, Tex, from October 1997 to June 2000. Each subject had a history of reversible airway obstruction by symptoms and met American Thoracic Society guidelines for the diagnosis of asthma, with symptoms compatible with asthma and a documented abnormality by PFTs. These guidelines included either a decreased forced expiratory volume at 1 second (FEV₁) with an FEV₁/forced vital capacity (FVC) increase greater than 12% after a bronchodilator challenge or a history of a positive methacholine challenge. In addition, women had to be postmenopausal for more than 2 years and undergoing estrogen hormone replacement therapy (0.625 or 1.25 mg/d) for at least 6 months. Exclusion criteria included any of the following: active tobacco smoking within the last 5 years, documented chronic obstructive or other concomitant pulmonary disease, clinical evidence of severe asthma (more than 3 hospital admissions in the previous year, any history of intubations for asthma), oral steroid use in the previous 3 months, age older than 70 years, or a history of documented coronary artery disease. Before enrollment, each subject had a detailed discussion with the principal investigator and signed a written informed consent document. The Institutional Review Board at Brooke Army Medical Center reviewed and approved the investigational protocol and the informed consent document.

A sequential crossover design was used, as depicted in Figure 1. The independent variable was the administration of ERT, and PFTs, PEFRs, and the daily use of short-acting β-agonist inhalers were the 3 dependent variables measured in this study. The duration of the study was 70 days per subject. Subjects continued long-term ERT for a 28-day run-in period, stopped undergoing ERT for 28 days (study days 29-56), and resumed ERT for the final 14-day period (study days 57-70). The subjects underwent 2 baseline PFTs while undergoing ERT (at days 14 and 28 of the study) followed by PFTs while not undergoing ERT (days 42 and 56). A final PFT was performed on day 70, after the subject had resumed ERT for 2 weeks. The PEFR was measured for each subject twice daily for all 70 days to accommodate any potential diurnal variation.

Subjects underwent PFTs with a spirometer (Vmax 22 series; Sensormedics, Yorba Linda, Calif) using standard techniques. Three maneuvers were performed, and the highest value was recorded. Predicted values for spirometry were those of Crapo et al. A peak flow meter (Truzone; Monaghan Medical Corp, Plattsburgh, NY) was provided to each subject to record PEFR in the morning on first awakening and in the evening (5 to 8 PM). Three maneuvers were performed, and all 3 results were recorded in a diary at each time point; the maximum value was used for later analysis. Subjects received a detailed explanation on the correct use of these peak flow meters and were instructed not to perform peak flow measurements directly after using their inhalers. The use of short-acting β-agonist inhalers was recorded in a diary. Study participants recorded each episode of β-agonist inhaler use, rather than individual puffs (ie, if a subject used 2 puffs of her inhaler at 8 AM one morning, she would record the use of inhalers as 1). Serum estradiol levels were measured on day 28 of ERT and on day 56 after discontinuation of ERT for 1 month.

Five study subjects were taking progesterone in combination with ERT. To eliminate progesterone as a possible confounding factor, the use of progesterone was stopped on day 0 of the study in these subjects. These participants resumed progesterone after day 70; no subject had substantial vaginal bleeding when use of the progesterone was restarted. Subjects were instructed to continue their previously prescribed maintenance medications for asthma and any other chronic condition.

Statistical comparisons of results were made using a multiple measures analysis of variance (SPSS standard version; SPSS Inc, Chicago, Ill). Comparisons were made of the FEV₁, PEFR, and the use of inhalers from 3 time periods: the initial 28 days taking estrogen, the 28 days not taking estrogen, and the final 14 days taking estrogen. Power analysis predicted that the sample size of 20 would be sufficient to provide significance at the .05 level with 80% to 85% power, assuming a change in FEV₁ of 15% would be clinically significant.

Results

Twenty-three women were initially recruited for the study. Twenty subjects completed the investigation. One subject had a clinical diagnosis of asthma, but on further review of available records did not meet strict American Thoracic Society criteria for this diagnosis, and her participation was terminated. One subject was excluded because of elevated serum estradiol levels while not taking estrogen for 28 days. Another subject was excluded for persistently low levels of estradiol while taking estrogen. Complete data from 20 patients were analyzed. The Table contains the demographic characteristics of our patient population. Most of our patients (15/20) had undergone hysterectomy and were not taking progesterone at study entry. The average serum estradiol level at day 28 (with baseline estrogen dose) was 91 pg/mL (range, 31-321 pg/mL) (334 pmol/L [114-1178 pmol/L]), which indicated adequate oral intake of estrogen during the study period. Serum estradiol levels on day 36 were substantially lower. Sixteen of 20 women had levels less than 20 pg/mL (73 pmol/L), the lower limit of the serum estradiol measurement in our laboratory. Two subjects had estradiol levels slightly higher than 20 pg/mL (29 and 30 pg/mL) (73 pmol/L [106 and 110 pmol/L]), but their estradiol levels while undergoing ERT were above 100 pg/mL (105 and 103 pg/mL) (367 pmol/L [385 and 378

Figure 1. Study design. Time line depicting 70-day course of estrogen administration, withdrawal, and readministration, with concurrent measurements. The numbers in the PFT (pulmonary function test) row indicate the timing of the first through the fifth set of PFTs. The numbers in the serum estradiol row indicate the timing of the first and second levels.
pmol/L). One patient missed her serum estradiol measurement while not taking estrogen, but reported hot flashes and emotional lability during the 28 days without estrogen. A final patient had an 8-point decline in serum estradiol levels from 43 pg/mL (158 pmol/L) while undergoing ERT to 35 pg/mL (128 pmol/L) while not undergoing ERT, but she had mild estrogen withdrawal symptoms. Mild estrogen withdrawal symptoms during the month not undergoing ERT were perceived by 7 of 20 subjects, but no subject felt the need to be terminated from the study when this option was offered.

**EFFECT OF ESTROGEN MANEUVERS ON SPIROMETRY RESULTS**

The mean ± SD percent predicted FEV$_1$, depicted in **Figure 2**, for each time point was as follows: day 14, 78.6% ± 22.5%; day 28, 75.6% ± 19.8%; day 42, 76.2% ± 16.1%; day 56, 78.3% ± 15.0%; and day 70, 76.3% ± 14.4%. Data from days 14 and 28 (taking estrogen) were combined for statistical analysis, as were the data from days 42 and 56 (not taking estrogen). No differences were found when these data were compared with each other or with the day 70 data (P > .05). No individual subject demonstrated significant changes in FEV$_1$ throughout the study period as well.

**EFFECT OF ESTROGEN MANEUVERS ON USE OF BRONCHODILATORS**

Two subjects were unable to adequately document inhaler use in their diaries. Eighteen of 20 subjects in the study recorded and submitted adequate diaries. The mean (SD) daily use of inhalers was 1.5 (1.4) (range, 0-5) from days 1 to 28, 1.1 (1.1) (range, 0-4) from days 29 to 56, and 1.1 (1.1) (range, 0-4) from days 57 to 70 (taking estrogen) (P > .05).

**COMMENT**

These prospective data indicate that in a population of postmenopausal, asthmatic women undergoing ERT, discontinuation and reinstitution of ERT did not affect objective measurements of asthma. Our study presents alternative data to previously published basic science data, epidemiologic analyses, case series, and one prospective study that suggest that asthma may worsen when patients are exposed to estrogen.

Data from in vitro studies suggest that estrogen may be instrumental in both the potentiation and relief of bronchial smooth muscle contraction; this effect, however, may be modulated by progesterone. Observational studies also conflict regarding the effect of the estrogen milieu on asthma, whether controlled or not controlled for progesterone effect. When ERT was prescribed to postmenopausal women who did not have asthma, no differences in FEV$_1$ measurements could be detected.

Data from the Nurses Health Study, a large observational epidemiologic analysis, suggest a slight increase in the relative risk (RR) of asthma among postmenopausal women who ever underwent ERT (RR, 1.49; 95% confidence interval [CI], 1.1-2.0) or were currently undergoing ERT (RR, 1.50; 95% CI, 0.98-2.30). This study used the self-reported physician diagnosis of asthma as its main outcome measure, although it presented no objective documentation of asthma by the participants. In addition to selection...
crease of 14.3 L/min was imperceptible to the subjects, and 15 perimenopausal women when first starting ERT. The decrease starting ERT vs 226.7 L/min after starting ERT) among the women. Instead of oral estrogen replacement, their study used estrogen transdermal patches, which is prescribed for a few patients in the United States. The adequacy of the estrogen intervention could be questioned in this study, because there was no objective evidence that study subjects had ceased to produce endogenous estrogen and no mechanism to monitor absorption of estrogen from the patches except for the improvement of perimenopausal symptoms.

Our study demonstrated no differences in spirometry or FEV1 values when ERT was stopped in postmenopausal, asthmatic women. Our subjects included women with mild-to-severe asthma, as demonstrated by the wide variety of baseline FEV1 and PEFR values. Our data are not consistent with the observations of Lieberman et al, since they noted worsening objective PEFRs when ERT was initiated in women with preexisting asthma. Although we studied a slightly different population (women undergoing stable ERT), no worsening of objective measurements of airway obstruction was observed when our subjects began taking estrogen again (from days 57–70).

One of the limitations of our study is the possibility of selection bias by including subjects with asthma who were already undergoing ERT. Any women who might have a problematic reaction to estrogen (either asthma or other complications) might have discontinued ERT, and these women would be excluded from this study. However, if estrogen had an overall effect on bronchial reactivity, we would have expected to observe at least subtle changes in airflow measurements during this study. It is possible that worsening of asthma with estrogen is a rare effect only seen in a small number of women, and thus may be detectable in an epidemiologic study but not observed in a smaller sample population measured objectively.

The sample size and exclusion criteria of this study could limit its applicability for all asthmatic women. Women with corticosteroid-dependent asthma, women older than 70 years, and smokers were not studied, and ERT may have a different effect in these subpopulations. The role of progesterone was deliberately not investigated in our study. Seasonal variation could also affect the results of our study. To minimize the impact of seasonal variability, subjects participated throughout the year, and the double-crossover design was used to control for temporal changes in seasonal allergen exposures.

The clinician faced with an asthmatic patient undergoing long-term ERT must consider whether discontinuing hormonal therapy may be beneficial to the patient. Our data suggest that discontinuation of ERT would have neither a beneficial nor deleterious effect in these patients. These data support previous recommendations that, until data to the contrary are available, ERT should not be withheld from postmenopausal women.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Department of the Army or the US Department of Defense.

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