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Estrogen Replacement Therapy Improves Pulmonary Function in Postmenopausal Women with Genital Prolapse

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Abstract

Objective: This study examined the impact of estrogen replacement therapy with spirometry on pulmonary function in surgically castrated (salpingo-oophorectomy) postmenopausal women with genital prolapse.
Methods: The study included 60 postmenopausal women with pelvic organ prolapse. The study received institutional Ethics Committee approval, and all subjects signed an informed consent. Women were randomly divided into two groups of 30 subjects: Group 1 ($n=30$) was administered estrogen replacement with 1 mg of stradiol hemihydrate (1 mg/day) orally for 6 months, and group 2 ($n=30$) was not taking estrogen. Both groups were matched by age, height, body mass index, parity, and duration of postmenopause. All subjects were evaluated with spirometry initially and after 6 months. For statistical analysis, descriptive and analytical methods were used, based on data type and distribution. The mean and standard deviations were used as measures of central tendency and variability. Categorical data were expressed as absolute and relative numbers (percentage). The *t*-test for independent samples (for comparison of groups) and *t*-test for dependent samples (for comparison of serial measurements in the same patients) were used. The analysis was performed using R software (www.r-project.org), with the level of significance set at $p<0.05$.
Results: Analysis of spirometry parameters showed statistically significant differences between the estrogen users and the nonusers groups.
Conclusion: The most important study result was the significantly improved lung respiratory function in postmenopausal women with genital prolapse after 6 months of taking estrogen, confirming that hormone replacement therapy should be recommended to postmenopausal women. The findings of our study suggest the need for further research into the effect of estrogen on pulmonary function.

Introduction

In the postmenopausal years, all women experience physical effects of aging. The most important changes occurring in postmenopausal women are due to the weakening of ovarian function. These changes can include serious health conditions such as osteoporosis, heart disease, urogenital prolapse with urinary incontinence, and others.[1–4] Furthermore, other conditions such as lung function are associated primarily with aging but certainly are impacted by ovarian hormones. All sex steroid hormone receptors have been shown to be expressed in lung tissue.[5] The respiratory system undergoes various structural, physiological, and immune changes with age. There is an increase in airspace size with aging, resulting from the loss of supporting tissue. Loss of lung function occurs quickly in postmenopausal women, and respiratory muscle strength decreases with age.[6,7]

Spirometry is an interesting biomarker of aging and a physiological test that measures how an individual inhales or exhales volumes of air as a function of time. The primary signal measured in spirometry may be volume or flow. Spirometry performed by dozens of thousands of individuals has resulted in large databases that can be used to determine lung age.[8–10] It is known that estrogen can affect women's pulmonary functions.[11–15] One such study showed that postmenopausal women who used estrogen replacement therapy (ERT) had higher levels of forced expiratory volume in first second (FEV1) and less airway obstruction.[13] Most postmenopausal women who are treated with hormone

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replacement therapy (HRT) use a combined form of estrogen–progestin therapy, but women having undergone hysterectomy generally use estrogen-only treatment.[3,4,16–18] Several lines of evidence in young women suggest that sex steroids may play a role in modifying lung function.[19,20] Oral contraceptive users have been found to have significantly higher total lung capacities when compared with nonusers.[19,21]

There is limited knowledge about the relationship between HRT and lung function in postmenopausal women. It is well known that estrogen is traditionally used to improve the structural integrity of all tissues, so it can be assumed that the estrogen has a good effect on lung tissue. To provide more objective data on the relationship of ERT and lung function, we designed a prospective crossover study to measure lung function with spirometry in postmenopausal women taking and not taking estrogen. We hypothesized that ERT would be independently associated with better pulmonary function in postmenopausal women.

Material and Methods

Subjects

The study included 60 postmenopausal women with pelvic organ prolapse (POP), all admitted to the hospital for surgery. The study was carried out at Department of Gynecology and Obstetrics, University Hospital in Split, Croatia, between March, 2009, and November, 2010. The study protocol was approved by the University Hospital Ethics Committee, and a written informed consent to participate was obtained from each patient. Women with previous pelvic surgery or pelvic radiation therapy, pelvic inflammatory disease, pelvic or other malignancies, age older than 70 years, cardiopulmonary disease, especially chronic obstructive pulmonary disease (COPD) or asthma, corticosteroid use, hypertension, anemia, diabetes mellitus, anticoagulant therapy, neurologic disease that may be associated with bladder disorders, anticholinergic or duloxetine medication, immobility, previous HRT, and previous active tobacco smoking were excluded from the study. The study and control group women were matched by age, height, body mass index (BMI), parity, and duration of postmenopause. Previously, all women had been in postmenopause for more than 2 years and had undergone hysterectomy and bilateral salpingo-oophorectomy.

Protocol

Patient evaluation included medical history, gynecologic examination, and dynamic spirometry testing. Signs of POP were recorded on pelvic examination and described according to the International Continence Society Pelvic Organ Prolapse (POP-Q) Classification.[19,22] The study group had POP-Q prolapse stage 1 or more. BMI (kg/m^2) was calculated, and spirometry was performed in all women. Evaluation was generally performed between 9 a.m. and 11 a.m., with the respiratory laboratory personnel being unaware of the subject's status.

Testing of pulmonary function

Spirometry was done in all women prior to surgery and repeated at 6 months. The forced expiratory maneuvers were performed according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommendations.[8,9,20,23] Spirometry was performed using a computed spirometer (MASTERLAB, Jaeger, Germany). Volume calibrations were performed before each test. The participants were seated, with the nose clip in place. They were instructed to breathe spontaneously, then, without rushing, the subject would inhale her vital capacity, followed by complete, most forceful expiration through the mouthpiece. The following parameters of the flow–volume curve were considered: Forced expired vital capacity (FVC), FEV1, peak expiratory flow (PEF), forced expiratory flow at 75% of FVC (FEF75), forced expiratory flow at 50% of FVC (FEF50), and forced expiratory flow at 25% of FVC (FEF25). Real time–generated flow–volume curves were checked; if high-frequency irregularities were present, the measurement was discarded. The subjects repeated the test until three acceptable maneuvers were collected, in which the highest two values of FVC and FEV1 differed by 5% or less. Last, the data corresponding to the maneuver with highest FEV1 were taken.[8,9]

Hormone replacement therapy use

None of the subjects had previously received HRT. The participants were randomly divided into two groups of 30 subjects: ERT group ($n=30$) administered orally 1 mg estradiol hemihydrate (1 mg/day) for 6 months; and non-ERT group ($n=30$) not taking ERT.

Statistical analysis

In statistical analysis, descriptive and analytical methods were used, based on data type and distribution. The mean and standard deviations were used as measures of central tendency and variability. Categorical data were expressed as absolute and relative numbers (percentage). The *t*-test for independent samples (for comparison of groups) and *t*-test for dependent samples (for comparison of serial measurements in the same patients) were used. The analysis was performed using R software (www.r-project.org), with the level of significance set at $p<0.05$.

Results

This study included 60 postmenopausal women who had undergone surgery for uterine prolapse. All women had surgical hysterectomy and salpingo-oophorectomy (castration). Women were randomly divided into two groups of 30 subjects: Group 1 ($n=30$) administered ERT with 1 mg of estradiol hemihydrate (1 mg/day) orally for 6 months, and group 2 ($n=30$) not taking ERT. Comparison of the basic anthropometric indicators and age showed no statistically significant difference between the two groups. There was no statistically significant difference in the number of deliveries and abortions in the patients' histories or in the postmenopause duration (Table 1).

Analysis of changes in spirometry indicators between the ERT and non-ERT groups showed statistically significant differences in the former but not in the latter, with the exception that the FVC parameter was elevated, although not significantly, in the ERT group (Table 2).

Discussion

It is known that estrogen can affect women's pulmonary functions.[5,11–15,19–21] Studies investigating the relationship

Table 1. Comparison of Age and Basic Anthropometric Indicators Between ERT Users and Non-ERT Subjects

Indicator	*ERT users* (n = *30*)	*Non-ERT users* (n = *30*)	p*
Age (years); mean ± SD	57.54 ± 4.27	57.61 ± 4.98	0.775
Height (cm); mean ± SD	165.75 ± 7.21	165.67 ± 6.50	0.871
Body weight (kg); mean ± SD	73.15 ± 9.71	73.57 ± 8.45	0.525
Body mass index (kg/m^2); mean ± SD	26.74 ± 3.32	26.19 ± 3.57	0.458
Number of deliveries; median (IQR)	2.0 (1.0)	2.0 (1.0)	0.161**
Postmenopause duration (years); median (IQR)	4.2 (6.0)	4.7 (6.0)	0.492**

The *t*-test was used for independent samples, except for cases where the Mann–Whitney test was used (**).
ERT, Estrogen replacement therapy; SD, standard deviation; IQR, interquartile range.

between hormones and pulmonary function among postmenopausal women are limited.[13–15] Estrogen deficiency after the menopause accelerates adverse effects of biological aging on the lung mechanics in postmenopausal women. These effects can be studied in a female animal model with a long life span after ovariectomy (castration) and postoperative administration of ERT. Ovariectomy in adult mice resulted in the loss of alveoli, absence of estrogen receptors, and diminished alveolus formation, whereas ERT in ovariectomized mice resulted in alveolar regeneration.[24,25]

In the present study, we investigated spirometry parameters in postmenopausal women with genital prolapse. They were chosen as a representative group with damaged muscular and connective tissue. Pulmonary respiratory function depends on the integrity of connective tissue. Previously, Strinic et al. have hypothesized that connective tissue abnormalities are general. According to this hypothesis, it is likely that the lung contains a lower concentration of collagen. The authors found the pulmonary ventilation function to be weakened in women with genital prolapse.[21,26]

We hypothesized that ERT would be independently associated with better pulmonary function in castrated postmenopausal women with POP. We investigated the effect of ERT on respiratory lung function with spirometry testing. There are various views in the literature about the restorative effects of estrogen on lung function. It is known that estrogen has receptors in the lung and can have general effects on the lung respiratory function through receptors.[5,11–15,20,24,25]

Analysis of changes in spirometry indicators in the two study groups of ERT administered and non-ERT women yielded statistically significant differences in the ERT group but no changes in the non-ERT group, with the exception of the nonsignificantly increased FVC parameter in the former.

Previously, two small studies examined pulmonary function in postmenopausal women who were on estrogen therapy, one in a group of women without asthma and one in a group of women with asthma.[11,22,27] Women without asthma did not have significantly different FEV1 values after the initiation of ERT. However, estrogen therapy was associated with an inhibitory effect on airway reactivity of bronchial smooth muscle.[11] Women with asthma experienced a significantly decreased peak expiratory flow and increased bronchodilator requirements after estrogen use, but there was no significant difference in spirometry values.[22,27] Both of these studies were small ($n = 15$ and $n = 36$, respectively), did not control for potential confounders, and considered only unopposed estrogen therapy. Pata et al. examined the effects of three different treatment protocols, *i.e.*, estrogen, estrogen with progestin, and tibolone, on respiratory function in three separate small groups of postmenopausal women. A significant difference was observed in FVC and FEV1 only in the group of estrogen with progestin after 3 months. There was no significant difference between pre- and posttherapy values in other parameters.[14] A similar study was performed by Cevrioglu et al., who investigated the effects of HRT on lung function in

Table 2. Spirometry Indicators According to ERT Use

	ERT (n = *30*)			*Non-ERT* (n = *30*)		
	Mean ± SD, 1	*Mean ± SD, 2*	p*	*Mean ± SD, 1*	*Mean ± SD, 2*	p*
FVC	103.45 ± 18.2	107.62 ± 17.8	0.135	102.64 ± 14.65	102.38 ± 14.84	0.527
FEV1	91.18 ± 16.97	98.89 ± 17.32	0.017	87.56 ± 12.09	86.19 ± 12.52	0.035
PEF	75.72 ± 28.86	92.82 ± 28.93	< 0.001	72.59 ± 20.93	73.96 ± 20.86	0.205
FEV1/FVC	97.23 ± 12.75	102.46 ± 10.4	0.005	93.91 ± 11.18	93.66 ± 12.7	0.717
FEF25–75	64.55 ± 20.97	81.08 ± 25.62	0.001	61.17 ± 19.71	60.76 ± 21.41	0.768
MEF75%	75.21 ± 27.26	92.25 ± 26.48	< 0.001	69.08 ± 22.04	68.95 ± 22.93	0.922
MEF50%	66.31 ± 20.8	80.33 ± 23.63	0.003	61.09 ± 17.58	59.82 ± 18.82	0.350
MEF25%	62.82 ± 27.58	81.29 ± 36.21	0.001	58.21 ± 26.45	58.54 ± 27.36	0.880

t-test for independent samples.
ERT, Estrogen replacement therapy; SD, standard deviation; FVC, forced vital capacity; FEV1, forced expired volume in 1 sec; PEF, peak expiratory flow; FEF25–75, forced expiratory flow at 25%–75% of FVC; MEF25%, flow at 25% of FVC; MEF50%, flow at 50% of FVC; MEF75%, flow at 75% of FVC.

postmenopausal women. The authors divided the respondents into three small groups. A statistically significant increase was observed only in the FVC and FEV1 parameters of the estrogen + progestin group after 3 months of therapy.[15] The only relevant study that is comparable to our study is the one by Carlson et al.[13] These authors examined the relationship of HRT with spirometry in 2,353 women older than 65 years and participating in the Cardiovascular Health Study in 1993/1994. Current HRT use was defined as estrogen or estrogen/progestin use. Of the women using HRT, 81.4% were using unopposed estrogen, and 18.6% were using combined estrogen/progestin. The study showed that estrogen + progestin users had the highest levels of FVC and FEV1, which the authors could not explain.[13] Among the respondents were women with asthma and smokers, and they were on average significantly older than our subjects were. Furthermore, individual doses and duration of therapy were unknown.[13]

On the other hand, in women aged 24–35, the use of an oral contraceptive containing estradiol and progestin increased the FEF rates, especially flow rates at low lung volumes.[21] Hence, these findings in young women point to the alveolar-maintaining effect, and perhaps alveolar-regenerating ability, of ovarian hormones. The loss of alveoli in mice after ovariectomy and their regeneration during estradiol replacement suggest estrogen to be the ovarian hormone responsible for maintaining alveolar structural stability and for inducing alveolar regeneration in women.[24,25]

It is important that we analyzed postmenopausal women because postmenopause is a factor involved in weakening of the lung mechanical function. Because estrogen deficiency is a known risk factor for the processes of aging of many tissues, organs, and systems in the human body, ERT has been traditionally used to improve structural integrity of the tissues. Estrogen receptors (ER) were identified in the nuclei of connective tissue and of the smooth muscle cells of the lung. These receptors participate in maintaining the connective tissue by increasing the synthesis or decreasing the breakdown of collagen. These findings suggest that estrogen restores the collagen metabolism and increases the turnover of connective tissues of the lung.[5,7,11,22,27] Animal studies have shown that ERs regulate estrogen action on the lung tissue.[11]

To our knowledge, our article is the first report with significantly higher values of spirometry parameters in postmenopausal women with POP after 6 months of ERT. It should be noted that our study population was a specific one. The main strength of the present study is sample size, strict inclusion criteria, and the fact that study women were matched for age, height, BMI, parity, and menopausal status. This reduced the potential errors due to the influence of sex hormones. Our results are different from the results reported by other authors because our methodology was different. The leading reason is that our subjects were a representative group of women with very poor muscle and connective tissue. Furthermore, our pattern was large enough, all subjects were surgically castrated postmenopausal women with previous hysterectomy and oophorectomy, and the study group women were taking unopposed estrogen. The most important evidence for a favorable effect of estrogen on the lung is that the postmenopausal women with genital prolapse showed improved spirometry parameters following estrogen therapy administration.

The results of our study may be explained by a few reasons; however, we adjusted for many factors that could have influenced our results. The results remain significant and clinically detectable and are supported by *in vitro* models. Estrogen and progestin have been associated with relaxation of bronchial and airway smooth muscle. Animal and human models have shown that both progestin and estrogen induce relaxation of bronchial muscle. An alternative explanation of the positive association could be that ERT improves muscular integrity, thus improving pulmonary function. Estrogen and progestin have been found to increase both muscle strength and function and to induce skeletal myoblast growth. However, if ERT improves musculoskeletal integrity, which increases total lung capacity, then spirometry tests should have been significantly higher among ERT users.[24,25,28,29] Recently, it has been discovered that estrogen could play a crucial role in collagen production, and it is a possible explanation of our results.[27,32] A major handicap for our research is the very small number of articles regarding the effects of estrogen in the human lung.

Finally, this study indicated a beneficial effect of estrogen on bronchial or lung tissue. Also, these data confirm that HRT should be recommended to all postmenopausal women, especially to those with pelvic organ prolapse. Our findings call for additional studies of the potential effects of estrogen replacement administration on pulmonary function in postmenopausal women, especially to those with pelvic organ prolapse.

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Author Disclosure Statement

We certify that all of the authors did not have any relationship with companies that may have a financial interest in the information contained in the manuscript.

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