

Occurrence of climacteric symptoms in postmenopausal women after prophylactic bilateral ovariectomy

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Summary

Purpose of investigation: To analyse the quality of life in postmenopausal women after prophylactic bilateral ovariectomy depending on the time from menopause. **Materials and Methods:** The study involved 252 postmenopausal women grouped according to the time from last menstruation: one to five years (group A), five to ten years (group B), and > ten years (group C). All women were ovariectomized during laparotomy performed for benign diseases of the uterus. Climacteric symptoms were measured with the Kupperman Index one day before and three months after surgery. **Results:** Highly significant age differences and no substantial BMI differences were demonstrated among the study groups. Before and after surgery climacteric symptoms were reported by 17.06% and 57.8% of women, respectively. After surgery, group A women significantly more often had hot flushes, sweating, nervousness, and sleep disorders, the women in group B significantly more often reported sleep disorders, nervousness, and sweating, and the women in group C significantly more often complained of nervousness. **Conclusion:** In postmenopausal women, ovaries play the most important role during the first ten years from the last menstruation.

Key words: Menopause; Climacterium; Ovariectomy; Benign diseases.

Introduction

The lengthening average lifespan has evoked interest in the health problems experienced by women during climacterium; especially ovarian steroid deficiency and related clinical symptoms have become a subject of clinical research and scientific conferences [1-5].

According to the literature, menopause is the last menstrual bleeding in a woman's life followed by a 12-month transition period caused by the loss of ovarian follicles [6-9]. After menopause ovarian volume decreases and structure changes; ovaries are not divided into the cortex and medulla, follicles are no longer present, and the ovarian stroma is limited to fibrous connective tissue, corpora albicantia, blood vessels, and nerves [3, 10-14]. However, ovarian steroidogenesis, as well as stromal and hilar cells continue to be active [10, 15-17]. Estradiol and androgens (mainly testosterone and androstenedione) are still synthesized in the gonads of postmenopausal women [18-21]. It should be emphasized that postmenopausal ovarian androgenesis acquires special importance because of the fact that androgens are those hormones which have a substantial direct effect on the whole body and serve as substrates for es-

trogen synthesis [8, 18, 22]. Androgens stimulate libido, reduce the incidence of sexual dysfunction, enhance bone tissue density and muscle strength, improve mood, and increase physical activity. Furthermore, peripheral aromatization of androgens converts them to estrogens, which reduce a risk of osteoporosis and cardiovascular diseases, the latter being the most frequent cause of death in postmenopausal women [15, 17, 18, 20, 23, 24]. Therefore prophylactic ovariectomy may soon result in the occurrence of climacteric symptoms, sexual dysfunctions, and hypertension [21, 25-27]. On the other hand, ten to 20 years after ovariectomy, patients are at a higher risk of death from cardiovascular diseases, osteoporotic fractures, and neurological diseases such as dementia, Parkinsonism, depression and Alzheimer's disease [28-32]. A research conducted in the USA in groups of postmenopausal women similar in terms of age and size revealed that the death rate from cardiac and neurological complications and osteoporotic fractures in the patients after prophylactic ovariectomy performed at the age of 50-54 was higher by 8% and at the age of 55-59 – by 4% than in the women with gonads; in patients older than 64 years, the removal of gonads had no

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influence on the lifespan [28, 29]. There are also studies which prove that even in cases of patients with a positive family history of ovarian cancer, prophylactic ovariectomy recommended before natural menopause considerably raises the risk of acute cardiovascular episodes, serious neurological diseases, and severe osteoporosis [28-33].

At present in Poland, there are no epidemiological data on postmenopausal women after prophylactic ovariectomy, therefore it is not known how many of them have suffered or died from cardiovascular diseases. According to the data of the Central Statistical Office and directives of the Polish Forum of Cardiovascular Diseases Prophylaxis, cardiovascular diseases were in the years 2008–2009, the leading cause of death in postmenopausal women (53% of women's deaths per year) [34]. It signifies that in Poland, every second postmenopausal woman dies from cardiovascular complications, which is twice as many as those dying from cancerous diseases. Hence, the presented assessment of the incidence and severity of climacteric symptoms caused by prophylactic ovariectomy seems reasonable.

Materials and Methods

The study involved 252 postmenopausal women hospitalized in the Department of Reproduction and Gynecology, the Pomeranian Medical University in Szczecin in the years 2004–2010. All of them gave their written consent to take part in the study.

The research was approved by the Bioethical Commission of the Pomeranian Medical University in Szczecin (permission number BN-001/76/03 of April 28, 2003). It was carried out within the Research Project of the State Committee for Scientific Research (KBN), no. 2 PO5E-10527.

Patients included in this study were allocated to groups A, B, or C depending on the time from last menstruation (LM): one to five years in group A, five to ten years in group B, and more than ten years in group C. Group A consisted of 102 patients, group B of 88 patients, and group C of 62 patients.

All the patients had normal results of prophylactic tests: cervical smear, mammography, and arterial blood pressure. They had no current or past history of endocrinopathy or neoplastic disease, did not undergo surgeries which would impair blood flow to the ovaries, and did not take menopausal hormone therapy. All the women were ovariectomized during laparotomy performed for benign diseases of the uterus (myomas, endometriosis, pelvic organ prolapse).

Climacteric symptoms in the study group were measured one day before and three months after surgery with the use of the Kupperman Index. The patients assessed the incidence of hot flashes, sweating, sleep disorders, nervousness, depression, dizziness, general fatigue, aching joints, headaches, palpitation of the heart, and paresthesias. The symptoms were scored as follows: hot flashes (4), paresthesias (2), insomnia (2), nervousness (2), and all other symptoms (1). Each symptom on the Kupperman Index was rated from 0 to 3 for no, slight, moderate, and severe complaints. To calculate the Kupperman Index, the values assigned to particular symptoms were multiplied by the values reflecting their severity. The highest potential score was 51. Statistical analysis was done using Statistica 6.0. The accepted level of significance was $p < 0.05$.

Table 1. — *Description of age distribution in three study groups of women.*

Description of distribution	Age [years]		
	Group A (n=102)	Group B (n=88)	Group C (n=62)
Min-max	39-63	40-67	54-78
Q ₁ -Q ₃	48-57	53-59	60-70
Me	52	56	65
x±SD	52±4.2	57±4.7	64.9±6.1
N	> 0.26 (+)	< 0.001 (-)	> 0.35 (+)

n = the number of people in the group; min-max = range of values;

Q₁-Q₃ = interquartile range; Me = median;

x±SD = arithmetic mean and standard deviation; N = normality of distribution; yes (+), no (-) (the Shapiro-Wilk test)/N-normal distribution yes (+), no (-).

Table 2. — *Description of age distribution at last menstruation (LM) in the study groups of women.*

Description of distribution	Age at LM [years]		
	Group A (n=102)	Group B (n=88)	Group C (n=62)
Min-max	39-63	33-59	30-59
Q ₁ -Q ₃	48-54	46-52	44-50
Me	50	52	49
x±SD	51.2±2.4	46.4±3.7	47.5±5.4
N	> 0.33 (+)	< 0.0002 (-)	< 0.03 (-)

n = the number of people in the group; min-max = range of values;

Q₁-Q₃ = interquartile range; Me = median;

x±SD = arithmetic mean and standard deviation; N = normality of distribution; yes (+), no (-) (the Shapiro-Wilk test)/N-normal distribution yes (+), no (-).

Table 3. — *Description of BMI distribution in the study groups of women.*

Description of distribution	BMI [kg/m ²]		
	Group A (n=102)	Group B (n=88)	Group C (n=62)
Min-max	18.8-39.2	17.2-39.1	17.7-41.6
Q ₁ -Q ₃	21.9-30.1	22.6-30.2	24.2-32.9
Me	25.6	26.7	28.8
x±SD	25.4±3.7	26.8±3.4	28.5±5.1
N	>0.06 (+)	>0.31 (+)	>0.63 (+)

n = the number of people in the group; min-max = range of values;

Q₁-Q₃ = interquartile range; Me = median;

x±SD = arithmetic mean and standard deviation; N = normality of distribution; yes (+), no (-) (the Shapiro-Wilk test)/N-normal distribution yes (+), no (-).

Results

The authors demonstrated highly significant age differences between the three study groups A, B, and C; the oldest patients were in group C (Table 1). Also, the age at menopause significantly differed between groups A and B and groups A and C, and was similar in groups B and C. The oldest average age at LM was noted in group A (Table 2). There were no significant BMI differences between the study groups of women (Table 3).

Prior to surgery climacteric symptoms had been reported only by 17.06% of 252 women (22.51% of group A,

Table 4. — *Frequency of climacteric symptoms according to the Kupperman Index.*

Climacteric symptoms	Hot flashes			Sweating			Sleep disorders			Nervousness		
	Before surgery n (%)	Three months after surgery n (%) <i>p</i>		Before surgery n (%)	Three months after surgery n (%) <i>p</i>		Before surgery n (%)	Three months after surgery n (%) <i>p</i>		Before surgery n (%)	Three months after surgery n (%) <i>p</i>	
Group A, n=102	10 (9.8)	49 (48.1)	<0.05	4 (3.92)	29 (28.43)	<0.05	5 (4.9)	56 (54.9)	<0.05	1 (0.98)	43 (42.16)	<0.05
Group B, n=88	8 (9.1)	13 (14.77)	>0.05	3 (3.4)	16 (18.18)	<0.05	4 (4.55)	29 (32.95)	<0.05	0 0	29 (32.95)	<0.05
Group C, n=62	2 (3.22)	5 (8.1)	>0.05	1 (1.61)	5 (8.1)	>0.05	2 (3.22)	3 (4.84)	>0.05	0 0	7 (11.29)	<0.05
Total group, n=252	20 (7.9)	67 (26.58)	<0.05	8 (3.17)	50 (19.84)	<0.05	11 (4.37)	88 (34.92)	<0.05	1 (0.4)	79 (31.35)	<0.05

I = before surgery, II = three months after surgery, *p* = level of significance.

Table 5. — *Frequency of climacteric symptoms according to the Kupperman Index (cont.).*

Climacteric symptoms	Depression			Fatigue			Dizziness		
	Before surgery n (%)	Three months after surgery n (%) <i>p</i>		Before surgery n (%)	Three months after surgery n (%) <i>p</i>		Before surgery n (%)	Three months after surgery n (%) <i>p</i>	
Group A, n=102	2 (1.96)	29 (8.43)	<0.05	0 0	16 (15.69)	<0.05	0 0	9 (8.82)	<0.05
Group B, n=88	0 0	10 (11.36)	<0.05	0 0	5 (5.68)	<0.05	0 0	5 (5.68)	<0.05
Group C, n=62	0 0	2 (3.22)	>0.05	0 0	2 (3.22)	>0.05	0 0	4 (6.45)	>0.05
Total group, n=252	2 (0.79)	41 (16.27)	<0.05	0 0	23 (9.13)	<0.05	0 0	18 (7.14)	<0.05

I = before surgery, II = three months after surgery, *p* = level of significance.

17.04% of group B, and only 8.06% of group C). None of the patients had climacteric symptoms strong enough to require therapy. Only three patients from group A (2.94% of all women included in the study) suffered from three mild climacteric complaints occurring at one time; others reported only one clinical problem. Symptoms that the patients mainly complained of before surgery included hot flashes, sleep disorders, and sweating. Three months after surgery, on the other hand, 57.8% of 252 women (mainly group A) had climacteric problems. They were as follows group A: sleep disorders (54.9%), hot flashes (48.1%), and nervousness (42.2%); group B: sleep disorders (33.0%), nervousness (11.3%), and sweating (18.8%); and group C: nervousness (11.3%), hot flashes (8.1%), and sweating (8.1%) (Table 4). A comparison of climacteric symptoms before and after surgery in particular groups of women revealed that hot flashes were significantly more common after surgery in group A ($p < 0.05$), sweating and sleep disorders in groups A and B, and nervousness in all groups.

A general analysis of all participants in the study showed that the aforementioned climacteric symptoms i.e. hot flashes, sleep disorders, nervousness, and sweating were significantly more common in women after surgery ($p < 0.05$), (Tables 4 and 5).

Discussion

The results presented in this study prove that prophylactic removal of gonads, in which folliculogenesis does not occur, has considerable effects on women's well-being. Prior to surgery, none of 252 women included in the study had reported climacteric symptoms troublesome enough to

use menopausal hormone therapy (MHT). However, merely three months after surgery, as many as 57.8% of the women complained of severe climacteric symptoms, over 30% of whom had three different clinical problems.

A detailed analysis of particular groups of women revealed that climacteric symptoms occurred significantly more often in women who underwent ovariectomy up to five years after menopause. It suggests that the synthesis of androgens and estrogens in the ovaries is at its peak up to five years from LM, which in turn proves that especially in this group of women, decision about ovariectomy should be considered very carefully. Also the women who had LM five to ten years before their inclusion into the study complained of the occurrence or higher intensity of climacteric symptoms no sooner than after removal of gonads. The smallest number of climacteric symptoms was noted in the patients operated over ten years after LM, which means that ovariectomy performed in these women has no significant clinical consequences.

The most common climacteric symptoms after surgical menopause included: sleep disorders (34.92%), nervousness (31.35%), and hot flashes (26.58%). Available studies show that the types of climacteric symptoms in the analyzed patients were different than in those after natural menopause (they mainly report hot flashes and sweating) [35-37].

Over 30% of the operated women had indications for MHT, and some of them required also hypnotic and sedative drugs, as well as blood pressure-lowering medicines used as a permanent treatment, which was unnecessary before surgery. This confirms that after menopause, ovaries are an important source of steroid hormones. Their removal

may lower quality of life, induce hypertension, and result in the necessity of permanent treatment.

Climacteric symptoms appear to be most severe immediately after surgery (the first six months) [35, 36, 38–40]. There are no significant differences in quality of life and the incidence of sexual dysfunction between non-operated patients and those examined two years after prophylactic ovariectomy [29, 35, 36, 38, 41]. On the other hand, it is known that if estrogens are not administered soon after surgery and the patient has hot flashes, it leads to irreversible changes in the central nervous system resulting in memory and concentration problems. Administration of estrogens later than one year after ovariectomy should not be practiced [8, 40, 42].

Aside from climacteric symptoms and hypertension, prophylactic removal of gonads in postmenopausal women causes also an increase in concentration of the insulin growth factor (IGF-1), which substantially raises a risk of colonic carcinoma [43].

While discussing the occurrence of depression in women after hysterectomy or removal of the uterine body and appendages, it should be emphasized that though ovariectomy and related deficiency of androgens and estrogens contribute enormously to the aforementioned symptoms [22, 32], the range of the surgery is also important. Operated women lose their ovaries and uterus or its body i.e. organs which are thought to be attributes of femininity, therefore their self-esteem often drops after surgery. Similar conclusions have been found in other reports [15, 35, 37, 44]. Nevertheless, some authors claim that consequences of ovariectomy which are particularly dangerous for patients are those occurring five to ten years after surgery, leading to a higher death rate. A long-term deficiency of ovarian hormones results in a considerably higher incidence of cardiovascular diseases [4, 5, 44–47], osteoporosis [28, 37], and neurodegenerative diseases such as dementia, Parkinsonism, and Alzheimer's disease [32, 33]. The rate of deaths from these diseases in the group of ovariectomized women is several times higher than from ovary and/or breast carcinoma compared to the group of non-operated patients similar in terms of age and size [28, 35–38, 48]. The research of Shuster *et al.* [26, 27] shows that the relative risk of death in women who underwent ovariectomy before 45 years of age increases from 1.16 (general population) to 1.67.

The risk of cardiovascular diseases for women who experienced a natural menopause is 1.27, whereas for women after prophylactic ovariectomy, 4.55 if ovaries were removed before 50 years of age, and as much as 8.7 if gonads were removed before the age of 40 years [26, 27]. Due to a short-term observation of the patients, long-term effects of ovariectomy on women's lifespans were not analyzed in the present study.

In summary, the results of the present research on the incidence and severity of climacteric symptoms in post-

menopausal women prove that up to five years from LM, gonads produce clinically significant amount of estradiol and androgens. Not only are these hormones essential for women's well-being, but they also play an important part in the context of distant consequences, such as the development of fatal systemic diseases, especially cardiovascular complaints, osteoporosis, depression, dementia, Parkinsonism, and Alzheimer's disease [4, 19, 26, 27, 35–38]. Hence, a decision about prophylactic ovariectomy in women operated up to five years after menopause should be properly considered. In cases of older women who had LM ten years earlier, prophylactic removal of gonads can be recommended. In these patients, the advantages of surgery outweigh the risk of early or distant clinical complications.

Conclusion

In postmenopausal women ovaries play the most important part during the first ten years from the last menstruation.

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