Effects of hormone replacement therapy on depressive and anxiety symptoms after oophorectomy

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ABSTRACT

Aim To assess the effect of hormone replacement therapy on postoperative depression and anxiety symptoms.

Methods In observational prospective study 80 women divided into two groups were evaluated: women who received estrogen and androgen replacement therapy after hysterectomy with bilateral oophorectomy before onset of menopause (35-45 years old) and a control group that consisted of perimenopausal women (45-55 years old). Hormone replacement therapy began one week after surgery. The severity of depression and anxiety was evaluated through the use of Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale. Subjects from the study group were interviewed right after the surgical treatment, one, two and three months later. Subjects from the control group were interviewed only once.

Results The women who underwent surgery had a statistically significantly higher score in Hamilton Depression Scale (p<0.001) and Hamilton Anxiety Scale (p=0.002) compared to the control perimenopausal women. There was a significant reduction of depressive and anxiety symptoms during hormone replacement therapy. Statistically significant difference in depressive score was found immediately after one month of hormone replacement therapy (first week/one month later: p=0.0057). Statistically significant difference in anxiety score appeared three months after the introduction of hormone therapy (first week/one month later: p=0.309; first week/two months later: p=0.046; first week/three months later: p<0.001). Level of serum luteinizing hormone was in correlation with depressive and anxiety score.

Conclusion Estrogen-androgen replacement therapy may reduce the risk of psychiatric disorders developing in women with bilateral oophorectomy (indication for hysterectomy with oophorectomy was leiomyomata uteri).

Keywords: hysterectomy, mood disorders, women health, HAMD, HAMA
INTRODUCTION

In women with surgically removed uterus and ovaries before natural menopause, there is a sudden and drastic decrease in levels of ovarian hormones in the circulation which causes surgical menopause. Women who experienced this menopause have increased morbidity. They have a higher risk of developing cardiovascular (1), neurological (2,3) and psychiatric diseases (4,5) and osteoporosis (6) compared to referent population. Study of Rocca 2009 found that bilateral oophorectomy performed before the onset of menopause is associated with an increased long-term risk of depressive and anxiety symptoms, especially at younger age (4).

The pattern of psychiatric disorder development is multifaceted. The possible role of hormone deprivation in occurrence of psychiatric symptoms in this population is not clear. The association between oophorectomy and increased risk of depressive and anxiety symptoms development may be explained by deficit in ovarian hormones and by the disruption of hypothalamic–hypophysal–ovarian axis (7). However, this association may be due to some undergoing psychological factors. Whether the abrupt onset of hormone imbalances will affect and how it will affect the mental and physical health of women depends on many factors (indications for surgery, mental and physical health of women before the operation, her sexual function, specific surgical procedure, age, marital status, socio-economic status, parenting) (8). The effect of the hormone does not cause behavior changes, but the likelihood of response to stimuli (9).

It is known that hysterectomy only leads to the development of depressive and anxiety symptoms (10-12). However, results of some studies are inconsistent with these findings because there no association was found between surgical treatment and psychological symptoms (13,14) or any data that would imply that an intervention may improve psychological health (15,16). In most researches, it is not precise what the secretory function of ovary was.

Also, age specific data are limited although some researches show that women who had undergone hysterectomy in young age had more severe psychological reaction (13).

Although there are many preclinical studies regarding the role of testosterone in depression and anxiety disorders, there are very few clinical studies on this subject (17). On the other hand, it is a known fact that women are twice as prone to anxiety disorders and depression than men. It is possible that sexual hormones are some of the key factors in the discrepancy between men and women, which leads to the possible role of testosterone and its possible protective benefits against anxiety and depression (18).

The aim of our study is to determine whether hysterectomy with bilateral oophorectomy and consequent ovarian hormone disruption leads to an increase of anxiety and depression, and if it is possible eliminate or reduce those symptoms by hormone substitution therapy. The purpose of our research is to better understand these issues and improve mental health of women.

PATIENTS AND METHODS

Patients

This observational prospective study was conducted during a two-year period at the Clinic of Gynecology and Obstetrics of the Clinical Centre Kragujevac, Clinic of Psychiatry of the Clinical Centre Kragujevac and Dispensary for Women of the Primary Health Care Centre Kragujevac.

It evaluated 80 women who were divided into two groups: women who received estrogen and androgen replacement therapy after hysterectomy with bilateral oophorectomy before onset of menopause, and the control group that consisted of women in perimenopause. The first group included 40 women who were 35-45 years old. The control group included 40 women aged 45-55. Most of the women finished high school. Majority were from urban environments while 16.78% were from rural environments; 52 women were married, eight were single and 20 were divorced. By comparing the socio-demographic characteristics, (except for the age) no statistically significant difference between the two groups in any of the categories was found (p>0.001).

The indication for hysterectomy with oophorectomy was leiomyomata uteri. The inclusion criteria was age between 35-45 for the clinical and 45-55 for the control group, no hormone therapy for one year prior, body mass index (BMI)
<33kg/m². The women with mental retardation, with known or suspected history of breast carcinoma, any malignant disease in the last 5 years, severe liver or renal disease, thromboembolic history or treatment with liver enzyme inducing medications or those that could have affected bone metabolism were excluded. Women did not use any antidepressants and anxiolytics. A written informed consent was obtained in all cases. The study was approved by the Ethics Committee of Faculty of Medical Sciences Kragujevac.

Methods

The severity of depressive and anxious symptoms was evaluated with the hetero-administered Hamilton Depression Rating Scale (HAM-D 21) (19) and Hamilton Anxiety Rating Scale (HAM-A) (20). In all patients diagnosis was confirmed by two experienced psychiatrists based on DSM-IV criteria for depression/anxiety. Hormone replacement therapy began one week after the surgery. The therapy included estradiol valerianate-dehydroepiandrosterone enanthate at a 1:50 ratio (Gynodian Depo). Subjects from the study group were interviewed during the first week after surgery and then again during follow-up visits when they received hormonal therapy, four times in total. Subjects from the control group were interviewed only once. Blood was taken for analysis from patients on the same day the psychiatric interview was conducted.

Statistical methods

Data were expressed as mean ± standard deviation. The Kolmogorov-Smirnov test was used for testing variables normality. Because of non-normal distribution of data the statistical significance between the study groups was assessed by using the non-parametric Kruskal-Wallis Tests (three or more categories) and Mann-Whitney Tests (two categories). Wilcoxon Test was used to estimate if there were statistically significant differences among repeated measurements in the group with hormone substitution therapy. Linear correlation was used to examine relation between blood hormone level and HAMD and HAMA score. Statistical significance of p <0.001 was used.

RESULTS

Eighty women divided into two groups were evaluated: women who received estrogen and androgen replacement therapy after hysterectomy with bilateral oophorectomy due to leimyomas and the referent group of perimenopausal women. The first group included 40 women who were 35-45 years old (mean age of 42±6.9). Control group included 40 women who were 45-55 years old (mean age of 53±7.1).

The women who had undergone surgery had a statistically significant difference in HAMD (p<0.001) and HAMA (p=0.002) score compared to women with physiological perimenopause (Table 1). It is apparent that women who had surgically undergone hysterectomy with bilateral oophorectomy had significantly more depressive symptoms than perimenopausal women. Anxiety symptoms were also more drastic in that group of women.

<table>
<thead>
<tr>
<th>HAMD/HAMAn perimenopausa</th>
<th>HAMAn hysterectomy</th>
<th>p</th>
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<tbody>
<tr>
<td>(mean± SD)</td>
<td>(mean± SD)</td>
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<tr>
<td>HAMD score</td>
<td>16.10 ± 4.74</td>
<td>10.75 ± 3.71</td>
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<tr>
<td>HAMA score</td>
<td>38.00 ± 11.78</td>
<td>29.00 ± 13.00</td>
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*first week after surgery; SD, standard deviation

Scores of depression (HAMD scale) in the first week (1), one month (2), two months (3) and three months (4) after the surgical procedure are shown in Table 2. Hormone replacement therapy began in the first week after the procedure, e.g., when the first interview with the subjects was conducted. Statistically significant difference in depressive score immediately after one month of hormone replacement therapy (the first week/one month later: p=0.0057) was found; the depressive score significantly reduced each month.

<table>
<thead>
<tr>
<th>HAMD scores during different time intervals</th>
<th>Xsr ± SD</th>
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<th>p</th>
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<tbody>
<tr>
<td>1-2</td>
<td>16.10 ± 4.74</td>
<td>15.62 ± 4.67</td>
<td>0.0057</td>
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<td>(n=40)</td>
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<td>1-3</td>
<td>16.10 ± 4.74</td>
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<td>1-4</td>
<td>16.10 ± 4.74</td>
<td>13.05 ± 3.56</td>
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<td>2-3</td>
<td>15.62 ± 4.67</td>
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<td>(n=40)</td>
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<tr>
<td>3-4</td>
<td>14.42 ± 4.17</td>
<td>13.05 ± 3.56</td>
<td>0.0003</td>
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<td>(n=40)</td>
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*first week (1), one month (2), two months (3), three months (4); SD, standard deviation
Scores of anxiety (HAMA) in the first week (1), one month (2), two months (3) and three months (4) after the surgical procedure were shown in Table 3. The anxiety score was reduced one month after the hormone replacement therapy. Statistically significant difference in anxiety score appeared three months after the start of hormone therapy (after the subjects received the 3rd dose of the therapy) (first week /one month later: p=0.309; first week /two months later: p=0.046; first week /three months later: p<0.001).

The Pearsons linear correlation test showed existence of strong negative correlation between the level of serum luteinizing hormone and HAMD and HAMA score (Figures 1, 2).

**DISCUSSION**

Menopause is a universal and irreversible part of the overall aging process as it involves a woman’s reproductive system. It is the final menstrual period which is diagnosed after 12 months of amenorrhea and is characterized by a myriad of symptoms that may include changes from regular, predictable menses, vasomotor and urogenital symptoms and sleep and mood dysfunction (21,22). Hormonal changes and clinical symptoms occur over a period leading up to menopause. This period is termed the climacteric or perimenopause or menopausal transition and it characteristically begins years before menopause, typically occurring between the ages of 45 and 55, with median age at inception of perimenopause 4.75 years (21-23). Until recently, perimenopause was not recognized as a period with a higher risk for new or repeated depression. It

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<td>1-3</td>
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<td>36.90 ± 10.10</td>
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*first week (1), one month (2), two months (3), three months (4); SD, standard deviation

Figure 1. Correlation between serum level of LH and HAMD score HAMD, Hamilton Depression Rating Scale; LH, luteinizing hormone

Figure 2. Correlation between serum level of LH and HAMA score HAMA, Hamilton Anxiety Rating Scale; LH, luteinizing hormone
is still unclear whether and to what extent changes in estrogens, progesterone and androgens that occur in menopause period influence psychological status in women.

The first important result of this study was the finding of a difference in HAMD and HAMA score between women who underwent surgery and the control group of perimenopausal women. Previous studies show that women who underwent hysterectomy with bilateral oophorectomy had more pronounced psychiatric symptoms (4,5,7). In the studies of women undergoing natural menopause an increase in depressive symptoms was demonstrated, generally revealed during perimenopause with a decrease in risk during postmenopausal years (5).

Very interesting finding of this study is the indication of moderate depression according to average HAM-D value found in the control group, which was in line with some of the other researches (24). Previous research suggests that the estrogen deficiency caused by bilateral oophorectomy may be the initial step in a chain of causality that determines an increased long-term risk of depression or anxiety (4). Although the precise mechanisms are still unknown, depression during perimenopause is likely to occur due to the influence of estrogen to actions of serotonin and norepinephrine. A decline in estrogen concentrations may decrease levels of these hormones and thus contribute to depression (25,26). The hormonal changes induced by premenopausal bilateral oophorectomy are different from those occurring during natural menopause (27-29). In natural menopause, as well as after menopause, the ovary leads testosterone production. In widespread tissues and organs including the brain, testosterone is aromatized into estrone and estradiol, the most potent estrogen. Bilateral oophorectomy before menopause results not only in an abrupt drop in levels of circulating estrogen but also an abrupt drop in levels of circulating testosterone and in a disruption of the hypothalamic-pituitary-ovarian axis with an increased release of the gonadotropins luteinizing hormone and follicle stimulating hormone (27-29).

According to the correlation between hormonal status and score of depression and anxiety was found in this study, it is a question if deteriorated mental health in hysterectomized and oophorectomized women could be attributed only to hormonal abruption. These results can be explained by losing uterus and ovary as symbols of femininity and maternity in woman’s life, which leads to psychological problems (28,29).

The loss of the uterus and scarring after surgery may result in impairment of body image, which includes the perception of a loss of femininity and vitality (33,34). Impairment of body image has been found in oophorectomized women (35). Conserving their uterus may be important for gender identity, sexuality, marital relations, and self-esteem for many women in our population (36).

A statistically significant decrease in depression and anxiety across post surgical time period has been found in this study. The scores for depression decreased significantly earlier (after first measure) and moved in a positive direction during the time compared to the anxiety score which did not change considerably for longer time (it decreased significantly after three months). Cohen 2011 showed that anxiety and depression after hysterectomy were highest in the immediate post-operative period and decreased significantly over the period of eight weeks (37).

The results of this study have shown a correlation between the level of serum luteinizing hormone and score of depression and anxiety; the levels of LH had a negative correlation with the levels of depression and anxiety in the investigated groups of women. Similar results were obtained in a study (38) showing that psychiatric disorders should be considered in polycystic ovarian syndrome women in which significantly higher LH level has been found in the investigated group as compared to the control group.

The main finding of this study is that postoperative estrogen therapy in combination with androgen therapy may decrease anxiety and depression in women who underwent hysterectomy with oophorectomy. There are some studies which examined the effect of estrogen replacement therapy on anxiety and depressive symptoms in such women, but results are inconsistent. The study of Rocca et al. (2008) found that the treatment with estrogen in women who are 50 years old and underwent bilateral oophorectomy at younger age did not modify the risk (4). Nathorst-Bööss et al. (1993) reported less anxiety and depression and more well-being in oophorectomized women who received estrogen replacement therapy (39). There are two important mechanisms by which estrogen influences depression and depressive-like behavior: interactions with neurotrophic
factors and influence on the serotonergic system (40). On the other hand, there are almost no studies that examine the effect of combined estrogen-androgen on anxiety and depressive symptoms. One of the shortcomings of this study is that the levels of hormones were determined solely on the basis of morning blood samples. Another shortcoming is that we did not have a group of women who underwent an operation, and who did not have a hormonal therapy. Furthermore, the control and clinical group were not comparable in terms of age. Therefore, there is a possibility that difference in the levels of depression and anxiety between these groups, in that case, would be much higher. All this should be taken into consideration in the future research.

**REFERENCES**


Even though our results show that appropriate hormone therapy can have a considerable effect on anxiety and depression in women with hysterectomy and bilateral oophorectomy, it is necessary to continue research in this field. It is also necessary to reduce the limitations of our study in future research.

**FUNDING**

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**TRANSPARENCY DECLARATION**

Competing interest; none to declare.


EFIKSI HORMONSKIH SUPSTITUCIONIH TERAPIJE NA SIMPTOME DEPRESSIVNIH I ANKSIOZNIH KOD ŽENA POSLE UKLANJANJA JAJNIKA

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SAŽETAK

CILJ Proceniti uticaj efekata hormonske supstitucione terapije na postoperativne simptome depresije i anksioznosti.

METODE U opservacionoj prospektivnoj studiji pratili smo 80 žena, podeljenih u dve grupe: žene pre početka menopauze (od 35 do 45 godina starosti) koje su posle operativnog uklanjanja materice i jajnika dobijale supstitucionu terapiju estrogena i androgena, i perimenopauzalne žene (starosti od 45 do 55 godina) koje su činile kontrolnu grupu. Hormonska supstituciona terapija započeta je nedelju dana nakon uklanjanja jajnika. Depresivnost i anksioznost je procenjivana Hamiltonovom skalom depresivnosti i Hamiltonovom skalom anksioznosti.

REZULTATI Operisane žene, u poređenju s perimenopauzalnim ženama, imale su statistički značajno više skorova na Hamiltonovoj skali depresivnosti (p<0.001) i Hamiltonovoj skali anksioznosti (p=0.002). Tokom primene hormonske supstitucione terapije došlo je do značajne smanjenja simptoma depresivnosti i anksioznosti. Statistički značajna razlika u depresivnosti utvrđena je jednom u nedelju nakon početka hormonske terapije (nedelja/mesec dana kasnije: p=0.0057). Statistički značajna razlika u depresivnosti utvrđena je mesec dana nakon početka hormonske terapije (nedelja/mesec dana kasnije: p=0.046; neljedna/tri meseca kasnije: p=0.001). Nivo luteinizirajućeg hormona bio je u korelaciji sa skorovima depresivnosti i anksioznosti.

ZAKLJUČAK Estrogen-androgen supstituciona terapija može smanjiti rizik od razvoja simptoma depresivnosti i anksioznosti kod žena kojima su uklonjeni jajnici (indikacija za histerektomiju s adneksektomijom bio je benigni miom materice).

KLJUČNE REČI: histerektomija, poremećaji raspoloženja, žensko zdravlje, HAMD, HAMA