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*The effect of FSH and estradiol levels on the rate
of neurovegetative symptoms in perimenopausal women*

The state of hormonal balance exists in the organism of each mature woman. The decrease in estrogen concentration, which occurs in the perimenopausal period, leads to the balance upset. The anterior pituitary stimulation to elevated secretion of gonadotrophins (first – mainly follicle stimulating hormone (FSH), to a smaller extent – luteotrophin (LH), which is later secreted in greater amounts) follows the process, which starts approximately 6 years before true menopause begins. Despite hypergonadotrophism, ovaries are not able to respond with the increased estrogen secretion. It leads to further elevation of gonadotrophin secretion and their concentration 3–5 years before menopause is approximately twice and 2.5 years before menopause – three times higher than during the regular cycle (9).

The effect of decreased estrogen secretion is the occurrence of disturbances of the vegetative system in the forms of menopausal neurovegetative symptoms. Estrogens influence the parasympathetic system and their deficit leads to a relative predominance of the sympathetic system. Simultaneously, there occur disturbances of hypothalamus vegetative centers functioning. Estrogen deficiency may cause the decrease in catecholic amine concentrations in hypothalamus, which can have an adverse influence on sleep and temperature regulation (9).

Duration of neurovegetative symptoms and their bothering nature is individual and depends mainly on individual adaptation abilities of the vegetative system to diminished ovarian hormone concentrations (9). The neurovegetative symptoms are as follows: ● asomotor symptoms: hot flushes, sweating ● Somatic symptoms: dizziness, headache, paresthesia ● Psychic symptoms: insomnia, restlessness, mood swings, irritability, impaired memory ● decrease in concentration, loss of libido.

Menopause can be also accompanied by metrorrhagia, atrophic changes of the reproductive organs, disturbances of the urinary system functioning, osteoporosis, imbalanced lipid metabolism, which affects the cardiovascular system (6).

Most of neurovegetative symptoms can occur as a result of overstimulation of the sympathetic system. A wide range of vegetative function disturbances indicates that the changes, besides the system hypothalamus – anterior pituitary – ovary, also cover other endocrine organs, thus causing their dysfunction. It concerns particularly the systems: hypothalamus – anterior pituitary – thyroid gland as well as: hypothalamus – anterior pituitary – adrenal cortex (9).

Hot flushes and sweating are the most frequent and, at the same time, most bothering for women. The symptoms have the greatest impact on the quality of life and functioning. The occurrence of vasomotor symptoms is not directly conditioned by low concentrations of estrogens in blood. They do not occur in girls in the prepuberty period, in women with ovary dysfunction, or in gonadal dysgenesis (Turner's syndrome). Estrogen administration and afterwards discontinuation of treatment may result in neurovegetative symptom occurrence in some of those women (3). Hot flushes are due to the decreased production, and not lack, of estrogens. They are synchronized with pulsating secretion of luteinizing hormone (LH). Imbalanced functions of the thermoregulatory centres, localized in the anterior hypothalamus preoptic region, are probably a source of

vasomotor symptoms. A high concentration of gonadoliberin (GnRH) was also observed to accompany the process (14).

According to other authors, menopausal symptoms can occur due to catecholic amine metabolism changes together with estrogen secretion decrease. The special role in the regulation of catecholamine transformations is attributed to catecholestrogens (they have an additional hydroxyl group in the ring A at the second or fourth carbon – ortho position). Unlike other estrogens, they have the ability to bind with both estrogen and catecholic receptors. They are produced locally in the brain due to their fast disintegration and inactivation and their concentrations in hypothalamus reach the level 10 times higher than that in blood (2).

Catecholestrogens regulate catecholamine activities in the central nervous system through two antagonistic mechanisms: 1) they protect catecholamines against too fast a disintegration as they have 18 fold higher affinity than catecholamines to catecholic methyltransferase (COMT), the enzyme taking part in inactivating catecholamines by methylation (7), 2) they decrease the compound synthesis (mainly dopamine) through inhibiting tyrosine hydroxylase (3).

Aging and accompanying decrease in estrogen concentrations can induce changes of catecholamine activities, particularly dopamine and noradrenaline, which conditions the autonomic nervous system disturbances (5).

Most of the reports connect the presence of neurovegetative symptoms with low levels of estradiol. It is rather rare to meet any report concerning the evaluation of higher FSH level and its influence on the frequency of the symptom occurrence. Thus, we decided to take up the study to assess the effect of FSH and estradiol on the occurrence of neurovegetative symptoms in women in the perimenopausal period.

MATERIAL AND METHODS

The age of 41–60 years, and the written consent to participate in the study were the inclusion criteria into the study. The examination was performed in 151 women, inhabitants of the Podlasie Region, aged 41–59 years (mean 49.4). Patients taking hormone replacement therapy, psychotropic drugs, and those with surgical menopause were excluded from the study.

Menopause Rating Scale II (MRS II) was used to evaluate the rate of neurovegetative symptoms occurrence. The scale fulfils high methodological standards and is very convenient in the quantitative assessment of a wide range of complaints connected with menopause in everyday practice (8, 12). Each patient filled the form by herself during her visit in the Province Outpatient Clinic of the Independent Public Health Care Unit, Provincial Hospital in Białystok.

The determination of follicle stimulating hormone (FSH) and estradiol (E_2) levels in blood serum was performed using the immunoenzymatic method with chemiluminescence technique (Bayer Centaur apparatus) (USA). The control was performed on three levels on the apparatus, using the same method, which is highly sensitive and specific and is completely automated. The assessment of interdependence between the features was conducted using the exact test according to Fisher (for the tables of correlation 2×2) or independence test χ^2 (for larger tables of correlation). The statistical description of quantitative features was performed using arithmetic means, standard deviations, and by indicating the maximum and minimum values. One-factor analysis of variance was used to assess the influence of the estradiol level. The pairs of groups were compared using the test of multiple comparisons NIR. T-Student test for two means was to compare the levels of features in two groups. In order to evaluate the interdependence between measurable features, the coefficient of Pearson's linear correlation was used, and its significance was assessed with t-Student test for correlation coefficient. The mean differences and interdependence of the features were assumed to be significant at $p < 0.05$ and they were assumed "on the border of significance" at $0.05 < p < 0.1$. The calculation was performed using the statistic programme STATISTICA 6.0 PL (1, 10, 11).

In order to assess the effect of FSH and estradiol levels on the rate of neurovegetative symptoms in perimenopausal women, the group was divided regarding the concentrations of both

hormones. The criterion of the first division was a low/high FSH level, which enabled to distinguish: group 1 – 85 women (56.3%) with FSH levels lower or equal to 30 mIU/ml and group 2 – 66 patients (43.7%) with FSH levels above 30 mIU/ml. The second division, considering a low/high estradiol level, made up three groups: group A – estradiol levels lower or equal to 20 pg/ml – 40 women (26.5%), group B – estradiol levels from 21 to 60 pg/ml – 40 patients (26.5%), and group C – with the levels of estradiol above 60 pg/ml – 71 cases (47%).

RESULTS

The analysis covered 11 features included in the Menopause Rating Scale II questionnaire (Table 1). As the aim of the study was the evaluation of FSH and estradiol levels influence on neurovegetative symptoms, except for an individual disturbance profile, the analysis did not include the intensity of complaints. The values given in Table 1 concern the rate of particular feature occurrence, without their intensity, described by patients as mild (1), moderate (2), severe (3), or extremely severe (4).

Table 1. Evaluation of particular symptoms occurrence in the examined groups on Menopause Rating Scale II

| Symptoms | | FSH≤30 Group 1 N=85 100% | FSH>30 Group 2 N=66 100% | E≤20 A N=40 100% | E21-60 B N=40 100% | E>60 C N=71 100% | Total N=151 100% |
|--------------------------------|---|-----------------------------------|-----------------------------------|---------------------------|-----------------------------|---------------------------|------------------------|
| Hot flushes and sweating | N | 40 | 53 | 34 | 27 | 32 | 93 |
| | % | 47.1 | 80.3 | 85.0 | 67.5 | 45.1 | 61.6 |
| | | p<0.001 | | p<0.001 | | | |
| Heart discomfort | N | 47 | 39 | 24 | 24 | 38 | 86 |
| | % | 55.3 | 59.1 | 60.0 | 60.0 | 53.5 | 57.0 |
| | | p<0.7 NS | | p<0.8 NS | | | |
| Sleep problems | N | 41 | 41 | 26 | 23 | 33 | 82 |
| | % | 48.2 | 62.1 | 65.0 | 57.5 | 46.5 | 54.3 |
| | | p<0.1 ~ | | p<0.2 NS | | | |
| Depressive mood | N | 45 | 27 | 18 | 19 | 35 | 72 |
| | % | 52.9 | 40.9 | 45.0 | 47.5 | 49.3 | 47.7 |
| | | p<0.2 NS | | p<1.0 NS | | | |
| Irritability | N | 54 | 45 | 26 | 29 | 44 | 99 |
| | % | 63.5 | 68.2 | 65.0 | 72.5 | 62.0 | 65.6 |
| | | p<0.6 NS | | p<0.6 NS | | | |
| Anxiety | N | 37 | 29 | 20 | 16 | 30 | 66 |
| | % | 43.5 | 43.9 | 50.0 | 40.0 | 42.3 | 43.7 |
| | | p<1.0 NS | | p<0.7 NS | | | |
| Physical and mental exhaustion | N | 43 | 41 | 27 | 21 | 36 | 84 |
| | % | 50.6 | 62.1 | 67.5 | 52.5 | 50.7 | 55.6 |
| | | p<0.2 NS | | p<0.3 NS | | | |
| Sexual problems | N | 38 | 45 | 28 | 24 | 31 | 83 |
| | % | 44.7 | 68.2 | 70.0 | 60.0 | 43.7 | 55.0 |
| | | p<0.005 | | p<0.025 | | | |
| Bladder problems | N | 25 | 23 | 12 | 13 | 23 | 48 |
| | % | 29.4 | 34.8 | 30.0 | 32.5 | 32.4 | 31.8 |
| | | p<0.5 NS | | p<1.0 NS | | | |
| Dryness of vagina | N | 20 | 21 | 12 | 12 | 17 | 41 |
| | % | 23.5 | 31.8 | 30.0 | 30.0 | 23.9 | 27.2 |
| | | p<0.3 NS | | p<0.8 NS | | | |
| Joint and muscular discomfort | N | 56 | 44 | 28 | 24 | 48 | 100 |
| | % | 65.9 | 66.7 | 70.0 | 60.0 | 67.6 | 66.2 |
| | | p<1.0 NS | | p<0.7 NS | | | |

Generally, the complaints of "joint and muscular discomfort" (66.2%), "irritability" (65.6%), "hot flushes and sweating" (61.6%), "heart discomfort" (57.0%), "physical and mental exhaustion" (55.6%), "sexual problems" (55.0%), and "sleep problems" (54.3%) dominated in the group of patients. The ailments mentioned above occurred in more than a half of the examined women.

Psychic symptoms, such as "depressive mood" and "anxiety" were admitted by less than the half, 47.7% and 43.3%, respectively. "Dryness of vagina" (27.2%) and "bladder problems" (31.8%) were the most rare complaints occurring in the group of patients (Table 1). On the other hand, "hot flushes and sweating" were most frequent and mentioned by 93 patients (61.6%). FSH level affected the rate of the symptom occurrence. Patients of group 2 (80.3%), as compared to group 1 (47.1%), were those who complained of "hot flushes and sweating" more frequently, the value was significant ($p < 0.001$). There was also a statistically significant interdependence ($p < 0.001$) between the estradiol level and "hot flushes and sweating" occurrence. However, together with the increase in estradiol level the symptom was more rarely notified (Table 1).

"Sleep problems" were reported by 82 women (54.3%) and FSH level was observed to affect "sleep problems". The comparison of the distribution in both groups of patients showed the interdependence on the border of significance ($p < 0.1$). More frequent occurrence accompanied the increase in FSH concentration. However, estradiol level had no influence on the symptom occurrence (Table 1). "Sexual problems" had 83 women (55.0%). The higher levels of FSH influenced the occurrence of the symptom. Patients of group 2 complained significantly more often (68.2%) than patients of group 1 (44.7%) ($p < 0.005$). There was also a significant interdependence ($p < 0.025$) between estradiol level and "sexual problems"; the increase in estradiol level caused more rare notification of the problem (Table 1).

FSH and estradiol levels did not have any essential effect on the rate of the following symptoms occurrence: heart discomfort depressive mood, irritability, anxiety, physical and mental exhaustion, bladder problems, dryness of vagina and joint and muscular discomfort (Table 1).

The sum of points obtained by each patient on the Menopause Rating Scale II (MRS II) was used to analyse the intensity of neurovegetative symptoms in the course of menopausal syndrome. The higher number of points, the higher intensity and rate of symptoms (Table 2). To obtain reliable conclusions, four divisions of results were established. FSH and estradiol levels did not have any significant effect on the sum of points obtained by patients on the Menopause Rating Scale II (MRS II) (Table 2).

Table 2. Analysis of results obtained on Menopause Rating Scale II

| | | FSH \leq 30 Group 1 N=85 100% | FSH > 30 Group 2 N=66 100% | E \leq 20 A N=40 100% | E 21-60 B N=40 100% | E > 60 C N=71 100% |
|---|--------|--|-------------------------------------|--|------------------------------|-----------------------------|
| \leq 5 | N % | 38 44.7 | 22 33.3 | 14 35.0 | 14 35.0 | 32 45.1 |
| 5-10 | N % | 19 22.4 | 15 22.7 | 7 17.5 | 9 22.5 | 18 25.4 |
| 10-15 | N % | 15 17.6 | 15 22.7 | 10 25.0 | 8 20.0 | 12 16.9 |
| >15 | N % | 13 15.3 | 14 21.2 | 9 22.5 | 9 22.5 | 9 12.7 |
| The evaluation of significance of distribution differences $p <$ | | $p < 0.5$ NS | | A-B $p < 1.0$ NS A-C $p < 0.3$ NS B-C $p < 0.5$ NS A-B-C $p < 0.7$ NS | | |

CONCLUSIONS

1. The higher FSH concentration occurred together with more frequent symptoms: "hot flushes and sweating" and "sexual problems".

2. The higher FSH concentration accompanied the tendency to more frequent occurrence of "sleep problems" (interdependence on the border of statistical significance).

3. The lower estradiol concentration occurred together with more frequent presence of "hot flushes and sweating" and "sexual problems" in clinical picture.

Menopause Rating Scale (MRS II)

Which of the following symptoms apply to you at this time?

Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

| Score | Symptoms: | | | | |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | none | mild | moderate | severe | extremely severe |
| 1. Hot flushes, sweating (episodes of sweating) | <input type="checkbox"/> |
| 2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness) | <input type="checkbox"/> |
| 3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking early) | <input type="checkbox"/> |
| 4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings) | <input type="checkbox"/> |
| 5. Irritability (feeling nervous, inner tension, feeling aggressive) | <input type="checkbox"/> |
| 6. Anxiety (inner restlessness, feeling panicky) | <input type="checkbox"/> |
| 7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness) | <input type="checkbox"/> |
| 8. Sexual problems (change in sexual desire, in sexual activity and satisfaction) | <input type="checkbox"/> |
| 9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence) | <input type="checkbox"/> |
| 10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse) | <input type="checkbox"/> |
| 11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints) | <input type="checkbox"/> |

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SUMMARY

The examination was performed in 151 women, aged 41–59 years. Patients taking hormone replacement therapy, psychotropic drugs, and those with surgical menopause were excluded from the study. Menopause Rating Scale II (MRS II) was used to evaluate the rate of neurovegetative symptom occurrence. The determination of follicle stimulating hormone (FSH) and estradiol (E₂) levels in blood serum was performed using the immunoenzymatic method with chemiluminescence technique.

Wpływ stężenia FSH i estradiolu na częstość występowania objawów wypadowych
w populacji kobiet w okresie okołomenopauzalnym

Badaniem objęto 151 kobiet w wieku od 41 do 59 lat. Wykluczono pacjentki odbywające hormonalną terapię zastępczą, zażywające leki o działaniu psychotropowym oraz kobiety u których menopauza została wywołana sztucznie. Do oceny częstości występowania objawów wypadowych użyto *Menopause Rating Scale II* (MRS II). Oznaczeń stężenia estradiolu (E₂) i folikulostymuliny (FSH) w surowicy krwi dokonano metodą immunoenzymatyczną w technice chemiluminescencji.