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Factors affecting the increase of follicle-stimulating hormone in women with cardiovascular pathology

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Summary

A number of scientific studies have shown that elevated levels of follicle-stimulating hormone (FSH) greater than 25 IU/L act as a marker of women's reproductive age. In this article we show the influence of cardiovascular risk factors on the likelihood of increasing the FSH above 25 IU/L. The study was conducted with 160 women with an average age of 52 years (SD 45–59). All patients had the content of sex hormones determined (FSH, prolactin, estradiol, testosterone, and progesterone) and serum aldosterone by enzyme immunoassay. Among the patients included in this study, hypertension was detected in 105 patients (65.6%); history of myocardial infarction – in 38

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(23.7%); heart failure – in 101 (63.1%); smoking – in 35 (21.9%). SPSS 21, a computer program for Windows XP, was used for statistical analysis of results. To predict the likelihood of increasing the FSH to more than 25 IU/L under the influence of various parameters, the method of binary logistic regression was used. A number of factors that significantly affect the risk of increasing the FSH levels greater than 25 IU/L were identified, and the mathematical method for predicting an increase in FSH more than 25 IU/L was developed. A statistically significant effect on the potential of increasing the FSH more than 25 IU/L was exerted by patient's age; presence of hypertension and diabetes; cholesterol, estradiol, and prolactin levels, and statin therapy. The model was statistically significant; the value of Nagelkerke's R squared was 0.704. This was appropriate for predicting the onset of reproductive aging and the development of intermediate and late complications of menopause.

Keywords

Menopause, perimenopause, cardiovascular risk, follicle-stimulating hormone

Introduction

Follicle-stimulating hormone (FSH) is one of the earliest markers of women of reproductive age. Increased levels of FSH in the blood appear a few years before menstrual dysfunction and reduction in estradiol [1]. A number of publications show the relationship between FSH level and various factors of cardiovascular risk. It has been demonstrated that in women with retained menstrual function, elevated FSH was associated with the formation of an unfavourable lipid profile. In patients with FSH levels more than 7 IU/L on the 3rd day of the menstrual cycle, levels of total cholesterol and low-density lipoprotein (LDL) cholesterol were significantly higher than in patients with FSH levels less than 7 IU/L. It should be noted that in this study, estradiol levels in groups of patients with varying FSH were not significantly different [2]. A positive correlation between the FSH levels and intima-media thickness (IMT) in patients during perimenopause has been revealed, while there were no established links between IMT and levels of estradiol and testosterone [3]. In the same study, a positive correlation between the FSH levels and the homeostasis model assessment (HOMA) index was revealed, which also was not confirmed for estradiol and testosterone. The relation between the FSH levels and adventitia diameter was found in the sufficiently large SWAN (Study of the Women Health Across the Nation) study which persisted even after normalization of data on the level of estradiol [4]. The study shows an increase in HOMA index with an increase in FSH, although the authors have linked impaired glucose tolerance with the severity of menopause symptoms [5].

Thus, the change of the FSH during natural menopause is associated with a variety of cardiovascular risk factors. It should be kept in mind that natural menopause, an increase in atherogenic cholesterol fractions, and the development of diabetes are the processes associated with aging. Perhaps not only natural menopause is a risk factor for cardiovascular disease, but also the presence of cardiovascular disease contributes to female reproductive aging.

The aim of this study was to examine the factors of cardiovascular risk in women during perimenopause and to distinguish those factors that have the most significant effect on the risk of increasing the FSH levels.

Materials and Methods

We have conducted a cross-sectional study with participation of 160 female patients during their perimenopause. A gynecologist examined all women to rule out genital diseases and to confirm the nature of the natural perimenopause.

The study excluded patients with acute coronary syndrome, the New York Heart Association (NYHA) functional class III-IV heart failure, severe hypertension (blood pressure 180/110 mmHg), violations of a hormone-producing function of the thyroid gland, gastric and duodenal ulcers, diseases limiting life expectancy to 1 year, the duration of menopause more than 5 years, surgical menopause. To verify the coronary heart disease (CHD), the data of stress tests, coronary angiography or a history of Q wave myocardial infarction were used.

All patients had a standard examination, which included a physical examination, general clinical blood and urine tests, ultrasound scan of the heart, and electrocardiography. To assess the lipid metabolism, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were determined. All biochemical investigations were carried out in the Laboratory of Immunological and Biochemical Research Methods with Immunohistochemistry of the National Institute

of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine.

All patients had their serum FSH determined by using enzyme immunoassay with reagent kit of Gonadotropin EIA-FSH produced by Alcor Bio (Russian Federation). To determine progesterone, Progesterone-EIA was used, prolactin – Prolactin EIA, testosterone – Testosterone EIA. All these reagents were produced by XEMA (Russian Federation). Estradiol was determined using the Estradiol ELISA kit produced by DRG Instruments GmbH (Germany). Contents of aldosterone in blood plasma were determined using the Aldosteron ELISA reagent kit produced by DRG International Inc. (USA).

The semi-automatic immunoassay analyzer Immunochem-2100, 2012 p., №501322057FSE was used for the analysis.

The study protocol was approved by the local Ethics Committee of the National Institute of General Practice named after Maloy L.T. of the National Academy of Medical Sciences of Ukraine.

Patients, included in the study, were divided into two groups: in group 1, FSH levels were less than 25 IU/L (n=76) and in group 2 – more than 25 IU/L (n=84). This FSH level was chosen in accordance with the classification of the menopausal transition, STRAW +10 (Stages of Reproductive Aging Workshop +10) [1].

The computer program SPSS 21 for Windows XP was used for the statistical analysis of the results. Descriptive statistics, the Mann–Whitney U test, and logistic regression were also used. To test for normality, the Kolmogorov-Smirnov test was conducted. To predict the likelihood of FSH increasing greater than 25 IU/L under the influence of various parameters, there was used binary logistic regression.

In addition to the selection of factorial signs, their reduction was carried out which was aimed at improving the quality of statistical model and contributed to clearer interpretation of the results and possibilities of using it. At the second stage, the created model was tested from the point of its statistical significance and the possibility of practical use of the results of the conducted work was considered.

Results and discussion

Patients in the group 1 were significantly younger than patients in the group 2 (P=0.03). There were no significant differences between the groups on such parameters as a menopause age, levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), left ventricular ejection fraction (EF) and body mass index (BMI) (Table 1).

The clinical characteristics of included in the study patients presented in table 2. In the group 2 (FSH>25 IU/L), there were significantly less patients with type II diabetes. Also in the group 2 significantly greater number of patients experienced hot flashes from 10 to 20 times per day. At the same time, the groups did not differ significantly in the number of patients with less than 10 and more than 20 times of tides per day. In the group 2, also significantly more patients had two abortions. Groups did not differ significantly in the number of patients with 1 abortion as well as 3 or more.

Levels of cholesterol and its fractions were not significantly different in the groups investigated. When comparing hormonal status in groups, estradiol and progesterone levels differed significantly (Table 3).

To identify the predictors that may have a potential impact on the risk of changing the FSH level, the following factors were used: age, the changing nature of menstruation, hypertension, presence of heart failure, functional class of heart failure, the presence of angina, functional class of angina, the presence of diseases of the cardiovascular system (hypertension + CHD + heart failure), smoking, history of cardiac revascularization, type II diabetes, levels of SBP and DBP, HR, BMI, history of myocardial infarction, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, TG), SCORE level, EF, the presence of left ventricular hypertrophy, levels of sex hormones in blood (prolactin, estradiol, testosterone), blood al-

Table 1. **Characteristics of patients according to the level of follicle stimulating hormone in groups**

Parameters	FSH<25 (n=76)	FSH≥25 (n=84)	Mann-Whitney U, (*P*)
Age, years	49 [45.00–52.00]	55.00 [49.00–59.00]	399.5, (0.03)
BMI, kg/m^2	28 [24.00–32.00]	28.00 [26.00–31.65]	617.0, (0.54)
Menopause age, years	49 [45.00–51.00]	50.00 [49.00–53.00]	86.5, (0.19)
SBP, mmHg	125 [110.00–150.00]	130.00 [110.00–140.00]	645.0, (0.76)
DBP, mmHg	80 [71.25–90.00]	80.00 [70.00–90.00]	618.0, (0.54)
HR, beats per minute	74.50 [65.50–83.00]	71.00 [65.00–80.50]	641.0, (0.73)
EF, %	61.50 [55.25–66.00]	63.00 [59.00–66.00]	582.0, (0.32)

Table 2. **Clinical characteristic of patients, depending on the level of follicle stimulating hormone**

Parameters		FSH<25 (n=76)	FSH>25 (n=84)	$\chi 2$, (*P*)
Hypertension		51 (67.1%)	54 (64.3%)	0.14, (0.710)
History of myocardial infarction		17 (22.4%)	21 (25.0%)	0.50, (0.480)
NYHA functional class I heart failure NYHA functional class II heart failure NYHA functional class III heart failure		15 (19.7%) 26 (34.2%) 7 (9.2%)	18 (21.4%) 30 (35.7%) 5 (5.9%)	0.07, (0.790) 0.04, (0.840) 0.61, (0.430)
NYHA functional class II stable angina NYHA functional class III stable angina		17 (22.4%) 4 (5.3%)	17 (20.2%) 5 (5.9%)	0.11, (0.740) 0.04, (0.850)
Cardiovascular disease (CVD)*		51 (67.1%)	60 (71.4%)	0.35, (0.550)
Revascularization		14 (16.3%)	11 (13.1%)	0.86, (0.350)
Menopause		24 (31.6%)	60 (71.4%)	25.41, (0.003)
Smoking		20 (26.3%)	15 (17.9%)	1.67, (0.200)
Diabetes		15 (19.7%)	5 (5.9%)	6.93, (0.009)
Tides, per day	Up to 10 10–20 >20	31 (40.8%) 13 (17.1%) 8 (10.5%)	26 (30.9%) 32 (38.1%) 13 (15.5%)	1.68, (0.190) 8.70, (0.003) 0.86, (0.350)
Births	1 2 3	40 (52.6%) 28 (36.8%) 2 (2.6%)	48 (57.1%) 28 (33.3%) 2 (2.4%)	0.33, (0.570) 0.22, (0.640) 0.24, (0.620)
Abortions	1 2 >3	23 (30.6%) 7 (9.21%) 8 (10.5%)	18 (21.4%) 17 (20.2%) 6 (11.9%)	1.63, (0.200) 7.85, (0.005) 0.24, (0.600)
Myoma		20 (26.3%)	33 (39.3%)	3.03, (0.082)
ACE-inhibitor therapy		47 (61.8%)	48 (57.1%)	0.71, (0.210)
Therapy with beta-adrenergic receptor antagonists		27 (35.5%)	23 (27.4%)	0.21, (0.141)
Statin therapy		54 (71.1%)	51 (60.7%)	0.51, (0.133)
Aspirin therapy		22 (28.9%)	29 (34.5%)	0.40, (0.641)
Therapy with calcium channel antagonists		17 (22.4%)	13 (15.5%)	0.21, (0.551)

* CVD (hypertension + CHD + heart failure)

Table 3. **Parameters of lipid metabolism, sex hormones and aldosterone depending on the level of follicle stimulating hormone**

Parameters	FSH<25 (n=76)	FSH>25 (n=84)	Mann-Whitney U, (*P*)
Total cholesterol, mmol/L	4.96 [4.49–5.69]	5.33 [4.52–5.91]	627.00 2508.00, (0.394)
TG, mmol/L	1.10 [0.90–1.56]	1.36 [1.03–1.75]	2322.00, (0.117)
LDL cholesterol, mmol/L	3.15 [2.35–3.65]	3.16 [2.47–3.60]	2696.00, (0.896)
HDL cholesterol, mmol/L	1.28 [1.12–1.49]	1.23 [1.03–1.52]	2510.00, (0.398)
Prolactin, nmol/L	240.88 [161.10–350.80]	205.08 [161.37–256.58]	2256.00, (0.069)
Testosterone, nmol/L	0.45 [0.32–0.88]	0.48 [0.34–0.63]	2712.00, (0.945)
Progesterone, nmol/L	3.50 [2.46–5.61]	3.45 [2.62–4.11]	2228.00, (0.054)
Estradiol, pg/mL	103.05 [48.67–175.63]	38.87 [31.26–57.37]	1208.00, (0.0001)
Aldosterone, pg/mL	291.87 [241.22–326.60]	292.78 [245.87–356.07]	2518.00, (0.415)

dosterone levels, therapies with ACE-inhibitors, beta-adrenergic receptor antagonists, statins, calcium channel antagonists, and aspirin. All indicators were coded and placed according to 32-dimensional vector, which takes into account the absence, presence, direction and magnitude of each indicator.

When estimating the regression equations, a method of stepwise inclusion of predictor variables was used, which ranks the features according to their contribution to the model. The result was to construct the regression function, which included 7 indicators: X_1 – age; X_2 – presence of hypertension; X_3 – pres-

ence of diabetes; X_4 – statin therapy; X_5 – an increase in cholesterol more than 5.2 mmol/L; X_6 – estradiol level of less than 11 and more than 65 pg/mL; X_7 – prolactin level.

Taking into account the considered indicators, a logistic regression equation was composed, according to which the probability of increasing the FSH levels of more than 25 IU/L was determined

$$\hat{P} = \left[\frac{1}{1 + \exp^{-(0.314 \cdot X_1 - 3.867 \cdot X_2 - 2.986 \cdot X_3 - 1.534 \cdot X_4 + 1.989 \cdot X_5 - 4.847 \cdot X_6 + 2.460 \cdot X_7 - 3.877)}} \right]$$

Where $\hat{P}$ – the likelihood that FSH exceeds 25 IU/L; X_1 – age; X_2 – presence of hypertension; X_3 – presence of diabetes; X_4 – statin therapy; X_5 – increase in cholesterol more than 5.2 mmol/L; X_6 – estradiol level of less than 11 and more than 65 pg/mL; X_7 – prolactin level.

The model itself and its individual coefficients are statistically significant; the value of Nagelkerke's R squared is 0.704. High quality model is confirmed by the calculated value of chi-square (χ^2 =55.051) and almost zero probability (P=0.001) to confirm the null hypothesis.

During the assessment of available publications, we found that there is not much research on the effects of diseases of the cardiovascular system on indicators reflecting female reproductive aging. It was shown, in a small Polish study conducted by Ablewska U. *et al.*, that patients with hypertension have higher FSH levels, although these differences were not statistically significant. The study was conducted with the participation of young patients with myocardial infarction. In this study, FSH levels were slightly lower in the group of patients with myocardial infarction than in the group of healthy women. The observed differences were not statistically significant [6]. In the Hussein Z. and Al-Qaisi J. study, the lower FSH levels were identified in women with type II diabetes [7]. One possible explanation of the lower FSH levels in patients with diabetes is relatively high estrogen levels. An indirect confirmation of the relative hyperestrogenia in patients with diabetes is more frequent development of hyperplastic etsrogen-dependent processes [8,9,10,11,12]. There are almost no articles about the effect of BP on the FSH level. Several authors have demonstrated a link between the level of sex hormones, menopause and an increase in BP [13,14,15]. At the same time in one of the largest studies, SWAN, which was looking into the influence of hormonal changes during menopause on cardiovascular risk, an increase in BP was not seen as a change associated with changes in hormonal status. A rise in BP was classified by authors' as an influence of chronological aging [16].

A special place is occupied by such factor as statin therapy. There is no evidence in publications on the ability of statins to influence the age of menopause. It is known that statins reduce cholesterol which is the precursor of sex steroids. At the same time the metabolism of simvastatin and atorvastatin, as well as estradiol is associated with cytochrome P450, and they all compete for it. Theoretically, estradiol levels may increase in patients receiving statin therapy. At the same time, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) showed that during therapy with statins and exogenous sex steroids, plasma estradiol levels did not change significantly [17]. It should be noted that most of the patients in this study received pravastatin. In a small pilot study, conducted on animals, it has been shown that statins can reduce the number of hot flashes. The authors attributed this effect to the influence on nitric oxide system and not reaction with hormones [18]. It was not also revealed any significant effect of simvastatin on the levels of estradiol and estrone in patients with breast cancer [19]. Apparently, the effect of statins, which was revealed in our study, on the risk of increasing FSH is not related to the estradiol level. Some confirmation of our findings is evident in the study conducted by Rashidi B. et al. The authors have studied the effect of simvastatin therapy on the efficacy of exogenous human chorionic gonadotropin therapy in patients with polycystic ovaries. It was found that patients in the group treated with simvastatin for 8 weeks had a higher level of maturation of oocytes, higher levels of fertilization and pregnancy [20].

We have also revealed the influence of prolactin levels on the risk of increasing the FSH. It has been established that prolactin is usually reduced in the second year after menopause [22]. The changes of prolactin in this study did not depend on receiving exogenous sex steroids by patients.

Conclusion

Thus, we have identified a number of factors that may influence the risk of increasing the FSH levels greater than 25 IU/L. Of all the evaluated factors, the most statistically significant effect on the probability of increasing the FSH more than 25 IU/L includes age, presence of hypertension and diabetes, levels of cholesterol, estradiol and prolactin, and statin therapy. This method of calculation of the risk of increasing

the FSH can be used to predict the onset of reproductive aging and the development of medium- and long-term complications of menopause.

Conflict of interest: None declared

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