

Characteristics of the hormonal background in women with abnormal uterine bleeding and extragenital disorders

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ABSTRACT

Aim: To establish the peculiarities of the hormonal background in women with abnormal uterine bleeding and extragenital disorders.

Materials and Methods: The study involved examination of 100 women of reproductive age with concomitant ED and AUB (MG). CG included 50 healthy women. MG women were additionally divided into subgroups depending on the detected pathological changes in the uterine cavity. When examining the hormonal status, concentrations of FSH, LH, estradiol, progesterone, and leptin in BS were determined. Additionally, the level of 25-hydroxyvitamin D (25-OH D) was determined.

Results: The decrease in FSH level in subgroups of GP, PSL, EH, EHL was 1.8-2.4 times (KWT, $p < 0.01$). LH in BS of MG patients was statistically lower than that of CG patients (MWT, $p = 0.0083$). The lowest level of LH was registered in patients with EHL, which was 2 times lower than this indicator in CG. A statistically significant increase in the level of estradiol was registered in 73% of MG patients (MWT, $p = 0.044$). The lowest level of progesterone was registered in patients with EHL - 8.40, which is 4.7 times lower than in CG (MWT, $p = 0.0021$). A statistically significant increase in the level of leptin in BS was observed in MG patients (KWT, $p = 0.0021$). The highest level of leptin was found in women with AFP, 2.3 times higher than CG indicators. A statistically significant correlation between the level of leptin and BMI ($r = 0.86$, $p = 0.011$) and a statistically significant ($p = 0.023$) correlation between the level of leptin and estradiol in BS of patients of the examined groups ($r = 0.42$) were revealed. In 87% of MG women, vitamin D deficiency was observed in BS (KWT, $p = 0.03$). A statistically significant ($p = 0.01$) negative correlation between the level of estradiol and vitamin D in the BS of female patients was revealed ($r = -0.61$, $p = 0.01$).

Conclusions: Women of reproductive age with AUB and ED were found to have disorders in the hypothalamic-pituitary-ovarian system. Most patients are characterized by an elevated level of leptin, the concentration of which is closely correlated with BMI, and an elevated level of estradiol is correlated with the level of vitamin D.

KEY WORDS: abnormal uterine bleeding, extragenital disorders, hormonal status, vitamin D level

INTRODUCTIONS

The problem of preserving the reproductive health of women of reproductive age is relevant both throughout the world and in Ukraine, which is associated with a significant increase in the level of gynecological morbidity in this population of women [1].

AUB is a debilitating symptom that affects up to one third of women of reproductive age [2]. According to foreign researchers [3], this condition is the most common disorder in women of reproductive age, the fourth most common reason for referral to gynecological services. Approximately 20% of 1.2 million visits to specialized gynecological services are related to this disorder [4].

AUB most often does not threaten life, but significantly reduces its quality [5]. It is reported that throughout the world the prevalence of AUB is observed within fairly wide limits from 3 to 52%. Such a discrepancy can be explained by a slightly different interpretation of the specified disorder and evaluation system: subjective or objective [4,6]. Subjective assessment is most likely to show a higher prevalence of AUB versus objective assessment, as it is based on the woman's personal perception of bleeding. Studies have found that women with AUB score below the 25th percentile on health-related quality of life scores when compared to the general female population of the same age [7]. Menstrual cycle impairments affect

all aspects of a woman's life, even increasing the risk of premature death [8]. Women with AUB are more likely to seek medical care due to social and physical factors [9], while 50% of female patients have mental health problems due to anxiety and depression [10].

Structural causes of uterine bleeding increase with increasing reproductive age and can affect reproductive health. Women in high-income countries on average decide to postpone childbirth [11]. Therefore, structural changes of the myometrium, such as uterine myoma, can have a negative impact on reproductive outcomes, reduce the probability of natural conception and reduce the success of assisted reproductive methods, even contributing to pregnancy complications [12].

AUB can also be caused by extragenital disorders (ED). This is explained by the features of the endometrium, which significantly depends on changes in the general hormonal status of a woman, which is largely influenced by the functional state of some organs and systems [13]. AUB can result from thyroid dysfunction, uncontrolled diabetes, obesity, blood coagulation disorders (most often von Willebrand's disease), infectious diseases, taking certain medications (corticosteroids, antipsychotics or antiepileptics), climate change and nutrition, psychological stress, etc. [14].

Individuals with this disorder often form a group, which leads to significant problems with the choice of individual treatment. Therefore, scientific research on the assessment of hormonal status, vitamin D level will allow to identify a certain group of patients in accordance with the principles of personalized medicine and will contribute to more effective treatment. Solving these problems will help improve the quality of life of women and avoid invasive surgical treatment.

AIM

To establish the peculiarities of the hormonal background in women with abnormal uterine bleeding and extragenital disorders.

MATERIALS AND METHODS

The research was conducted in the Communal non-profit enterprise "Kharkiv Maternity Hospital No. 1" of Kharkiv City Council. The study involved 100 women of reproductive age with accompanying extragenital disorders, who sought help for AUB and made up the main group (MG). Control group (CG) included 50 women of reproductive age who visited

the clinic for a prophylactic examination. The most common extragenital disorder were circulatory, endocrine and digestive diseases. Moreover, 12 patients (12%) were simultaneously diagnosed with hypertension and obesity, 5 (5%) with obesity and varicose veins, 11 (11%) with neurocirculatory dystonia and chronic gastritis, and 10 (10%) with obesity and diabetes, 3 (3%) had chronic gastritis and obesity [15]. MG women were further divided into subgroups depending on the detected pathological changes in the uterine cavity: endometrial polyp (EP) (glandular polyp (GP), adenofibromatous polyp (AFP), submucous leiomyoma (SL), endometrial polyp and submucous leiomyoma (PSL), endometrial hyperplasia (EH), endometrial hyperplasia in combination with submucosal leiomyoma (ESL) [16].

To determine the state of the endocrine function of the pituitary gland and ovaries, the level of gonadotropic and steroid hormones in blood plasma was established. When examining the hormonal status of the women of the studied groups, concentrations of LH, FSH, progesterone, estradiol in blood serum (BC) were determined by enzyme-linked immunosorbent assay (ELISA) using standard "Biointernational" test kits, France. Leptin was determined in BS by solid-phase ELISA, NTI Immunochem 2100 analyzer, using DRG Leptin ELISA Kits. 25-hydroxyvitamin D ((25-OH)D) was determined in BS by the competitive ELISA method using a luminescent reagent (Siemens Healthcare Diagnostics (Germany) on an Atellica IM 1600 analyzer (Germany).

Methods of statistical analysis. For statistical data processing, the general-purpose data processing software package "Statistica for Windows" was used.

Median and mean values were employed to present the data as measures of location; standard deviation and quartiles as measures of dispersion; minimum and maximum value as indicators of sample size.

The Kruskal-Wallis test was used as a non-parametric method of comparing independent groups, the Mann-Whitney test was used to compare two independent groups, and the Spearman correlation coefficient was used to assess the closeness of the relationship between indicators.

RESULTS

Conducting an exploratory analysis of a group of variables using the Kruskal-Wallis rank test (KWT) demonstrated the presence of a statistically significant dependence on the group ($p < 0.05$) of all the indicators used. That is, the analysis of indicators in groups is appropriate and potentially informative.

Table 1. FSH level in women with AUB and ED, (mIU/ml)

Clinical groups	Statistical indicators						
	Average	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
GP	3.81	3.20	1.80	7.40	2.00	5.40	2.12
AFP	5.50	6.1	2.90	7.40	3.2	7.3	1.82
SL	4.88	5.30	2.00	6.40	4.30	5.90	1.37
PSL	3.30	3.00	1.90	7.10	2.70	3.50	1.24
EH	3.41	3.10	1.90	6.30	2.70	3.80	1.17
ESL	3.83	3.80	1.80	6.40	2.90	4.20	1.16
MG	7.35	7.15	3.60	10.70	6.40	8.40	1.54

Table 2. LH level in women with AUB and ED, (mIU/ml)

Clinical groups	Statistical indicators						
	Average	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
GP	3.61	3.00	1.90	6.30	2.70	4.90	1.43
AFP	3.34	3.70	1.90	4.20	2.00	4.20	0.97
SL	3.65	3.70	2.10	5.20	2.90	4.30	1.02
PSL	3.53	3.50	1.90	5.30	2.70	4.20	1.01
EH	4.10	3.70	2.20	6.30	3.10	5.20	1.18
ESL	3.35	2.95	1.90	6.10	2.50	3.80	1.24
MG	5.83	5.95	2.10	7.90	5.20	6.70	1.44

Data on the level of FSH in the BS of women of the main and control groups are shown in Table 1.

From these data, it can be seen that the characteristics of the central tendency and range of blood FSH levels of MG patients are generally lower than those of CG patients. The decrease in the level of this hormone in the subgroups of GP, PSL, EH, ESL was 1.8-2.4 times and had a statistically significant character (KWT, $p < 0.01$), while in the subgroup of patients with AFP and SL there is a tendency to its increase to normal.

Data on the level of LH in the BS of women of the main and control groups are shown in Table 2.

From the given data, it can be seen that LH in the BS of MG patients is statistically lower than that of patients in the control group (Mann-Whitney test (MWT), $p = 0.0083$). Thus, the lowest level of this hormone occurred in patients with SL and was 2 times lower than this indicator in CG.

Data on the level of estradiol in the BS of women of the main and control groups are shown in Table 3.

A statistically significant increase in the level of estradiol was registered in 73% of MG patients (MWT, $p = 0.044$). The median value, as well as the levels of the minimum and maximum levels of this hormone in BS exceeded this indicator in the control group by 2.7-3.8 times.

Table 3. Estradiol level in women with AUB and ED, (pg/ml)

Clinical groups	Statistical indicators						
	Average	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
GP	345.98	385.40	200.30	400.50	296.30	397.90	68.56
AFP	282.37	275.40	223.10	390.70	226.40	345.90	64.87
SL	365.96	364.90	321.10	396.50	352.10	378.30	22.81
PSL	376.02	385.20	278.80	400.50	363.20	395.40	30.51
EH	297.71	289.60	214.90	399.50	256.40	344.80	56.17
ESL	316.05	311.30	211.80	405.30	276.80	368.40	60.23
MG	94.97	99.10	28.90	150.30	58.20	124.80	38.96

Table 4. Progesterone level in women with AUB and ED, (nmol/l)

Clinical groups	Statistical indicators						
	Average	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
GP	11.22	10.10	7.30	19.70	8.30	13.20	3.98
AFP	14.45	14.90	12.50	16.10	13.70	15.30	1.19
SL	16.84	17.50	12.50	19.20	14.60	18.90	2.50
PSL	14.40	15.10	9.70	17.20	12.70	16.30	2.24
EH	13.02	12.60	7.90	18.60	10.50	16.00	3.19
ESL	10.39	8.40	7.30	19.60	7.90	11.90	3.172
MG	47.21	39.75	15.60	90.10	29.50	64.50	22.53

Data on the level of progesterone in the BS of women of the main and control groups are shown in Table 4.

When examining the level of the hormone progesterone in the BS of MG patients, there is a statistically significant decrease in its level compared to the control group (MWT, $p=0.0021$). The lowest level of this hormone was registered in patients with ESL - 8.40, which is 4.7 times lower than in CG and in patients with GP - 10.10, which is 3.9 times lower than in CG. The highest level of progesterone is noted in patients with SL - 17.50, which is twice the level of this hormone in patients with ESL and 2.2 times lower than the level in CG.

Data on the level of leptin in the BS of women of the main and control groups are shown in Table 5.

A statistically significant increase in the level of leptin in BS was observed in MG patients (KWT, $p=0.0021$). The highest level of leptin is observed in women with AFP, 2.3 times higher than the control group.

The analysis of relationships revealed a statistically significant correlation between leptin level and BMI ($r=0.86$, $p=0.011$). In addition, a statistically significant ($p=0.023$) correlation was found between leptin and estradiol levels in the BS of patients of the examined groups ($r=0.42$).

Data on the level of vitamin D in the BS of women of the main and control groups are shown in Table 6.

Table 5. Leptin level in women with AUB and ED, (ng/ml)

Clinical groups	Statistical indicators						
	Average	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
GP	12.64	13.01	7.00	19.70	8.20	15.30	4.27
AFP	14.55	16.03	8.06	19.70	9.72	19.61	5.1
SL	11.71	9.06	6.80	18.04	7.60	16.05	4.83
PSL	12.51	13.65	6.30	18.09	8.65	16.05	3.93
EH	11.79	13.01	6.50	17.08	7.90	15.07	3.87
ESL	11.50	10.87	7.02	17.03	8.67	14.05	3.37
MG	7.88	6.78	3.63	15.07	5.07	10.06	3.42

Table 6. Vitamin D level in women with AUB and ED, (ng/ml)

Clinical groups	Statistical indicators						
	Average	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
GP	16.27	11.70	6.80	33.40	9.00	24.80	9.37
AFP	16.27	20.40	5.40	27.20	6.40	23.10	8.79
SL	23.54	19.43	11.00	41.07	13.80	37.80	12.42
PSL	15.70	10.50	6.35	32.80	8.60	23.80	9.51
EH	21.34	17.30	5.90	40.40	12.30	31.50	10.78
ESL	19.48	19.60	7.30	38.90	9.70	26.30	9.71
MG	39.85	37.85	26.70	70.40	32.80	43.10	9.56

In 87% of MG women, vitamin D deficiency was observed in BS, that is, its level was lower than 20 ng/ml, and in 13% insufficiency of this vitamin (20-29 ng/ml) (WMT, $p=0.03$). During the study, a statistically significant ($p=0.01$) negative correlation was found between the level of estradiol and vitamin D in the BS of patients of the examined groups ($r = -0.61$, $p=0.01$).

The conducted study showed that changes in the hormonal background were observed in patients with AUB and ED.

DISCUSSION

AUB refers to any irregular or unusual uterine bleeding that is not part of a woman's normal menstrual cycle. It can also indicate serious health problems. The modern theory of the pathogenesis of hyperplastic processes of the endometrium is based on the mechanisms of its estrogen stimulation. The main regulatory hormones in the endometrium are estrogens and progesterone, which can act directly or indirectly [17,18]. MG patients, on the background of hyperestrogeny, were

found to have insufficiency of the 2nd phase of the menstrual cycle.

The conducted research showed that changes in the hormonal background were observed in patients with AUB and ED. A decrease in the levels of FSH, LH, and progesterone was noted against the background of hyperestrogenemia and hyperleptinemia. The lowest levels of these hormones were registered in patients with PSL (FSH - 3.00 mIU/ml), with ESL (LH - 2.95 mIU/ml, progesterone - 8.40 nmol/l). The highest levels of estradiol (385.4 pg/ml) were determined in patients with GP. An elevated level of leptin was characteristic of most MG women (the highest in patients with AFP - 16.03 ng/ml), and its concentration was closely correlated with BMI ($r=0.86$, $p=0.0192$). In 87% of MG women, vitamin D deficiency was observed in BS, and in 13% insufficiency of this vitamin. Correlational dependences were determined between the level of leptin and estradiol ($r=0.42$, $p=0.0021$), estradiol and vitamin D ($r= -0.61$, $p=0.044$).

Therefore, leptin levels increased in MG women. The determined correlation between the level of leptin and estradiol, estradiol and vitamin D indicated that the examined women had a metabolic syndrome with additional synthesis of estrogens in adipose tissue and vitamin D deficiency in BS.

In the last decade, more and more literary data are found, which say that adipose tissue is one of the most important endocrine organs. [19,20] Adipose tissue is capable of producing many hormone-like substances, including leptin [21]. The main functions of these substances are the regulation of eating behavior, energy metabolism, control of the functional activity of the cardiovascular system, regulation of the processes of oncogenesis and metastasis [22,23]. Currently, adipose tissue cells are considered as endogenous regulators and modulators of reproductive system functions [24,25].

According to Lebrethon M. C. et al., leptin is a "tissue hormone" that takes part in the regulation of appetite, secretion of gonadotropin-releasing hormones (GRH) by the hypothalamus and gonadotropins by the pituitary gland. Leptin affects the sensitivity of gonadotrophs to GRH, stimulates the release of LH and FSH by gonadotrophs [26]. J. Kitawaki et al. obtained data on the stimulating effect of leptin on the synthesis of estrogens directly through the activation of aromatase in granulosa cells [27].

Vitamin D deficiency has become a problem today due to its increased prevalence among women of reproductive age [28]. Recently, much attention has been paid to the study of the relationship between vitamin D and the characteristics of the menstrual cycle of women. [29]. Thus, a study by K. Łagowska [30] demonstrated the relationship between the frequency of menstrual disorders and low levels of vitamin D in women. Vitamin D controls estrogen biosynthesis and directly regulates the aromatase gene [31].

CONCLUSIONS

In women of reproductive age with AUB and ED, there are impairments in the hypothalamic-pituitary-ovarian system: a decrease in the levels of FSH, LH, progesterone against the background of hyperestrogenemia, hyperleptinemia, and a reduced level of vitamin D. Most patients are characterized by an increased level of leptin, the concentration of which is closely correlated with BMI, and the increased level of estradiol correlates with the level of vitamin D. So, menstrual function is to some extent related to the content of leptin and its relationship with estrogens and the level of vitamin D in blood serum, which is an important link in the pathogenesis of AUB against the background of ED.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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