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IDENTIFICATION OF THE RELATIONSHIP OF BIOCHEMICAL CHANGES IN WOMEN WITH PREMATURE OVARIAN FAILURE WITH BODY MASS INDEX, LIVER DISEASE AND ANEMIA

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Keywords: BMI, fatty hepatosis, ovarian aromatase, AMH, ovarian reserve.

Relevance. Premature ovarian insufficiency (POI) - occurs in 1% of women under the age of 40. A typical manifestation of this syndrome is episodic or stable hypergonadotropic amenorrhea. It is diagnosed in approximately 10-28% of women with primary amenorrhea and in 4-18% of women with secondary amenorrhea. The purpose of our study was to identify the relationship between BMI and the above-mentioned biochemical markers, and, accordingly, with the number of follicles in POI.

Materials and methods of examination. The patients of the main group (n=92) were divided into two groups: the first group (n=49) included patients with POI who underwent surgery with a decrease in ovarian reserve; the second group (n=43) included patients with POI, without surgery, but with a decrease in ovarian reserve.

Results and discussion. The conducted studies showed that in women with STD of the 1st group with surgical interventions, the FSH content was 1.7 times higher than the values of the control group, In patients of the 2nd group we also observed an increase in the level of FSH by 1.58 times relative to the values of the control group. The most common secondary diseases were iron deficiency anemia (IDA - 33.3%), and fatty hepatosis (31.1%). 17.8% of patients were found to have endemic goiter (hypothyroidism), and they also suffered from cholelithiasis and cholestecitis (GI). In the control group, 20% of people suffered from endemic goiter, 10% - iron deficiency anemia, and 70% were practically healthy.

Conclusion. Comparison of the distribution of the results of biochemical markers of patients depending on their secondary disease showed that only in ovarian aromatase (between endemic goiter and fatty liver hepatosis; between endemic goiter and cholelithiasis) inhibin B (between fatty liver hepatosis and cholelithiasis) and estradiol (between all groups except fatty liver hepatosis and cholelithiasis) statistically significant differences were found.

Relevance. Premature ovarian failure (POF) occurs in 1% of women under the age of 40 (1,2,3,4). A typical manifestation of this syndrome is episodic or stable hypergonadotropic amenorrhea. It is diagnosed in about 10-28% of women with primary amenorrhea and in 4-18% of women with secondary amenorrhea (5,6). It is known that the metabolic syndrome, especially insulin resistance and obesity, play an important role in the development of the pathogenesis of POF and primary ovarian failure. Many obese patients with POI are insulin resistant and hyperinsulinaemic, especially in those with an abdominal phenotype.Briefly, an increase in adipose tissue mass, in particular visceral fat depot, increases the availability of several metabolites (e.g., free fatty acids, lactate, etc.) that can influence insulin secretion and metabolism, as well as its peripheral action [3, 4.5]. But the main induced mechanism of insulin resistance in obesity is a chronic inflammatory process [6,7,8]. In chronic inflammation, by increasing the amount of pro-inflammatory cytokines, in particular the cytokine TNF-α, by increasing the expression of stress-dependent kinase - c-jun N-terminal kinase (JNK), inhibits the activation of the insulin receptor by phosphorylation [9,10]. Insulin, acting through its

receptor, promotes androgen biosynthesis in the ovaries and adrenal glands, increasing luteinizing hormone (LH)-induced androgen production by theca cells and leading to hyperandrogenemia. Hyperinsulinemia can also activate insulin-like growth factor-1 (IGF-1) receptors, which are potent stimulators of LH-induced androgen synthesis and suppression of hepatic IGF-binding protein 1 (IGF-BP1) production. In a normal menstrual cycle, the granulosa cells of the dominant follicle become sensitive to LH in the middle of the follicular phase at a follicle diameter of 10 mm. In the preovulatory phase, LH enhances the synthesis of steroids, thereby triggering the terminal differentiation of granulosa cells, which leads to a stop in the growth of follicles. On the other hand, hyperinsulinemia leads to premature activation of granulosa cells, and LH induces terminal differentiation, which leads to arrest of follicle growth [1,2,7]. Insulin resistance and estrogen deficiency are associated comorbidities. Insulin resistance and compensatory hyperinsulinemia provoke an increase in androgen synthesis due to a decrease in estrogen production. As mentioned earlier, estrogens inhibit follicular apoptosis, so estrogen deficiency can lead to increased follicular apoptosis, thereby causing premature ovarian failure.

The purpose of our study was to identify the relationship between BMI and the above biochemical markers, and, accordingly, with the number of follicles in POF.

Materials and methods of examination. Currently, the activity of total aromatase in various tissues is determined by a radiometric method based on the conversion of tritium-labeled androstenedione to "heavy water" and tritium-labeled androstenedione to estrone. It is possible to determine the expression of aromatase in tissues using immunohistochemical analysis [4,6,8]. Often, real-time PCR is combined with reverse transcriptase PCR to measure small amounts of messenger RNA.A method for assessing the activity of aromatase or cytochrome P450 isoform is described, with the help of which the total aromatase activity can be measured by protein immunoblotting [2,3]. This is the method we used to evaluate aromatase activity. In accordance with the purpose and objectives of this study, we studied patients with premature ovarian failure. The patients of the main group (n=92) were divided into two groups: the first group (n=49) included patients with POI who underwent surgery with a decrease in ovarian reserve; the second group (n=43) included patients with POI, without surgery, but with a decrease in ovarian reserve. In the first group, 65% of patients had one ovary removed by surgery; the rest of the patients also underwent surgery, but without removal of the ovaries. In 22% of patients, various resection operations of one ovary were performed. Surgical interventions of both ovaries (2 times) were performed in 8.7% of patients, and uterine amputation was performed in 4.34% of them. In addition, in the control group, we collected 30 practically healthy women.

Results and discussion. Only in 4.44% of patients, BMI was within the normal range (18.5-24.9). In patients with a BMI of 25-19.9 and 30-34.9, there was no statistically significant difference in the volume of both ovaries and biochemical markers, with the exception of the results of aromatase and AMH ($p<0.05$). Using the AMH level, it can be concluded that, depending on the increase in body weight, the AMH level may decrease, which can lead to the entry of many preantral (primordial) follicles into active folliculogenesis (follicle recruitment), thereby causing premature depletion of the ovarian reserve. Interestingly, patients with a BMI of 30-34.9 had statistically higher aromatase results compared to patients with a BMI of 25-29.9. At the same time, the level of estradiol remained almost the same in both groups. In this case, we hypothesized that obese people are not able to convert androgen to estrogen in sufficient quantities due to the increase in aromatase. Probably, obesity can trigger signaling pathways that induce aromatase expression. It is known that obesity significantly increases the level of

tumor necrosis factor (TNF) in adipose tissue, aknown inducer of aromatase expression in adipose fibroblasts.Obesity can also increase levels of other local hormones such as prostaglandin E2 (PGE2), which are known to induce aromatase gene expression in breast adipose tissue and elsewhere [3,5].The most common secondary diseases were iron deficiency anemia (IDA - 33.3%), and fatty liver (31.1%). In 17.8% of patients, endemic goiter (hypothyroidism) was found, and they also suffered from cholelithiasis and cholestecitis (GSD). In the control group, 20% of people suffered from endemic goiter, 10% from iron deficiency anemia, and 70% were practically healthy.

To better understand the impact of secondary disease on POI, we compared these biochemical factors and ovarian volume in individual groups (see Table 1).

Table 1.

istribution of biochemical findings and ovarian volume in women with POI depending on their secondary disease

Parameters	Fatty hepatosis	IDA	Endemic goiter	GSD
Aromatase, ng/ml	7,91±1,13	6,43±0,98	4,01±1,2[a]	8,19±1,5[c]
inhibin B, pg/ml	53,68±5,83	47,1±6,6	55±8,4	36,3±4,6[a]
AMH, ng/ml	1,07±0,032	1,08±0,068	1,05±0,05	1,15±0,086
FSH, mIU/ml	9,77±0,278	10,4±0,48	9,7±0,23	9,08±0,23
Estradiol, pmol/l	38,76±1,6	32,2±2,13[a]	37,03±4,1[b]	46,56±2,8[abc]
Cytochrome P450, ng/ml	3,55±0,98	4,43±0,79	4,2±0,8	5,03±1,3
Right ovary, cm	2,94±0,12	3,14±0,113	3,14±0,11	3,05±0,156
Left ovary, cm	2,93±0,13	3,34±0,22	2,84±0,15	3,06±0,13

Instructions: a - statistical significance compared with the results of patients with fatty liver disease - $p<0.05$; b - statistical significance compared with the results of patients with IDA - $p<0.05$; c - compared with the statistical results of patients with endemic goiter - $p<0.05$.

Fatty liver disease is common in patients with POF. Obesity and insulin resistance are considered the main factors of fatty liver in POI. An excess of androgens can contribute to the rapid development of fatty liver [1,4]. As for the association of iron deficiency anemia with POI, iron deficiency anemia is one of the most common diseases in the

Uzbek population. The prevalence of iron deficiency conditions among adults and children, the importance of iron deficiency for the growth and development of children in the Republic of Uzbekistan. In our study, many women with POI also had iron deficiency anemia. The same can be said about endemic goiter, since the frequency of this disease was higher in the control group than in the main group. As for the increase in cholelithiasis (cholelithiasis) in patients with POI, it can be triggered by obesity (which also contributes to the development of POI and premature ovarian failure), since obesity increases the secretion of cholesterol into the bile, which can accumulate in the gallbladder and ultimately lead to to the formation of gallstones [3,9]. To better understand the impact of secondary disease on POI, we compared these biochemical factors and ovarian volume in separate groups.

When distributing patients into groups depending on their secondary disease, we found that in some groups there were differences only in some biochemical markers. In particular, women with secondary endemic gitera had the lowest aromatase (ovarian) scores, while women with gallstones had the highest aromatase (ovarian) scores. In addition, in relation to inhibin B, the results in patients with POI with cholelithiasis compared with women with fatty liver were almost 1.48 times lower ($p<0.05$). In addition, in women with POI with gallstone disease, the concentration in terms of estradiol ($p<0.05$) was the highest, while in patients with iron deficiency anemia it was the lowest ($p<0.05$). Relatively in other results, we could not find a statistically significant difference ($p>0.05$). At the end of the study, the number of follicles in the ovary decreased significantly compared to the control group, especially in the second group. In terms of the association between BMI and biochemical markers, statistically significant results were only between ovarian aromatosis and AMH results. In addition, the most common secondary diseases in women with POF were fatty liver disease, and iron deficiency anemia. Comparison of the distribution of the results of biochemical markers of patients depending on their secondary disease showed that only in ovarian aromatase of inhibin B and estradiol were found statistically significant differences.

Conclusion. In terms of the association between BMI and biochemical markers, statistically significant results were only in terms of ovarian aromatosis and AMH results. In addition, we found that the most common secondary diseases in women with POF were fatty liver disease and iron deficiency anemia. Comparison of the distribution of the results of biochemical markers of patients depending on their secondary disease showed that only in ovarian aromatase (between endemic goiter and fatty hepatosis of the liver; between endemic goiter and cholelithiasis) inhibin B (between fatty hepatosis of the liver and cholelithiasis) and estradiol (between all groups, except for fatty hepatosis of the liver and cholelithiasis), statistically significant differences were found.

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