BIOCHEMICAL AND HORMONAL METHODS FOR STUDYING THE CAUSES OF ENDOCRINE INFERTILITY IN WOMEN DEPENDING ON THE DEGREE OF OBESITY

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Abstract*. This article is devoted to the study of biochemical and hormonal studies of the causes of endocrine infertility in women, depending on the degree of obesity.*
Keywords*: obesity; metabolic and hormonal disorders; excess free fatty acids; menstrual dysfunction.*

Actuality of the problem. Over the past half century, obesity has become an epidemic in the developed world. In 2016, more than 1.9 billion adults over 18 years of age were overweight, of whom more than 650 million were obese (about 13% of the global adult population (15% of women)). The World Obesity Federation estimates that by 2025, the worldwide prevalence of obesity will exceed 21% among women [9,10]. The prevalence of obesity among the adult population of the Republic of Uzbekistan currently averages 31–34 per 1000 population, with significant differences in indicators depending on specific territories, and 50.1% of the population is overweight (BMI ≥25). The proportion of women (25.4%) with obesity is statistically significantly higher.

In 2016, more than 1.9 billion adults over 18 years of age in the world were overweight, of which over 650 million were obese (about 13% of the global adult population (15% of women)) [4,5]. According to the World Obesity Federation, by 2025 the prevalence of obesity worldwide will exceed 21% among women, and in some countries this figure will be much higher [6]. In Uzbekistan, 50.1% of the population is overweight (BMI ≥25 kg/m2), and a fifth (20.2%) is obese (BMI ≥30 kg/m2). The proportion of women (25.4%) with obesity is statistically significantly higher.

Among women, obesity increases significantly with age: obesity in the group of 18-29 years old is 7.3%, in the group of 30-44 years old – 22.9%, and in the group of 45-64 years old – already 38.7%. Excess weight negatively affects the reproductive health of women, since metabolic and hormonal disorders due to obesity or overweight in women of reproductive age disrupt the development of follicles, promote quantitative and qualitative defects of oocytes, disrupt fertilization and excess free fatty acids, can have a toxic effect on the reproductive health of women [7].

Dysfunction of the gonads is observed in 46-96% of obese women. This disorder is more pronounced in the neuroendocrine form of obesity. Moreover, the acceleration of the rate of puberty does not correspond to the rate of development of the genital apparatus (hypoplasia of the uterus, polycystic ovaries, hypofunction of the gonads, hypotrophy of the external genital organs) due to secondary damage to the diencephalic structures. Every fifth woman with the android morphotype experiences infertility, and every 4th has miscarriage [11, 12].

It is known that overweight women are statistically significantly more likely to experience irregular menstrual cycles compared to women with normal body weight. According to De Pergola

G, et al. (2009, 64.3% of obese patients had a regular menstrual cycle, 21.4% had oligomeric and amenorrhea, 14.3% had abnormal uterine bleeding. With the progression of obesity, the frequency of menstrual dysfunction increases by 6.1 times; this is due to changes in the extraglandular formation of estrone from androgens and inhibition of cyclic LH secretion. Perhaps obesity most affects the central mechanisms of regulation of reproduction [3, 7,20,21].

In connection with the above, we set a goal: to study biochemical and hormonal studies of the causes of endocrine infertility in women, depending on the degree of obesity. Material and research methods: For the period from 2021 to 2023, on the basis of the clinics of the Republican Scientific and Medical Center of Endocrinology named after Ya.Kh. Turakulova of the Ministry of Health of the Republic of Uzbekistan (director, MD Turaev F.F.), based on the city center of reproductive medicine and the clinic <Ayol Care>, 500 women with EB and obesity were studied at the age of 18-37 years, depending on BMI, who were were subjected to a full clinical, hormonal and imaging examination. Of these, 55 (11%) women with EB were selected depending on the degree of obesity (1st and 2nd degree). Group 1 consisted of women with 1st degree obesity (BMI=32.4±1.4), whose average age was 29.7±6.1 years, and 2nd groups were women with 2nd degree obesity (BMI=36.9±1. 2), whose average age was 30.8±5.9 years. Observation periods range from 3 to 12 months.

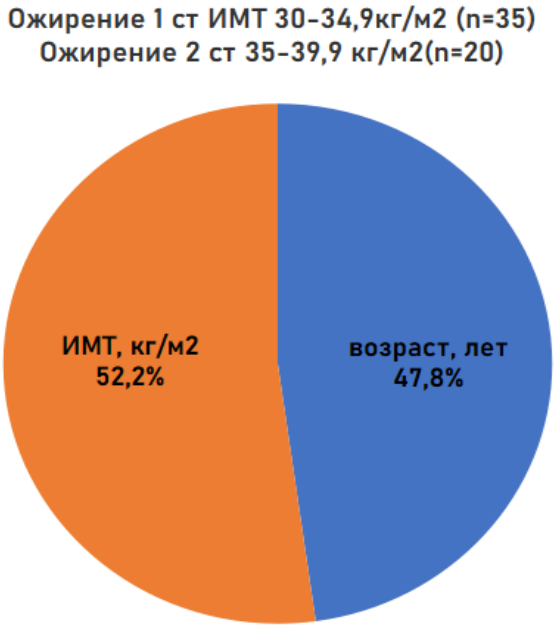

Figure 1. Distribution of patients by degree of obesity and age.

Inclusion criteria

• Age from 17 to 37 years

• Presence of infertility for 12 months or more, excluding all other causes

• Exclusion criteria

• Age over 37 years

• The presence of any endocrine pathology that aggravates fertile function (hypothyroidism, diabetes), etc.

• Presence of non-endocrine causes of infertility (tubal, peritoneal, uterine, cervical, immunological, psychosexual, unexplained)

• Couple infertility

• Women with hypothalamic-pituitary disorders and hyperprolactinemia

Research methods. Clinical and biochemical research methods, hormonal studies (blood serum), instrumental (ultrasound, radiological - MRI of the pituitary gland) and statistical methods were used.

The discussion of the results.

Reproductive function disorders are combined with changes in the neuroendocrine regulation of carbohydrate and fat metabolism in the form of various types of neuroendocrine disorders in women with metabolic disorders, often in the form of obesity [13,14,15, 16, 17, 18,19].

Table 1

Carbohydrate metabolism in women depending on the degree of obesity (n=55)

Index	Obesity 1st degree n=35	Obesity 2nd degree n=20	p
Glucose, mmol/l	5,53±0,45	5,74±0,45	0,10
Insulin, mU/ml	17,2±4,4	22,6±6,7*	0,001
HbAlc, %	5,61±0,63	6,15±0,63*	0,004
HOMA IR	4,26±1,24	5,75±1,77*	0,001

Analysis of carbohydrate metabolism showed (Table 1) that the level of insulin and glycated hemoglobin were significantly increased compared to the group of patients with 1 degree of obesity. The value of the HOMA-R insulin resistance index in patients with stage 2 obesity was significantly higher than the value of this indicator in the comparison group (p<05001).

table 2

Biochemical blood test of obese patients (n=55)

Index	Obesity 1st degree n=35	Obesity 2 degrees n=20	p
ALT, mmol/l	0,85±0,15	0,88±0,1	0,47
AST, mmol/l	0,44±0,09	0,43±0,09	0,62
Bilirubin, µmol/l	16,4±1,9	16,4±1,7	0,98
GGT, U/l	25,2±10,6	33,7±9,0*	0,004
Amylase, U/l	72,2±20,3	80±20,4	0,18

The biochemical blood test of patients with grade 1 and 2 obesity did not undergo significant changes in both groups (Table 2).

It is known that in obesity, menstrual dysfunction is observed 6 times more often, and primary infertility is 2 times more often than in women with normal body weight [8, 17,21]. During puberty, the incidence of menstrual irregularities in obese girls reaches 66.7% [7].

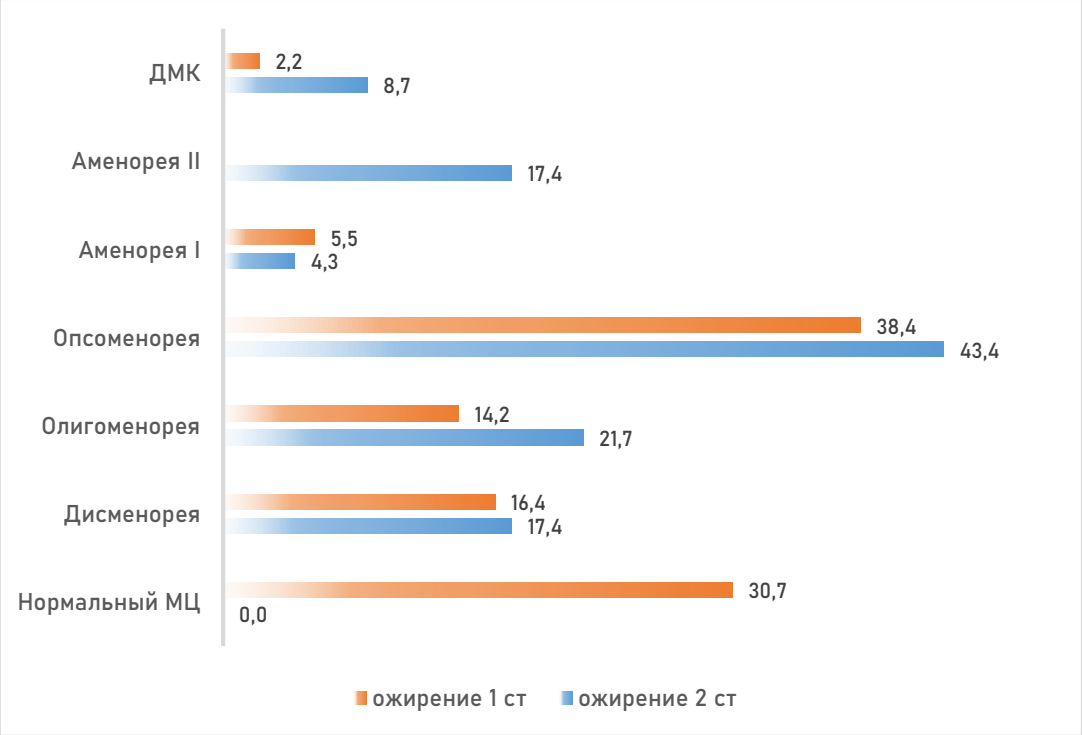

Figure 2. Characteristics of MF disorders in women with grade 1 and 2 obesity (n = 55)

Menstrual disorders manifested themselves mainly in the form of opsomenorrhea in 43.4%, oligomenorrhea in 21.7%. in patients with stage 2 obesity. Amenorrhea was present in 55.5% and 4.3%, respectively.

According to the literature, in obese women, a tonic increase in the level of estrogens, formed as a result of peripheral conversion of androgens, acts on the hypothalamus through a positive feedback mechanism, which leads to disruption of the cyclic secretion of GnRH and, as a consequence, gonadotropic hormones [12, 13,23] .

Hormonal status was studied in 55 patients with grade 1 and 2 obesity; the results of the study are presented in Table 3.

Table 3

Hormonal background of women depending on the degree of obesity (n=55)

Index	Obesity 1st degree n=35	Obesity 2 degrees n=20	p
Prolactin, ng/ml	29,6±12,3	28,2±11,5	0,67
FSH, mIU/l	12,1±9,4	13,9±9,7	0,50
LH, mIU/l	11,6±11,2	8,9±6,8	0,35
Estradiol, pg/ml	86,8±31,5	115,9±82,8	0,07
Progesterone 7 DMC, mg/ml	0,42±0,35	0,34±0,33	0,40
Testosterone, nmol/l	1,79±0,58	1,67±0,49	0,44

DHEAS, mcg/dl	2,05±0,82	1,34±0,53*	0,001
Cortisol, nmol/l	386±118,5	329,6±110,0	0,09
AMG, ng/ml	1,70±0,91	1,03±0,5*	0,01
17 OKS, ng/ml	0,79±0,21	0,83±0,13	0,49
Vitamin D, ng/ml	21,3±5,8	16,9±5,7*	0,01

Table 3 presents the indicators of gonadotropic hormones in the examined obese patients depending on the state of menstrual function and in women from the comparison group.

The table shows that in patients with grade 2 obesity with menstrual dysfunction (IMF), although LH levels were within normal limits, they were significantly higher than in women with grade 1 obesity with preserved menstrual function in the 1st phase of the cycle. With increasing age of obesity, the FSH indicator significantly increased. In a comparative analysis of FSH levels, no significant differences were found between the groups. DHEAS levels were significantly increased in the group with stage 1 obesity, and vitamin D was decreased in both groups. Analysis of AMH showed a significant decrease in both groups.

Recently, peptide hormones have attracted particular clinical interest in women with infertility. Some of these peptide hormones are follistatin and inhibin B, and numerous studies show the relationship between leptin and the female reproductive system. It is known that leptin is not only a hormone that informs the central nervous system of the level of energy reserves of the body, but also plays an important role in the formation and functioning of the reproductive system in women [1, 2, 3, 4,22].

Table 4

Analysis of neohormones in obese women of reproductive age (n=55)

Index	Obesity 1st degree n=35	Obesity 2 degrees n=20	p
Follistatin, pg/ml	1531±872,8	2269,7±1250,5*	0,01
Inhibin B, pg/ml	54,7±21,5	62,9±18,6	0,16
Activin, pg/ml	2,04±1,59	2,61±1,58	0,21
Relaxin, ng/ml	0,08±0,1	0,26±0,77	0,18
Leptin, ng/ml	13,2±5,4	17,7±3,6*	0,002

Analysis of the levels of neohormones, TGF and leptin showed the following. Follistatin levels were increased in both groups, but a significant increase was observed in women with grade 2 obesity compared with grade 1 obesity (P<0.01). Analysis of leptin levels in obese women depending on the type of adipose tissue deposition showed that with stage 2 obesity, the leptin level is significantly higher than in women of reproductive age with stage 1 obesity 17.7 ± 3.6 and

13.2 ± 5.46 accordingly, p <0.002. The levels of inhibin B and activin did not change significantly. We conducted a correlation analysis using the Pearson method, which showed a noticeable negative correlation between follistatin and relaxin (r=-0.415), (p<0.002). There was a weak negative relationship between follistatin and BMI (r=-0.420), (p<0.001), follistatin and St. T4 (r=-0.305), (p<0.02), leptin and AMH (r=-0.386), (p<0.004), follistatin and vitamin D (r=-0.283), (p<0.04) , leptin and vitamin D (r=-0.385), (p<0.004).

Table 5

Correlation analysis of obese women of reproductive age (n=55)

Indicators	Follistatin		Leptin		Relaxin		Activin	
	r	p	R	p	r	p	r	p
BMI	0,420	0,001	0,466	<0,0001				
TSH			0,391	0,003				
SvT4	-0,305	0,02	0,344	0,01				
AtTPO							0,356	0,04
AMG			-0,386	0,004				
LH					-0,287	0,03		
Testosterone							-0,343	0,01
DHEAS							-0,273	0,04
17OKS					-0,328	0,02		
Leptin	0,503	<0,0001						
Follistatin			0,503	<0,0001	-0,415	0,002		
Glucose			0,354	0,008				
HbAlc	0,379	0,004	0,304	0,02				
Insulin	0,525	<0,0001	0,500	<0,0001	-0,278	0,04		
NOMAIR	0,513	<0,0001	0,516	<0,0001				
Relaxin	-0,415	0,002						
Vitamin D	-0,283	0,04	-0,385	0,004				
GGT	0,398	0,003	0,415	0,002				

Amylase			0,374	0,005				
LDL							-0,290	0,03
LPNOP			0,277	0,04				
CA					-0,362	0,007		
ALT			0,297	0,03				
Bilirubin	0,298	0,03						

Table 5 shows that Pearson correlation analysis showed a strong positive relationship between follistatin and leptin (r=0.503), (p<0.0001), insulin (r=0.525), (p<0.0001), HOMAIR (r=0.513), (p<0.0001). There was also a strong positive relationship between leptin and BMI (r=0.466), (p<0.0001), follistatin (r=0.503), (p<0.0001), HOMAIR (r=0.516), (p<0, 0001).

Thus, the presence of metabolic disorders in obese women and relatively excessive stimulation of ovarian steroidogenesis by LH lead to a complex of clinical, biochemical and hormonal disorders that cause disruption of the regulation of the woman's reproductive system, which is the cause of menstrual irregularities with anovulation and infertility.

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