

Research Article

# Evaluation of Serotonin and Hystamine Exchange in Women with Premature Birth in Different Terms of Gestation

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## Abstract

In modern obstetrics and gynecology, the problem of preterm labor is considered one of the most urgent. A significant number of factors affects on the run of pregnancy and it's result, it's activity is realized through numerical metabolic interactions, where an important role is given to biogenic monoamines, in particular serotonin and histamine.

The aim of the study - to study the features of serotonin and histamine exchange in women's body with different periods of abortion by determining in the blood the content of biogenic amines level of excretion with daily urine of serotonin 5-oxyindoloacetic acid and activity in the blood serum of the enzyme inactivation of histamine - histaminase.

Material and methods of research - there were examined 227 pregnant women, 190 of these had clinical signs of the threat of preterm delivery in the gestation period of 23-36 weeks in the form of premature and timely childbirth.

Women with early premature pregnancy, which ended with childbirth in the period from 23 to 27 weeks have a depletion of the functional activity of the serotonergic system.

In women with late onset of pregnancy, there is an increasing of the serotonergic system's functional state, is probably with inhibition purpose of excessive excitement of stress-implementing systems.

In women with a physiological course of pregnancy indicating an increasing of the histamine-histamine system activity with signs of a balance between the synthesis of biogenic amine and its inactivation.

In women with early onset of pregnancy the inferiority of the blood system "histamine-histamine" develops, which is confirmed by a significant increasing of biogenic monoamine and reduction in the activity of the enzyme inactivation.

In women with onset of pregnancy, there is a probable increasing of the histamine concentration in the blood indicating some exhaustion of "histamine-histaminase" systems with predominance signs of biogenic amine synthesis over its inactivation.

Revealed changes in the state of serotonin and histamine in pregnant women indicate the violation of the adaptation mechanisms and the promoting possibility of the preterm labor development.

## Keywords

preterm labor; serotonin; histamine; biogenic monoamines

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## Problem statement and analysis of the recent research

In modern obstetrics and gynecology, the problem of preterm labor is considered one of the most urgent, it requires a thorough study and a comprehensive approach to its solution. The pathogenesis of abortion is quite complicated, according to modern views it has a multifactorial nature [1, 19], that promotâs for its comprehensive study in order to determine the effective complex of therapeutic and prophylactic measures for the prevention of reproductive losses and the obstetric complications remote development. A significant number of factors effects on the run of pregnancy and it's result, it's activity at the final stage is realized through numerical metabolic interactions at the level of the central nervous system, where an important role is given to biogenic monoamines, in particular serotonin and histamine [4, 16-18]. Many literary sources

highlight the participation of the monoamines in the maintenance labor activity, stimulation of uterus' contractile activity [4, 8, 16, 19].

Serotonin is synthesized in many cells, including placenta, endometrium, follicles [1, 19, 22]. It has been proved that the release of histamine from mast cells occurs as a result of their degranulation due to the numerical endogenous factors effects, including estrogen [9], catecholamines while interacting with  $\alpha$ -adrenergic receptors [19]. At the same time, literature has information on the existence of endogenous mast cell stabilizers, namely catecholamines, through action of  $\beta$ 2-adrenergic receptors and glucocorticoids [20].

There is a point of view regarding the expression of serotonin women's receptors before childbirth, connected with the high myometrium sensitivity to serotonin [4, 17] in this period. It is suggested that while decreasing the  $\beta$ -adrenoactivity of

biometrics and effectiveness of catecholamines on  $\beta$ -adrenergic receptors, the stimulatory effect of histamine on myometrium appears [17]. Some authors give details about the ability of serotonin to increase the platelet activity with the formation of blood clots, occurrence of platelet dysfunction, vasoconstriction, violation of the rheological and blood's coagulation properties with the hypoxia development, which is a trigger for miscarriage of pregnancy [12].

The controversy and, to some extent, the lack of literature information about the exchange of serotonin and histamine in women at risk of premature birth dictate the need for its study and the justification of the relationship with other etiological factors of pathogenesis.

The aim of the study - to study the features of serotonin and histamine exchange in women's body with different periods of abortion by determining in the blood the content of biogenic amines level of excretion with daily urine of the main end metabolite of serotonin 5-oxyindoloacetic acid (5-HIAA) and activity in the blood serum of the enzyme inactivation of histamine - histaminase.

## 1. Materials and methods

Material and methods of research - there were examined 227 pregnant women, who entered the Kharkiv city perinatal center, 190 of these had clinical signs of the threat of preterm labor in the gestation period of 23-36 weeks in the form of premature and timely childbirth. 48 women with early premature pregnancy were included in Group I (average age  $23.6 \pm 5.1$  years) which ended in childbirth in the period from 23 to 27 weeks. Depending on the gestational period, all pregnant women with pre-nose risk had the following distribution: 23-25 weeks - 23 pregnant women (Ia subgroup); 26-27 weeks - 25 pregnant women (Ib subgroup).

Group II involved 142 women (average age  $24.7 \pm 4.2$  years) with late term preterm pregnancy in the period from 28 to 36 weeks, which depending on the term of childbirth were divided into subgroups: IIa - 38 people, 28-30 weeks; IIb - 48 people, 31-33 weeks; IIc - 56 people, 34-36 weeks. To the III (control) group were included 37 women with a physiological course of pregnancy (average age  $26.1 \pm 2.7$  years), which ended with childbirth without complications at the time of 38-41 weeks. The criteria for including women in groups were: young reproductive age, single pregnancy, absence of gestosis, acute and chronic gynecological and somatic diseases. Diagnosis of preterm labor was carried out in the presence of abdominal pain syndrome and structural changes in the cervix. The research was carried out in compliance with the principles of bioethics.

The level of serotonin in blood plasma was estimated by fluorometric method (activation of the fluorophore's formation occurred by the addition of cysteine) [10]. To the blood plasma was added trichloroacetic acid and centrifuged followed by transferring the supernatant to n-butanol test tube and centrifuging for 5 minutes at 3000 rpm. The upper butanol bishar was transferred to the samples with the working solu-

tion of cysteine and n-heptane, centrifuged at 3000 rpm. The resulting lower aqueous bishar was transferred to a test tube with a solution of orthophthalic dialdehyde, heated, cooled and measured the fluorescence of samples at 360 and 480 nm. The control test was prepared by adding orthophthalic dialdehyde to the cysteine solution followed by heating and cooling. In the case of a standard sample, a solution of cysteine added a working solution of serotonin and orthophthalic dialdehyde. The concentration of serotonin was calculated according to the formula:  $E_{od} \times 0,026 \times 100 / St$ , where  $E_{od}$  is the fluorescence intensity of the experimental sample;  $St$  is the fluorescence intensity of a standard sample; 100 is a conversion factor of mcg per 100 ml of biological fluid.

The level of histamine in the whole blood was determined by the fluorescence of the products, which are formed in reaction with orthophthalic dialdehyde [8]. Firstly, histamine was extracted from blood with bleach acid, was purified from the impurities by extraction with a butanol-chloroform mixture with subsequent transfer to the aqueous phase, which was reacted with an orthophthalaldehyde reagent. The condensate was stabilized with phosphoric acid. Measurement of the fluorescence intensity was carried out at a wavelength of excitation of 360 nm and a wavelength of 470 nm. To prepare a control sample instead of blood 1 N solution of chloric acid was used. In parallel, a working standard solution of histamine dihydrochloride was prepared. As a result of measuring the optical density of standard samples a calibration curve was constructed. Calculation of the histamine content in whole blood ( $\mu M / l$ ) was carried out according to the calibration schedule, taking into account dilutions of blood samples concordance with the formula:  $E_1 \times 3 \times 0,0045 \times 1000 / E_2$ , where  $E_1$  is the intensity of the fluorescence of the sample;  $E_2$  is the fluorescence intensity of a standard solution containing 1 g of histamine; 3 - breeding; 0.0045 - conversion factor in  $\mu M$ .

To determine the activity of histamines in a flask for incubation we supplemented phosphate buffer and serum, adding a working solution of histamine, after incubation, a solution of trichloroacetic acid was subjoined followed by centrifugation at 3000 rpm [10]. Histamine activity in serum ( $\mu M / (h \cdot l)$ ) was performed according to the formula:  $(E_1 - E_2) \times 10 \times 2 \times 8.977 / E_1 \times 24$ , where  $E_1$  is the intensity of the glow of the control sample;  $E_2$  is the intensity of the glow of the experimental sample; 10 is the amount of histamine in the solution ( $\mu g$ ) introduced into the control and experimental samples; 2 - conversion factor of histamine activity on 1 ml of blood serum; 24 - coefficient of recalculation for 1 hour of incubation; 8.977 - conversion factor in  $\mu M$ .

Statistical processing of the obtained results was carried out using licensed standardized application packages multivariate statistical analysis of Statistica 6.1. Median sample (Me), the value of the lower (Q25) and upper (Q75) quartile were used given the lack of normal data distribution. Comparison of indicators in groups was carried out for non-parametric Mann-Whitney test.

## 2. Results and discussion

In women's of I group was noted probable ( $p = 0, 045$ ) increasing in the blood plasma serotonin an average of 38% in content in comparison with women of group III (table1). Attention is drawn to the probable ( $p = 0, 0011$ ) decreasing in serotonin levels in group I of women in relation to group II on average 39%. Meanwhile, an estimate of the changes in the indicator's content by subgroups showed opposite results: in patients Ia subgroup serotonin levels was statistically significantly lowered ( $p = 0.0018$ ) by 36%, whereas in subgroups of patients Ib - much increased ( $p = 0.001$ ) by 69%. It should be noted that 16 people (70%) Ia subgroup of serotonin content was considerably lower than the reference values, whereas in the subgroup the content of this indicator went beyond the reference values of all 25 people (100%).

Regarding the level of urinary excretion of 5-hydroxyindole acetic acid, then in patients of group I there was a decreasing of it in relation to patients of group III an average of 31% ( $p = 0.008$ ) and more definitely in relation to Group II - by 72% ( $p = 0.001$ ) (Table 1). In this case, when comparing the content of 5-hydroxyindole acetic acid in women Ia subgroups with content in women of group III, no probable changes were detected ( $p = 0.260$ ), whereas in women Ib subgroups registered a probable decrease by 49% ( $p = 0.0015$ ). In the Ia subgroup, the level of 5-HIAA in 11 cases (48%) went beyond the reference values, in subgroup it was characteristic in 15 cases (60%).

In the general picture, a decreasing of serotonin levels in the blood at a practically constant level of 5-HIAA excretion in women with preterm labor in the gestation period of 23-25 weeks (Ia subgroup) reflects the disorder of biogenic monoamine's metabolism and reduces its inactivation. According to the results, we can talk about the decline activity of the limiting serotonergic system in this category of pregnant women, the consequence of which is, as a rule, reduction of resistance to stress factors, development of maladaptation. Literary sources are known for participation serotonin in severe forms of gestosis, preterm labor [6, 7]. It is proved that contractile activity of the uterus is located in direct dependence on the functional state of the central nervous system, in particular, serotonin [7] is involved in paracrine regulation of uterine contraction and vascular tone. It is from these positions that the decrease in the plasma serotonin content women with preterm labor in the period of 23-25 weeks may be associated with its accumulation in tissues and organs, in particular in the uterus. But to explain this assumption the definition of its content in the placenta is necessary.

Increased levels of serotonin in women with preterm labor in the period of gestation 26-27 weeks (Ib subgroup) have been detected and may be associated with an increasing the reaction of tryptophan hydroxylation and a decreasing the activity of monoamine oxidase, which participates in catabolism of serotonin to 5-HIAA.

On the other hand, an increasing serotonin levels in the blood occurs on the background of a reduction the level of

excretion its final metabolite 5-HIAA which on the one hand indicates an strengthening the synthesis of serotonin and its separation into blood from tissues, and on the other - on the tension of functioning of serotonergic systems in this category of pregnant women.

In the blood plasma of women in Group II, serotonin levels are likely ( $p = 0.0018$ ) in relation to women with physiological the course of gestation, the pregnancy of which has ended with deliveries without complications, increased by an average of 95% (Table 1). In 142 patients (100%) of Group II serotonin concentration considerably exceeded the reference values. In subgroups of women, there was also a probable increase ( $p = 0.0018$ ) the level of serotonin, the pregnancy of which ended with childbirth in the period of 28-30 weeks on average 82%, 31-33 weeks - by 91% and most expressed in terms of 34-36 weeks - by almost 106%.

The results showed that in women of group II there is a important increase compared with women of group III ( $p = 0.001$ ) the level of urinary excretion of 5-HIAAs on average by 145% (IIa subgroup - by 87%, IIb subgroup - by 130%, IIv subgroup - by 198%). In all cases (100%), the content of 5-HIAAs went beyond the reference range. Integral increase in excretion level of 5-HIAA in women with preterm labor in the gestation period of 28-36 weeks indicates an increase in the exchange of serotonin, as well as the inclusion of the trigger mechanism of adaptation as a result of this. In this category of pregnant women, increased serotonergic activity the system occurs against the background of previously detected decreasing the activity of the sympathoadrenal system, which can be considered as a compensatory reaction, aimed at inhibition of excessive excitement of stress-implementing systems. On the other hand, increasing serotonin in the blood is a sign of psychoemotional stress, increased contractile activity of myometrium, which increases the risk of abortion.

In women with a physiological course of pregnancy that ended with childbirth without any complications (group III), the serotonin content in the blood plasma and the level of urinary excretion of 5-HIAA were in most cases above the reference values which is probably due to the preparation of the body for labor. In general, an increasing excretion of 5-HIAA indicates an intensification of serotonin exchange and hence the inclusion of the trigger mechanism of adaptation.

The analysis of the results showed that in 35 patients (95%) Group III level in the whole blood of histamine was higher than the reference values which are based on data [6] within the range of  $0.17-0.73 \mu\text{M} / \text{l}$ . In this case, activity in serum Histamineases in all 37 patients (100%) of this group considerably exceeded average rate of  $2.4 \mu\text{M} / (\text{h} \times \text{l})$ . Such results indicate an increasing of system activity "histamine-histamine" in women with normal course of pregnancy with signs of balance between synthesis biogenic amine and its inactivation.

In the blood of group I patients there was a significant increase ( $p = 0.000$ ) the level of histamine on average 8.5 times in relation to patients of group III (Table 2). Ia and Ib

**Table 1.** Changes in the serotonin content in blood plasma and 5-oxyindoloacetic acid in urine women of observation groups (Me (Q25; Q75))

Indicator	I group(23-27), n=48		II group (28-36), n=142			III group (38-41) n=37
	Ia (23-25) n=23	Ib (26-27) n=25	IIa (28-30) n=38	IIb (31-33) n=46	IIc (34-36) n=56	
Serotonin, $\mu\text{g} / \text{L}$	89.8 (40.2; 114.7) <sup>1</sup>		128.8 (118.8; 137.9) <sup>1,2</sup>			65.2 (51.0;77.5)
	40.0 (33.6; 50.6) <sup>1</sup>	114.0 (100.0;119.8) <sup>1</sup>	120.3 (110.2;128.3) <sup>1</sup>	124.2 (115.7;136.2) <sup>1</sup>	133.1 (128.2;145.6) <sup>1</sup>	
5-HIAA $\mu\text{M} / \text{day}$	17.4 (10.9; 22.1)		59.5 (49.8; 74.0) <sup>1,2</sup>			25.4 (18.1; 31.0)
	22.3 (18.3; 27.7) <sup>1</sup>	11.6 (9.5; 15.4) <sup>1</sup>	47.5 (39.0; 55.5)	59.6 (49.0; 65.3) <sup>1</sup>	78.2 (64.8; 85.8) <sup>1</sup>	

*Notes:*<sup>1</sup> - differences from group III are statistically significant at the level  $p < 0.05-0.001$ ;<sup>2</sup> - the differences between I and II groups are statistically significant at the level  $p < 0.05-0.001$ 

subgroups increase the level of this indicator was 10.4 and 6.6 times respectively. In relation to the values in women of Group II, the content of histamine also, it turned out to be statistically intrinsically elevated ( $p = 0.001$ ) on average by 191%. It should be noted that against this background, women of group I in relation to women of group III there was a significant decrease in the serum of histamine activity - an average of 19 times (Ia subgroup - 18 times; Ib subgroup - 20 times), whereas in relation to women in Group II - 79%.

It should be noted that 23 people (100%) of the Ia subgroup the concentration of histamine exceeds the reference range whereas in the case of histamine activity in 18 people (78%), on the contrary, there was a decrease in relation to the average value of the norm. Similarly, 25 patients (100%) of subgroups have histamine levels in their whole blood outperformed the upper norm of norm with values of histamine activity below the average rate in 24 patients (96%). Results were obtained for increasing the histamine content with a vital reduction in the activity of histamines may be indirect evidence about the inferiority of the histamine-histamine system, associated with a low level inactivation of biogenic amine in women with early onset of pregnancy which ended with childbirth in the term of 23-27 weeks. However, we should also take into account the possibility of increasing the level of histamine with an increasing the activity of the enzyme, histidine decarboxylase, which catalyzes the decarboxylation of histidine with the formation of histamine.

In the blood of group II patients, the concentration of histamine is likely ( $p = 0.0002$ ) in relation to women with a physiological course of gestation, whose pregnancy ended in childbirth without complications, also increased, but less significant - an average of 193%, and histamine activity, on the contrary, decreased by 76% (Table 2). In subgroups of women, there was a probable ( $p \leq 0, 001$ ) increase in the level of histamine, the pregnancy ended with childbirth in the period of 28-30 weeks on average by 241% 31-33 weeks - by

232%, while in the period of 34-36 weeks - by 99%. In this case, histamine activity in serum is likely ( $p = 0.001$ ) in relation to control was reduced by 93% in women IIa subgroups, by 70% - for women of IIb and IIv subgroups. The analysis of the results also revealed that 38 subjects (100%) of the IIa subgroups the concentration in the blood of histamine was higher than the reference range, whereas for histamine activity there was a deviation from the norm towards the decrease in 26 women (68%) and in the increase in 9 women (24%). Such results indicate some exhaustion of the "histamine-histamine" system with signs of predominance of the biogenic amine synthesis over its inactivation in most women with late premature pregnancy, which ended with childbirth in the period of 28-30 weeks. In addition, for histamine, all women (100%) have IIb and IIv subgroups went beyond the upper reference value, whereas for histamine activity it was observed in 42 cases (91%) of IIb subgroups and 53 cases (95%) of subgroups II. In general, such results indicate activation as a synthesis of histamine, and the process of its destruction in women with late premature pregnancy, which ended in childbirth in the period of 31-36 weeks, that is more likely to be adaptive.

Literature data about the dynamics of histamine content in the blood of pregnant women are few and ambiguous. For example, according to some data, increasing the level of histamine observed during preterm labor, preeclampsia, toxicosis, whereas according to other data at the physiological course of pregnancy, on the contrary, it is reduced [3]. According to observations [14, 16] the histamine content may increase by 1.5-2.0 times at physiological pregnancy. At the time of childbirth, some authors cite data for which the histamine level reaches 700 ng / ml at a rate of 20-80 ng / ml [16] and some indicate a decrease in it due to intense consumption of myometrium [14]. In the literature there is a point of view that excess synthesis and accumulation of histamine can lead to the formation of the threat of premature birth due to, in particular, ability increase contractile activity of the uterus

**Table 2.** Changes in the histamine content and histamine activity in the blood of women in the observation groups (Me (Q25; Q75))

Indicator	I group (23-27), n=48		II group (28-36), n=142			III group (38-41) n=37
	Ia (23-25) n=23	Ib (26-27) n=25	IIa (28-30) n=38	IIb (31-33) n=46	IIc (34-36) n=56	
Histamine, $\mu\text{M/l}$	18.7 (10.2; 26.5) <sup>1</sup>		5.85 (3.20; 9.81) <sup>1,2</sup>			2.25 (0.98; 3.22)
	21.3 (13.8; 33.2) <sup>1</sup>	12.7 (7.70; 21.4) <sup>1</sup>	7.95 (4.50; 10.9) <sup>1</sup>	7.40 (3.41; 10.2) <sup>1</sup>	4.25 (0.98; 3.22) <sup>1</sup>	
Histaminaze, $\mu\text{M}/(\text{year} \times 1)$	1.51 (0.96; 2.08) <sup>1</sup>		6.75 (3.27; 10.6) <sup>1,2</sup>			32.1 (20.0; 42.4)
	1.60 (0.96; 2.21) <sup>1</sup>	1.44 (0.90; 1.93) <sup>1</sup>	1.53 (1.08; 3.34) <sup>1</sup>	09.4 (5.02; 12.1) <sup>1</sup>	8.45 (5.68; 12.3) <sup>1</sup>	

Notes:

<sup>1</sup> - differences from group III are statistically significant at the level  $p < 0.05-0.001$ ;

<sup>2</sup> - the differences between I and II groups are statistically significant at the level  $p < 0.05-0.001$

of pregnant women [2, 3]. The latter is associated with the fact that histamine, depending on the concentration, is capable of stimulating the synthesis and secretion of estradiol, as well as insignificant progesterone [20]. In addition, histamine is important in the interaction between the uterus and the embryo, due to participation in ripening of the placenta [13]. Taking into account the above, the results obtained in this study clearly confirm the important role of histamine exchange in the pathogenesis of preterm labor in women, especially in the case of early signs of miscarriage with a distinct bias towards the predominance of the biogenic amine synthesis on the background of a significant reduction in the activity of the enzyme its destruction while comparing with women who have normal course of pregnancy. Among the possible causes of diminished histamine activity the action of stress hormones, capable of directly activating mast cells with release histamine and negatively affect the epithelium of the small intestine with the initiation of decreased activity of the enzyme's inactivation are often isolated [20].

The results of the conducted studies indicate a significant participation in the pathogenesis of preterm delivery of mediators of the trophotropic series - serotonin and histamine. To find out more expressive action of them were conducted calculation of the histamine / serotonin ratio (Table 3). Significant increase (on average, 8.1 times) was revealed in the case of women of group I ( $p = 0.0018$ ) in relation to the control group of women (in Ia and Ib subgroups it was respectively 17.5 and 3.9 times). For group II of women also there was a probable ( $p = 0.0077$ ) an increase in the value of the histamine / serotonin ratio compared with the control, but it was less clear than in the case of group I patients, on average 50%. In this case, an increase in the coefficient should be noted only in subgroups IIa and IIb 83% and 72% respectively, whereas in the IIv subgroup the value of the coefficient is practically did not differ from the control ( $p = 0.771$ ). The results obtained indirectly indicate dominance histamine-reactive system over

serotonergic in the pathogenesis of preterm labor, especially in the period of 23-27 weeks.

Consequently, compensatory-adaptive mechanisms in pregnancy is a complex neurohumoral process that is being implemented through monoaminergic systems, the destabilization of which is substantial a factor in its interruption. According to the results, in pregnant women with the threat of preterm birth there is a tensity of neuroendocrine regulation gestational process with the development of a breakdown of compensatory-adaptive reactions, which is confirmed by changes in the exchange of monoamines - serotonin and histamine. Reduced activity and reserve capacity of serotonergic systems increase in the synthesis of histamine with a significant decrease in activity his inactivation in pregnant women may be pathogenetic a factor in the development of preterm labor. Therefore, timely identification of the initial manifestations of imbalance in the exchange of biogenic monoamines may be allowed prevent pregnancy loss on the early lines.

### 3. Conclusions

1. Women with early premature pregnancy, which ended with childbirth in the period from 23 to 25 weeks, in relation to women with a physiological course of pregnancy, which ended with childbirth without complications at the time of 38-41 weeks, have a depletion of the functional activity of the serotonergic system, which is confirmed by the probable ( $p = 0.001$ ) reduction in serum levels of blood plasma (36%) against the background of a constant level of urinary excretion of 5-HIAA and evidence of adaptive mechanisms' failure that aimed at preserving pregnancy.
2. Women with early onset of pregnancy, which ended in childbirth in the period of 26-27 weeks, in relation to women with a physiological course of pregnancy, which ended with childbirth without complications at the time

**Table 3.** The relationship between the content of histamine and serotonin in the blood of women in the observation groups (Me (Q25; Q75))

Indicator	I group (23-27), n=48		II group (28-36), n=142			III group (38-41) n=37
	Ia (23-25) n=23	Ib (26-27) n=25	IIa (28-30) n=38	IIb (31-33) n=46	IIc (34-36) n=56	
Histamine/Serotonin	0.24 (0.15; 0.41) <sup>1</sup>		0.047 (0.025; 0.078) <sup>1,2</sup>			0.030 (0.019;0.049)
	0.54 (0.31; 0.99) <sup>1</sup>	0.11 (0.08; 0.18) <sup>1</sup>	0.067 (0.036;0.091) <sup>1</sup>	0.054 (0.029;0.088) <sup>1</sup>	0.031 (0.018;0.062)	

Notes:

<sup>1</sup> - differences from group III are statistically significant at the level  $p < 0.05-0.001$ ;

<sup>2</sup> - the differences between I and II groups are statistically significant at the level  $p < 0.05-0.001$

of 38-41 weeks, have a depletion of the functional activity of the serotonergic system, which is confirmed by the probable ( $p = 0.001$ ) reduction in serum levels of blood plasma (69%) against the background of a constant level of urinary excretion of 5-HIAA (49%)

- In women with late onset of pregnancy, which ended in childbirth in the period of 28-36 weeks, there is an increasing of the serotonergic system's functional state, which is confirmed by an increase ( $p = 0.001$ ) in blood plasma of serotonin content (an average of 95%) against a background of a substantial increase in the urinary excretion level of 5-HIAA (145%) and is probably with inhibition purpose of excessive excitement of stress-implementing systems.
- In women with a physiological course of pregnancy, ended in childbirth without complications in the period of 38-41 weeks, the level of histamine in the whole blood and activity in the serum of histamine exceed referencing ranges, indicating an increasing of the histamine-histamine system activity with signs of a balance between the synthesis of biogenic amine and its inactivation.
- In women with early onset of pregnancy, which ended in childbirth in the period of 26-27 weeks, in relation to women with a physiological course of pregnancy, which ended with childbirth without complications at the time of 38-41 weeks the inferiority of the blood system "histamine-histamine" develops, which is confirmed by a significant increasing ( $p = 0.001$ ) in the blood of biogenic monoamine (8.5 times) on the background of a significant reduction in the activity of the enzyme inactivation (19.0 times).
- In women with onset of pregnancy, which ended in childbirth in the period of 28-30 weeks, there is a probable ( $p = 0, 000$ ) increasing of the histamine concentration in the blood (by 241%) with diminished histamine activity (by 93%) in relation to control and the same dynamics of change in most patients of the subgroup in

relation to a range of reference values, indicating some exhaustion of "histamine-histamine" systems with predominance signs of biogenic amine synthesis over its inactivation.

- In women with onset of pregnancy, which ended in childbirth in the period of 31-33 and 34-36 weeks, there is a probable ( $p = 0, 000$ ) increasing of the histamine concentration in the blood (by 232% and 99%) with diminished histamine activity (in average by 70%) in relation to control, but against the background of exceeding the upper referencing ranges for these indicators in most patients of subgroups, indicating activation as a histamine synthesis and the process of its destruction and is generally adaptive in nature.
- Revealed changes in the state of serotonin and histamine in pregnant women indicate the violation of the adaptation mechanisms and the promoting possibility of the preterm labor development and worsening of the fetus fetal state due to the properties of monoamines to excitation of the vascular wall and uterus smooth muscle fibers.

## References

- Bezmeltseva OM, Tsirkin VI, Dmitrieva SL. Vliyaniye serotoninina na skorost agglyutinatsii eritrotsitov, indutsirovannoy anti-DIGM-reagentom, u beremennyih zhenschin, rozhenits i zhenschin s ugrozoy prezhdevremennyih rodov. Meditsinskiy almanah. 2015;4(39):55-58.
- Brew O, Lakasing L, Sulliva M. Differential activity of histidine decarboxylase in normal and pre-eclamptic placentae. Placenta. 2007;28:585-587. DOI: <https://doi.org/10.1016/j.placenta.2006.05.003> [PMid:16822545]
- Brew O, Sullivan MNF. The links between maternal histamine levels and complications of human pregnancy. Journal of Reproductive immunology. 2006;72:94-

107. DOI: <https://doi.org/10.1016/j.jri.2006.04.002> [PMid:16860879]
- [4] Cordeaux Y, Pasupathy D, Bacon J. Characterization of serotonin receptors in pregnant human myometrium. *JParmacol Exp Ther.* 2009;328:682-691. DOI: <https://doi.org/10.1124/jpet.108.143040> [PMid:19075042]
- [5] Dube F, Amireault P. Local serotonergic signal in mammalian follicles, oocytes and early embryos. *Life Sci.* 2007;81:1627-1637. DOI: <https://doi.org/10.1016/j.lfs.2007.09.034> [PMid:18023821]
- [6] Furs VV, Doroshenko EM. Nekotoryie pokazateli obmena triptofana pri fiziologicheski protekayushey beremennosti. *Zhurnal GrGMU.* 2011;4:36-38.
- [7] Furs VV. Rol biogennyih aminov pri beremennosti, oslozhennoy platsentarnoy nedostatochnostyu. *Zhurnal GrGMU.* 2010;4:12-16.
- [8] Gutikova LV, Bubeshko DA. Rol biogennyih aminov v realizatsii reproduktivnoy funktsii organizma. *Zhurnal Grodnenskogo gos. med.un-ta.* 2014;2:5-9.
- [9] Haeggstrom A, Ostberg B, Stjerna P. Nasal mucosal swelling and reactivity during menstrual cycle. *Journal of Oto-Rhino-Laryngology and Its Related Specialties.* 2000;62:39-42. DOI: <https://doi.org/10.1159/000027713> [PMid:10654316]
- [10] Kamyishnikov V S. Kliniko-biohimicheskaya laboratornaya diagnostika. *Spravochnik : V 2-h tomah.* 2003;2:463.
- [11] Kuharchik YuV, Gutikova LV. Sovremennyye metody diagnostiki nevyinashivaniya beremennosti rannih srokov. *Zhurnal GrGMU.* 2012;4: 23-25.
- [12] Kukharchik J, Gutikova L. Serotonin and products of its degradation as predictor of no carrying pregnancy in the I trimester. *The 20th international Scientific Conference 19-21 april 2012: abstr. Book.* 2012:64.
- [13] Menshikov VV. Unifitsirovannyiy metod opredeleniya gistamina v tselnoy krovi po reaktsii s ortohtalevyim aldegidom. *Laboratornyie metodyi issledovaniya v klinike.* 1987:258-260.
- [14] Semenyuchenko II. Sistema gistamin-gistaminaza pri normalnoy beremennosti, v rodah i pri nekotoryih anomalnyah rodovoy deyatelnosti. *Akusherstvo i ginekologiya.* 1975;1:44-48.
- [15] Shur VYu, Trizno NN. Adaptivnoe znachenie serotoninergicheskoy modulyatsii kletochnyih metabolicheskikh protsesov. *Astrahanskiy meditsinskiy zhurnal.* 2013;3(8):97-103.
- [16] Sotnikova LG, Sidorov NM, Kondrateva LT. O roli immunologicheskogo komponenta v vozniknovenii rodov. *Akusherstvo i ginekologiya.* 1975;1:23-28.
- [17] Tsirkin VI, Dvoryanskiy SA. Sokratitelnaya deyatelnost matki (mekhanizmyi regulyatsii). *Kirov;* 1997:270.
- [18] Vorobyova II, Zhivetska-Denisova AA, Tkachenko VB. Nevinoshuvnnyia vagitnostil: suchasni poglyadi na problemu (oglyad literaturi). *Zdorove zhenschinyi.* 2017;3 (119):113-117.
- [19] Vorontsov IM. Mekhanizmyi allergicheskikh reaktsiy i metodyi allergoobsledovaniya v klinicheskoy praktike. *SPb : GPMA;* 2004:76.
- [20] Zubchenko SA, Chopyak VV, Yurev SD. Sindrom narusheniya tolerantnosti k gistaminu: etiologiya, patogenez, klinika, sovremennyye podhodyi k diagnostike i lecheniyu. *Klinichna Immunologiya, alergologiya, Insektologiya.* 2016;7 (96):40-45.

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