

## Реферати

**АНАЛІЗ ОСОБЛИВОСТЕЙ СЕНСИБІЛІЗАЦІЇ ДО ПИЛКУ БУР'ЯНИВ І ЕФЕКТИВНОСТІ АЛЕРГОІМУНОТЕРАПІЇ У ПАЦІЄНТІВ ЦЕНТРАЛЬНОГО І ЗАХІДНОГО РЕГІОНІВ УКРАЇНИ**

**Зубченко С.О., Шарикадзе О.В.**

На території України налічується понад 1,5 тис. видів бур'янистих рослин. Вони значно засмічують сільськогосподарські угіддя, а деякі з них володіють значними алергенними властивостями. Найпоширеніші в цілому світі клінічно значущі алергени бур'янів наявні в пиляках полину, амброзії, лободі, подорожника, кураю поташевому. Розвиток молекулярної діагностики дає можливість чітко визначити головний алерген пиляку бур'янів і на цій основі запропонувати пацієнту персоналізований вибір алергоімунотерапії з прогнозом її ефективності. За результатами наших досліджень виявлені регіональні особливості у поширенні сенсibilізації до різних видів бур'янів у Центральному та Західному регіонах України. Використання SLIT зі стандартизованими медичними алергенами для лікування хворих різного віку з пилковою алергією є ефективним і безпечним.

**Ключові слова:** полин, амброзія, молекулярна діагностика, VAS, ефективність SLIT.

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**АНАЛИЗ ОСОБЕННОСТЕЙ СЕНСИБИЛИЗАЦИИ К ПЫЛЬЦЕ СОРНЯКОВ И ЭФФЕКТИВНОСТИ АЛЕРГОИМУНОТЕРАПИИ У ПАЦИЕНТОВ ЦЕНТРАЛЬНОГО И ЗАПАДНОГО РЕГИОНОВ УКРАИНЫ**

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На территории Украины насчитывается более 1,5 тыс. видов сорных растений. Они приносят вред сельскохозяйственным угодьям, а некоторые из них обладают значительными аллергенными свойствами. Распространенные во всем мире клинически значимые аллергены сорняков имеются в пыльце полины, амброзии, лебеды, подорожника, чертополоха. Развитие молекулярной диагностики дает возможность четко определить главный аллерген пыльцы сорняков и на этой основе предложить пациенту персонализированный выбор алергоимунотерапии с прогнозом ее эффективности. Согласно результатов наших исследований выявлены региональные особенности в распространении сенсibilізації к различным видам сорняков в Центральном и Западном регионах Украины. Использование SLIT со стандартизованными медицинскими аллергенами для лечения больных разного возраста с аллергией на пыльцу является эффективным и безопасным.

**Ключевые слова:** полынь, амброзия, молекулярная диагностика, VAS, эффективность SLIT.

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**PECULIARITIES OF GESTATION PROCESS WITH THREATENED MISCARRIAGE AND ITS CORRECTION**

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Certain positive outcomes have been achieved recently in prevention and treatment of miscarriages. However, the rate of this pathology not only failed to decrease but also tends to increase. Current approaches to diagnostics and choice of adequate therapy for preventing the onset of preterm labour promote further progress of pregnancy, developing foetus in a safe intrauterine environment. The effectiveness of therapy with phytometabolic preparations for improving gestation process in women with threatened preterm labour was studied. Women from two main groups and the comparison group were admitted for inpatient treatment with threatened preterm labour: 55 (30,6 %) patients – at 22-27 weeks of pregnancy, 79 (43,9 %) patients – at 28-33 gestation weeks, 46 (25,6 %) women – at 34-35 pregnancy weeks. Pregnant patients with threatened miscarriage underwent complex therapy according to standards of obstetrical and gynaecological care and clinical protocols approved by Ministry of health care of Ukraine (micronized natural progesterone in vaginal tablets by 50 mg twice per 24 hours during observation period due to clinical manifestations, tocolytics were drip-fed once per 24 hours during 24-48 hours in case of available marked uterine tone). Pregnant women of the group II with marked signs of maladaptation syndrome were administered phytometabolic preparation Cratal by 1 tablet thrice per 24 hours additionally. Excretion levels of adrenaline and noradrenaline ranged within the following margins (adrenaline:  $52,1 \pm 3,3$  nmol/24 hours and noradrenaline:  $61,2 \pm 4,3$  nmol/24 hours) in women who underwent phytometabolic therapy. Characteristic considerable decreasing of adrenaline excretion level was observed in 61 (76,2 %) cases, increased level was noticed in 19 (23,7 %) cases. Changes in serotonin level were more noticeable in blood of pregnant women after therapy with Cratal (serotonine level ranged in margins characteristic for the control group –  $1,37 \pm 0,06$  mcmol/l). Decreasing serotonergic system function was observed in 36 (45,0 %) patients, increased serotonin level was noticed in 31 (38,7 %) cases.

**Key words:** preterm labour, catecholamines, phytometabolic preparation.

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According to World Health Organization (WHO) estimates, approximately 15 million of preterm labour (PL) occur annually worldwide. [4,5,6]. High rate of PL in Ukraine causes detrimental effects on both mothers and newborns. Preterm labour is an integral indicator of response to any changes in mother's body and foetus as well as to adverse effect of external factors – social and economic, ecological,

psychoemotional, medical, professional, etc. Causes of PL are numerous, diverse and understudied, since it is not always possible to determine and define a true cause of miscarriages. [1,2].

Preventive and therapeutic issues of threatened miscarriages are still topical nowadays. The most common current ways of miscarriage treatment involve therapy with tocolytic medications, and spasmolytics that improve uterine-placental circulation. [3]. However, administration of these preparations is not always effective and often causes adverse side effects.

The abovementioned aspects premise researching new and effective preventive and therapeutic methods of gestation complications. Disbalance of stress-realizing and stress-limiting systems in pregnant patients with permanent threat of preterm labour causes reducing adaptation function of sympathoadrenal system under chronic psychoemotional stress. Considerable compensatory increasing of stress-limiting serotonergic system causes negative effect on pregnancy. Early diagnostics and choice of adequate therapy for preventing onset of PL will promote proper pregnancy course, developing foetus in a safe intrauterine environment [6].

Inclusion of the phytometabolic preparation into complex therapy influences catecholamines excretion level indirectly, provides improving indicators of heart rate variability and changes psychoemotional condition of the pregnant women.

**The purpose** of the work was to study effectiveness of therapy with phytometabolic medication for improving gestation period in patients with threatened miscarriages.

**Materials and methods.** The study involved 200 pregnant women with threatened preterm labour. They were divided into three groups due to terms of pregnancy, taking into consideration peculiarities of obstetrical tactics at different gestation periods: 22 – 27 weeks of pregnancy – 65 cases, 28 – 33 weeks of pregnancy – 89 cases and 34 – 36 weeks of pregnancy – 46 cases. The age of the pregnant patients ranged from 18 to 40.

Primary examination involved 23 patients of the group I at 22 – 27 weeks, 33 - 30 patients at 28 week, 17 patients at 34 – 35 weeks, in total - 70; respectively 22, 41 and 17 patients (80) of the group II; 10, 8 and 12 patients (30) of the comparison group.

The threat of PL was estimated by available patients' complaints and objective signs: uterine contractions experienced by the patients and identified during hystero-graphy, and the condition of uterine cervix. Patients with clinical signs of threatened miscarriages experienced pressure on pelvic floor, increased discomfort in inferior abdominal areas, manifested with uterine hypersthenia and "menstrual-like" pains in low back during examination.

Twenty-six (37.1 %) pregnant women of the group I were hospitalized preventively taking into consideration previous terms of miscarriages. Forty-four patients (62.9 %) were hospitalized with periodic increased uterine tone and non-specific complaints without labour activity and without structural changes of uterine cervix. Uterine contraction rate varied in the patients and depended on the day time, women's activity at different periods of day, that were not clinical signs of preterm labour.

The pregnant women of the group II were admitted into maternity hospital with signs of threatened miscarriage: increased uterine tone was experienced in 55 (68.8 %) patients, regular uterine contractions were accompanied with structural changes of uterine cervix (shortening, softening, smoothening, opening of cervical canal up to 1-2 cm) manifested clinically and during transvaginal ultrasonography in 25 (31.2 %) patients. Changes of uterine cervix were also accompanied with bloody discharge from reproductive organs in 8 (10.0 %).

Ultrasonic transabdominal and transvaginal examinations were performed with Aloka-5500 (Japan) at real time along with performing fetometry during pregnancy. Spectrophotometric determination of biogenic monoamine levels was carried out with Hitachi (Japan) before and after the treatment.

Internal obstetric examination of uterine cervix condition along with transvaginal ultrasonic examination were the primary methods of examining this group of pregnant women. Ultrasonic examination of the patients was performed with ultrasonic diagnostic system HDI 5000 Sono CT (Philips Ultrasound, USA). Structural changes of uterine cervix with its shortening by more than 80% from initial size were considered prognostically significant during estimation of uterine cervix.

The outcomes of transvaginal ultrasonic examination permitted to exclude or clarify the diagnosis of PL onset, to counterbalance inaccuracy and subjectivity of vaginal examination. The shortening of uterine cervix up to 20 mm and more was considered the indicator of high risk for PL during transvaginal ultrasonic examination.

Mathematical methods of data processing were performed with computer software Excel and Statistica for Windows 5.5 and included statistical analysis, methods of clinical epidemiology (calculation of relative risk — RR, 95% of confidence interval — CI). The distinctions of relative indicators were determined by means of Student's and Fisher's criteria. They were considered reliable with  $p < 0.05$ .

**Results of the study and their discussion.** Internal obstetrical examination for estimating uterine cervix condition along with transvaginal ultrasonic examination were the primary diagnostic methods for PL. Structural changes of uterine cervix with its shortening by more than 80% from initial sizes were considered prognostically considerable during estimation of uterine cervix condition.

Transvaginal ultrasonic examination allowed to exclude or confirm diagnosing the onset of PL contrary to inaccuracy and subjectivity of vaginal examination. Shortening of uterine cervix up to 20 mm and more was considered an indicator of high risk of PL during transvaginal ultrasonic examination.

At the moment of examination, ultrasonic data were the following: hypoplasia of placenta with 0-1 maturity rate was observed in 10 patients (14.3 %) of the group I and in 40 patients (50.0 %) of the group II; premature maturity of placenta was noticed in 20 patients (25.0 %) of the group II, low location of placenta was identified in 46 patients (25.5%) of the groups I and II and of the comparison group. Decreasing of placental thickness by 2-5 mm was observed in 12 patients of the group I – (17.1 %) cases, by 6-8 mm – in 15 patients (18.75 %) of the group II, thickening of placenta – in 5 patients (16.6% cases) of the comparison group.

Disturbances of foetus development were identified predominantly in pregnant women of the main groups I and II during ultrasonic fetometry (table 1).

Table 1

**Rate and degree of PL in studied pregnant women during primary examination**

Groups of studied patients	Delay in foetus development						Total	
	I degree		II degree		III degree			
	n	%	n	%	n	%	n	%
Control, n=20	-	-	-	-	-	-	-	-
Comparison, n=30	2	6.7	1	3.3	1	3.3	4	13.3
Main I, n=70	15	21.4	3	4.3	-	-	18	25.7
Main II, n=80	18	22.5	3	3.75	1	1.25	22	27.5

The outcomes of ultrasonic examination revealed that preterm labour risk factors and pregnancy course with frequent threatened miscarriages causes placenta changes, particularly its premature aging, delay in prenatal foetus development which, in their turn, are signs of placental insufficiency that is a risk factor for preterm labour.

The rate of premature rupture of foetal membranes in patients of the main groups and the comparison group made up 77 cases (42.8 %), of the control group – 2 (10.0 %) ( $p < 0.05$ ).

Clinical experience proves that statistically reliable increased rate of delay in foetus development is observed with decreasing amniotic fluid volume. Marked decreasing of amniotic fluid volume in case of threatened preterm labour is one of the signs of foetus condition deterioration.

Excessive amniotic fluid (polyhydramnios) was diagnosed in 4 (5.7 %) of patients of the group I, scanty amniotic fluid (oligohydramnios) was identified in 41 (27.3 %) pregnant women of both main groups.

Our objective was to estimate risk of threatened miscarriage and pharmacologic safety of therapy with the phytometabolic preparation Cratal. The treatment was regarded effective in case of disappearance or reliable decreasing symptoms of threatened miscarriage.

The medication Cratal (1 tablet three times per 24 hours) was added to complex therapy intended to preserve pregnancy (micronized natural progesterone in vaginal tablets by 50 mg twice per 24 hours), tocolytics were drip-fed once per 24 hours during acute period (1 – 2 days) in case of available marked uterine tone.

Due to reference sources data [3], Cratal may be regarded as both phyto- and metabolic medication due to its balanced composition: taurine – 0.867 g, 0.043 g of dense Hawthorn extract (*Crataegiae fructus extractum spissum*), 0,087 g of dense Motherwort extract (*Leonuriae herba extractum spissum*). Cratal shows manifold effect on adrenergic structures of CNS by decreasing mediators excretion; it possesses vasodilatory, neuroprotective, antioxidant, sedative effects. It is essential that leonurine of Hawthorn decreases tone of vessels due to inhibiting  $Ca^{2+}$  flow within cells and releasing intracellular  $Ca^{2+}$ .

Previous examinations showed that indicators of adrenaline and noradrenaline excretion range considerably in case of threatened miscarriage. It allowed to perform differential individual analysis of their level by the range of excretion level concerning indicators of control and indicators before applying modified therapy.

Patients of the group II, who experienced disturbance of catecholamines balance, were given the preparation Cratal (women with the history of miscarriages with marked signs of threatened preterm labour). Changes of catecholamines synthesis were inadequate response of the body to stress in those cases and showed imbalance of functional activity of sympathoadrenal system.

Variability of heart rate, stress hormones balance and psychoemotional condition were studied in patients of the group II with noticeable manifestations of maladaptation syndrome who underwent therapy with phytometabolic preparation Cratal during 4 weeks.

Considerable increase of both situational anxiety and personal anxiety was observed in patients of the main group I with previous miscarriage. Increased anxiety level was experienced by them throughout the whole pregnancy period, however, personal anxiety level decreased at the III trimester in comparison with the indicators of the II trimester ( $p < 0.05$ ), whereas reactive anxiety level remained practically at the previous level. High level of personal and reactive anxiety up to the III pregnancy trimester ( $p < 0.05$ ) was inherent to pregnant with threatened preterm labour.

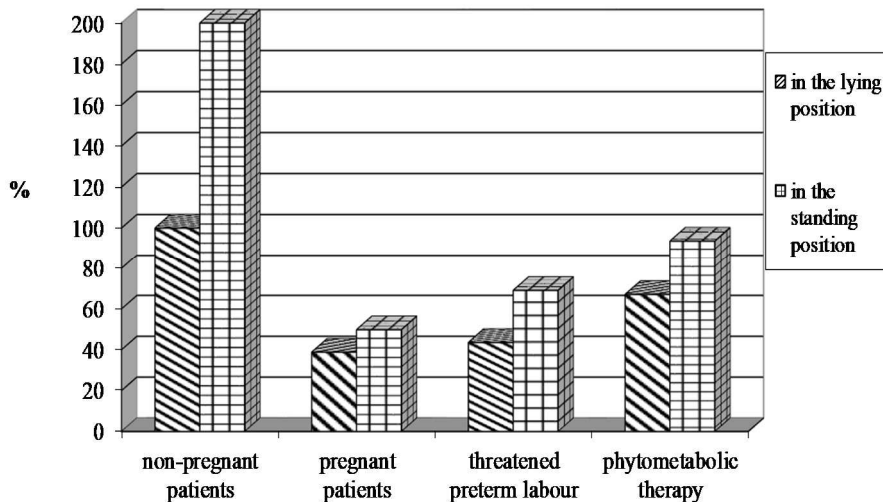


Fig. 1. Changes of common spectral capacity in patients throughout phytometabolic therapy during orthostatic test (concerning control, %).

Tendency to normalization of indicators in patients was observed after the modified therapy.

Excretion of adrenaline and noradrenaline ranged within the following margins – adrenaline:  $52.1 \pm 3.3$  nmol/24 hours and noradrenaline:  $61.2 \pm 4.3$  nmol/24 hours – in pregnant women after the therapy with phytometabolic medication. Characteristic considerable decreasing of adrenaline excretion level was experienced in 61 cases (76.2 %), increased level was observed in 19 cases (23.7 %).

Changes of serotonin level in blood were more noticeable. They ranged in margins characteristic for the control group ( $1.37 \pm 0.06$  mcmol/l) in all patients who underwent therapy with Cratal. Decreasing serotonergic system function was observed in 36 (45.0 %) patients, increased serotonin level was noticed in 31 cases (38.7 %).

Patients with decreased noradrenaline excretion at II and III pregnancy trimesters who underwent supplementary modified therapy according to clinical course and their psychoemotional condition prevailed in the group II. Excessive serotonin production in case of threatened preterm labour intended to inhibit excessive excitement of stress-realizing systems, triggered threatened miscarriage and deterioration of prenatal foetus condition due to constriction of both uterine and placental vessels.

Adequate condition of neurohumoral adaptation systems is particularly important for normal gestation process in pregnant patients. Determination of marked adaptation responses in women with threatened preterm labour will enable to prognosticate and correct further pregnancy course [6].

Analysis of clinical effectiveness of phytometabolic therapy proved that pregnancy ended with birth of full-time newborns weighing from 3050.0 to 3450.0 g with 8-9 scores according to Apgar score in 76 (95.0 %) cases at 37 – 39 weeks. It reveals, first of all, better adaptation resources of newborns from parous women of the main group I. The rate of premature rupture of foetal membranes in patients of the main groups and the comparison group made up 77 cases (42.8 %), of the control group – 2 (10.0 %) ( $p < 0.05$ ).

Preterm labour only occurred in 2 (2.5 %) patients at 33 weeks with a live prematurely born boy with 1660.0 g of weight. The duration of preterm labour was  $18.5 \pm 0.15$  hours in primiparous women (primagravidas) (timely delivery –  $8.4 \pm 0.45$  hours,  $p < 0.001$ ) and  $6.5 \pm 0.26$  hours in multiparous women (multigravidas) (timely delivery –  $8.4 \pm 0.5$  hours,  $p < 0.05$ ).

### Conclusion

Taking into consideration reference sources data and our observations, we may state that including Cratal into complex treatment of pregnant women with maladaptation syndrome is pathogenetically proved by its pharmacodynamic characteristics.

Clinical effectiveness of the modified therapy proved by full-time pregnancy in 32 (95.0 %) patients with birth of full-time newborns with 8-9 scores due to Apgar score, surpassed indicators of normalizing adaptation responses. It confirms diversity of preterm labour aetiology and requires complex approach to its

diagnostics and treatment. Applying phytometabolic therapy triggers reliable decreasing of preterm labour rate and promotes birth of a child with better anthropometric data and quick adaptation to life.

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### Реферати

#### ОСОБЛИВОСТІ ГЕСТАЦІЙНОГО ПРОЦЕСУ ПРИ ЗАГРОЗІ ПЕРЕРИВАННЯ ВАГІТНОСТІ ТА ЇХ КОРЕКЦІЯ

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За останні роки досягнуто значних успіхів в профілактиці і лікуванні невиношування вагітності. Разом з тим, частота цієї патології не тільки не зменшилася, але має стійку тенденцію до зростання. У зв'язку з труднощами визначення провідної причини і високою частотою невідомих за своїм генезу причин невиношування вагітності, важливого значення набуває розробка патогенетично обґрунтованих методів профілактики і лікування даного ускладнення вагітності. Сучасні підходи до діагностики та вибору адекватної лікарської терапії для запобігання початку передчасних пологів сприяють подальшому прогресуванню вагітності, росту плода в безпечному для нього внутрішньоутробному середовищі. Вивчали ефективність застосування фітometаболічних препаратів для поліпшення гестаційного процесу при загрозі передчасних пологів. Жінки, які склали дві основні групи і групи порівняння, надходили на стаціонарне лікування з загрозою передчасних пологів в терміні вагітності 22 - 27 тижнів 55 (30,6%) вагітних, в 28 - 33 тижні гестації - 79 (43,9%), 46 (25,6%) жінок - 34 - 35 тижнів вагітності. Вагітні з загрозою невиношування отримували комплексну терапію відповідно до стандартів надання акушерсько-гінекологічної допомоги та клінічних протоколів, затверджених МОЗ України (мікронізований натуральний прогестерон у вагінальних таблетках по 50 мг двічі на добу протягом періоду спостереження в залежності від клінічної картини, токолітики при наявності вираженого тонуусу матки внутрішньовенно крапельно 1 раз на добу протягом 1 - 2 діб). Вагітні II групи з вираженими проявами синдрому дезадаптації додатково отримували протягом 4 тижнів фітometаболічний препарат Кратал по 1 таблетці 3 рази на сутки. У вагітних, які отримували фітometаболічну терапію, екскреція адреналіну і норадреналіну коливалася в межах (адреналін  $52,1 \pm 3,3$  нмоль / добу і норадреналін  $61,2 \pm 4,3$  нмоль / добу). Значне зниження рівня екскреції адреналіну спостерігалось в 61 (76,2%) випадку, підвищений рівень спостерігався в 19 (23,7%) випадків. Зміни рівня серотоніну в крові були більш виражені у вагітних, які отримували Кратал (рівень серотоніну коливався в межах, характерних для контрольної групи,  $- 1,37 \pm 0,06$  мкмоль / л). Зниження функції серотонінергічної системи мало місце у 36 (45,0%) вагітних, а в 31 (38,7%) випадку виявлявся підвищений рівень серотоніну.

**Ключові слова:** передчасні пологи, катехоламіни, фіто-метаболічний препарат.

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#### ОСОБЕННОСТИ ГЕСТАЦИОННОГО ПРОЦЕССА ПРИ УГРОЗЕ ПЕРЕРЫВАНИЯ БЕРЕМЕННОСТИ И ИХ КОРРЕКЦИЯ

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В последние годы достигнуты значительные успехи в профилактике и лечении невынашивания беременности. Вместе с тем, частота этой патологии не только не уменьшилась, но имеет устойчивую тенденцию к росту. В связи с трудностью определения ведущей причины и высокой частотой неизвестных по своему генезу причин невынашивания беременности, важное значение приобретает разработка патогенетически обоснованных методов профилактики и лечения данного осложнения беременности. Современные подходы к диагностике и выбору адекватной лекарственной терапии для предотвращения начала преждевременных родов способствуют дальнейшему прогрессированию беременности, росту плода в безопасном для него внутриутробном среде. Изучали эффективность применения фитометаболитических препаратов для улучшения гестационного процесса при угрозе преждевременных родов. Женщины, которые составили две основных группы и группу сравнения, поступали на стационарное лечение с угрозой преждевременных родов в сроки беременности 22 – 27 недель 55 (30,6 %) беременных, в 28 – 33 недели гестации – 79 (43,9 %), 46 (25,6 %) женщин – 34 – 35 недель беременности. Беременные с угрозой невынашивания получали комплексную терапию в соответствии со стандартами предоставления акушерско-гинекологической помощи и клинических протоколов, утвержденных МОЗ Украины (микроинизированный натуральный прогестерон во влагалищных таблетках по 50 мг дважды в сутки в течение периода наблюдения в зависимости от клинической картины, токолитики при наличии выраженного тонуса матки внутривенно капельно 1 раз в сутки в течение 1 – 2 суток). Беременные II группы с выраженными проявлениями синдрома дезадаптации дополнительно получали в течение 4 недель фитометаболитический препарат Кратал по 1 таблетке 3 раза в сутки. У беременных, которые получали фитометаболитическую терапию, экскреция адреналина и норадреналина колебалась в пределах (адреналин  $52,1 \pm 3,3$  нмоль/сутки и норадреналин  $61,2 \pm 4,3$  нмоль/сутки). Значительное снижение уровня экскреции адреналина наблюдалось в 61 (76,2 %) случае, повышенный уровень наблюдался в 19 (23,7 %) случаев. Изменения уровня серотонина в крови были более выражены у беременных, которые получали Кратал (уровень серотонина колебался в пределах, характерных для контрольной группы,  $- 1,37 \pm 0,06$  мкмоль/л). Снижение функции серотонинергической системы имело место у 36 (45,0 %) беременных, а в 31 (38,7 %) случае выявлялся повышенный уровень серотонина.

**Ключевые слова:** преждевременные роды, катехоламыны, фито-метаболитический препарат.

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