

I.A. Zhabchenko¹,
N.G. Korniets²,
S.V. Tertychna-Telyuk²

FEATURES OF HORMONAL FUNCTION IN PREGNANT WOMEN - DISPLACED PERSONS

SI "IPAG named after acad. O.M. Lukyanova NAMS of Ukraine"¹

Department of pathology of pregnancy and childbirth

P. Mayboroda str., 8, Kyiv, 04050, Ukraine

e-mail: izhab@ukr.net

SI "Lugansk State Medical University"²

faculty of medicine

Department of obstetrics and gynecology

Budivelnkyiv str., 32, Rubizhne, 93012, Ukraine

ДУ «Інститут педіатрії, акушерства і гінекології ім. акад. О.М. Лук'янової Національної академії медичних наук України»¹

відділення патології вагітності та пологів

вул. П. Майбороди, 8, Київ, 04050, Україна

ДЗ «Луганський державний медичний університет»²

медичний факультет

кафедра акушерства та гінекології

вул. Будівельників, 32, Рубіжне, 93012, Україна

e-mail: kornietsnellia@gmail.com

e-mail: svetlana.tertichnaya@gmail.com

Цитування: Медичні перспективи. 2019. Т. 24, № 2. С. 52-58

Cited: Medicni perspektivi. 2019;24(2):52-58

Key words: pregnancy, stress-associated hormones, hormones of the fetoplacental complex, pregnant women - displaced persons

Ключові слова: вагітність, стрес-асоційовані гормони, гормони фетоплацентарного комплексу, вагітні – переміщені особи

Ключевые слова: беременность, стресс - ассоциированные гормоны, гормоны фетоплацентарного комплекса, беременные женщины - перемещенные лица

Abstract. Features of hormonal function in pregnant women - displaced persons. Zhabchenko I.A., Korniets N.G., Tertychna-Telyuk S.V. Harmonious and stable psycho-emotional state of pregnant women is an important condition of successful pregnancy course, fetal development and physiological childbirth. People are facing various problems related to mental health that vary from psycho-emotional stress to the mental disorders. Important factors that determine the physiology of pregnancy are the psycho-emotional state of the pregnant and fetoplacental complex. Among the consequences of severe stress during pregnancy is dizziness, tachycardia, trembling of limbs, elevated arterial pressure, unmotivated increase in nervousness and anxiety, sleep disorder, depression that lead to worsening of general condition of a future mother. The purpose of the study was to determine changes in the production of placental hormones and stress-associated hormones in pregnant women - displaced persons. To carry out the study, a randomised dynamic prospective clinical-paraclinical examination of 96 pregnant women (the main group) - displaced persons and 39 pregnant women (control group), who lived permanently in the territory of Ukraine under control, with gestation period after 22 weeks was used. Concentration of stress-associated (cortisol and prolactin) and placental (estradiol, progesterone, placental lactogen) hormones in serum was determined by solid-phase immunoassay. Increased estradiol concentrations and relative reductions in progesterone and placental lactogen, displacement of estrogen-progesterone equilibrium toward relative hyperestrogeny, increase in the concentration of stress-associated hormones were observed. The revealed hormonal and metabolic disorders in pregnant women, internally displaced persons, are biochemical markers of placental dysfunction, which testifies to the expediency of a comprehensive preconceptional preparation with the involvement of a psychologist and inclusion of preventive measures in the form of long-term progesterone support during pregnancy in the program of antenatal observation of such women.

Реферат. Особенности гормональной функции у беременных – перемещенных лиц. Жабченко И.А., Корниец Н.Г., Тertychna-Telyuk С.В. Гармоничное и стабильное психоэмоциональное состояние беременных женщин является важным условием успешного течения беременности, развития плода и физиологических родов. Люди сталкиваются с различными проблемами, связанными с психическим здоровьем,

которые варьируют от психоэмоционального стресса до психических расстройств. Важными факторами, определяющими течение беременности, являются психоэмоциональное состояние беременных и фетоплацентарный комплекс. Среди последствий сильного стресса во время беременности - головокружение, тахикардия, дрожание конечностей, повышенное артериальное давление, немотивированное повышение нервозности и тревоги, расстройство сна, депрессия, которые приводят к ухудшению общего состояния будущей матери. Целью исследования было определение изменений в выработке плацентарных гормонов и гормонов, связанных с перенесенным стрессом, у беременных женщин - перемещенных лиц. Для проведения исследования было случайным образом взято динамическое проспективное клинично-параклиническое обследование 96 беременных женщин (основная группа) и 39 беременных женщин (контрольная группа), постоянно проживавших на контролируемой Украиной территории в сроке гестации после 22 недель. Концентрация гормонов стресса (кортизол и пролактин) и плаценты (эстрадиол, прогестерон, плацентарный лактоген) в сыворотке крови определялась с помощью твердофазного иммуноанализа. Наблюдалась повышенная концентрация эстрадиола и относительное снижение прогестерона и плацентарного лактогена, смещение эстроген-прогестеронового равновесия в сторону относительной гиперэстрогении; увеличение концентрации стресс - ассоциированных гормонов. Выявленные гормональные и метаболические нарушения у беременных женщин из числа внутренне перемещенных лиц являются биохимическими маркерами дисфункции плаценты, что свидетельствует о целесообразности комплексной предконцепционной подготовки с привлечением психолога и включением в программу дородового наблюдения таких женщин профилактических мер в виде долговременной поддержки прогестероном во время беременности.

Maintaining the health and life of the mother and the newborn is a major task of public health. Modern socio-economic conditions, environmental problems, prolonged stay in conditions of stress as a result of the military conflict in the east of Ukraine cause a negative impact on the health indicators of pregnant women and their children forming an unfavorable medical and demographic situation in the country. That is why the current direction of modern obstetrics in Ukraine is the prevention of obstetric complications, which are the cause of maternal morbidity and high level of perinatal mortality, the birth of infants with extremely low weight and, consequently, the growth rates of morbidity and disability since childhood.

Placenta plays one of the leading roles in pregnancy, because it supports the physiological balance between the environment, mother and the uterus [13]. Thus, only the physiological level of the placental hormones provides the necessary conditions for implantation, normal fetal development and timely delivery. In recent years, the number of studies devoted to the study of the effects of long-term stress on the hormonal reproduction function of the placenta has increased significantly. Undeniable is the fact that there is an imbalance of placental hormones, circulatory disorders in the utero-placental and placental-fetal passages, pathological changes in the placenta [1, 4, 10, 11]. Negative emotions, prolonged stress, fear, depression of pregnant - displaced persons (PDP) greatly increase the risk of obstetric complications [1, 6] such as placental dysfunction (56.65%), preeclampsia (46.3%), miscarriage (10.9%) and premature (16.6%) pregnancy. Consequently, the psycho-emotional load that causes depression, fatigue, sleep disturbance, and increases anxiety, stimulates an

active negative response from the placenta. Newborns born to women who were in a state of chronic stress during pregnancy are more likely to suffer from cardiovascular disease, diabetes mellitus and mental illness more often in childhood and adolescence [11].

For this reason, the issues of studying the psycho-emotional state of pregnant women and its impact on the development of pregnancy in women living in the zone of military aggression has attracted our attention.

The purpose of the study was to determine the changes in the production of placental hormones and stress-associated hormones in pregnant women - displaced persons for further improvement of the antenatal observation program.

MATERIALS AND METHODS OF RESEARCH

In order to achieve this goal, a dynamic prospective clinical and paraclinical examination of 96 pregnant women (main group) - displaced persons in the gestation period after 22 weeks, which were on treatment and gave birth to child in the maternity department of CCH in Rubizhne city and perinatal center of the city of Severodonetsk, Luhansk region. The control group consisted of 39 pregnant women living in territories controlled by Ukraine, randomly selected for prospective study.

All pregnant women underwent a comprehensive clinical-laboratory and special obstetrical examination in full compliance with quality standards of the Order of the Ministry of Health of Ukraine dated July 15, 2011 N 417 [7]. The concentrations of stress-associated (cortisol and prolactin) and placental (estradiol, progesterone, placental lactogen) of serum hormones were determined by solid-phase enzyme-immunoassay using Cortisol-IFA, Prolactin-IFA, Estradiol-IFA test systems

(production of XEMA LLC, Russia), SteroidIFA-progesterone (LLC Alkor Bio Corporation, Russia), DRG hPL (DRG, USA) on the Lazurite machine, software DS Matrix 1.23 (Dynerx technologies, USA) at the Clinical-Diagnostic Center Pharmbiotest (Rubizhne). The statistical processing of the obtained results was carried out using descriptive and variational statistics using Student's criterion and Fisher's angular transformation method [8]. The calculation of the results was carried out on a personal computer using the licensed programs of Statistica for Windows and Microsoft Excel 7.0. Differences were determined as significant at $p < 0.05$.

RESULTS AND DISCUSSION

By age, family and social status pregnant of study groups were homogeneous, in further, this allowed to judge about differences associated with the state of the internally displaced person.

According to the results of the conducted studies, in the second trimester of pregnancy there is no significant difference in the concentration of estradiol (E_2) in pregnant of both groups under study. Thus, the average content of estradiol in pregnant women in the main group was 15.02 ± 1.2 nmol/l, control – 14.43 ± 0.88 nmol/l. However, in the dynamics of observation there was a progressive increase in the concentration of estradiol in the third trimester and pregnant of both groups had concentration of E_2 which corresponded to the limits of gestational norm. At the same time in pregnant – displaced persons the average concentration of E_2 was by 12.28% higher than the similar indicator in the control group and reached 17.65 ± 0.46 nmol/l (15.72 ± 0.85 nmol/l – control group, $p < 0.05$). These changes testified to the tension of the hormone-producing placental function and were considered by us as one of the signs of the initial stage of placental dysfunction (Table 1).

Table 1

Average concentrations of estradiol in the serum of women of the main and control group in the 2nd and 3rd trimester (M±m)

	Estradiol, nmol/l	
	22 – 23 weeks of gestation	32 – 33 weeks of gestation
Main group, (n=96)	15,02±1,2	17,65±0,46*
Control group, (n = 39)	14,43±0,88	15,72±0,85

Note. * – difference is statistically significant as compared to control group, $p < 0.05$

From the point of view of modern research [5, 9, 14], hyperestrogeny, which leads to the activation of the hypothalamus-pituitary-adrenal system against the persistent stress and causes stimulation of neurons secreting corticotropin-releasing hormone or norepinephrine has a negative effect on the degree of anxiety, increases excitement and insomnia, deepens changes in the psycho-emotional state and its consequences [5, 9, 11, 14].

Progesterone plays one of the main roles in the physiological course and pregnancy maintenance, as a protector of pregnancy. It blocks the α -adrenergic stimulation, reduces the number of receptors to oxytocin, directly affects the intracellular calcium concentration, synthesis of prostaglandin $F_{2\alpha}$ and receptors to it, enhances b-adrenergic tocolytic effect in pregnancy. By regulating the activity of the enzymes D-3b-hydroxysteroid-dehydrogenase and 3b-steroidsulfatase involved in the metabolism of steroids, progesterone controls the level of estrogen

in myometrium; PG metabolite (5α -pregnenolone), binding to the GABA receptors affects GABA-ergic structures of the brain, providing neuroprotective and anxiolytic effects and determining psycho-emotional status of the pregnant woman [5, 11]. The physiological level of PG has a positive effect on the ultrastructural organization of myometrium, since it inhibits the development of a coordinated contraction of the smooth muscle fibrils of the uterus.

Under the influence of long-term stress in the body of a pregnant woman, there is a shift in the losses of steroid hormones precursors towards biosynthesis of glucocorticoids, which leads to the development and manifestation of clinical effects of progesterone deficiency [5, 11].

According to the results of the conducted study, in pregnant women of both groups the average progesterone content corresponds to the gestational norm. At the same time in pregnant of the main

group already in the second trimester of pregnancy there is a significant decrease in the concentration of this hormone to 165.24 ± 14.71 nmol/l (control group – 219.96 ± 16.63 nmol/l; $p < 0.05$), which is by 24.9% lower than in the control group. In the dynamics of pregnancy in women of the main group, the intensity of biosynthesis of progesterone was reduced. This is

evidenced by an average index of its concentration, which in the third trimester of pregnancy was 200.91 ± 5.22 nmol/l (control group – 250.55 ± 17.93 nmol/l; $p < 0.05$), corresponding to the lower limit of the average gestation norm, but being lower by 19.81% than in the control group (Table 2).

Table 2

Average concentrations of progesterone in the serum of women of the main and control group in the 2nd and 3rd trimester (M \pm m)

	Progesterone nmol/l	
	22-23 weeks of gestation	32-33 weeks of gestation
Main group, (n=96)	165.24 ± 14.71 *	200.91 ± 5.22 *
Control group, (n = 39)	219.96 ± 16.63	250.55 ± 17.93

Note. * – difference is statistically significant as compared to control group, $p < 0.05$

Our results may testify to a persistent relative deficiency of this hormone, which plays one of the leading roles in the process of prolongation of pregnancy and birth of a mature newborn. That is why the relative lack of progesterone is one of the diagnostic criteria for the initial stages of placental dysfunction.

A specific marker of placental dysfunction is placental lactogen (PL) which has a purely placental origin [12], therefore, special attention was paid to the study of the dynamics of concentration of this particular hormone. As is known, a developed placenta synthesizes about 1 gram of PL per day, a small part of which enters the system of blood circulation of the fetus. This hormone is essential for the regulation of metabolic processes that occur between the body of the mother and the fetus, which grows intrauterinely. Together with prolactin, PL activates the processes of preparing the mammary glands of the pregnant woman for lactation and also

supports the function of the yellow body, providing a progressive synthesis of PG. Thus, insufficient level of PL is considered to be a pathological state in which the supply of important nutrients and oxygen to the fetus is interrupted [12, 13].

In the course of our researches, it was found that the average concentration of PL during pregnancy in the main group corresponds to the limits of gestational norm (4.92 ± 0.56 mg/l – in the second and 5.05 ± 0.33 mg/l – in the third trimester), however, these indicators are by 27.9% and 28.0% lower than in the control group (in the second trimester – 6.82 ± 1.67 mg/l, $p < 0.05$, in the third – 7.01 ± 0.57 mg/l, $p < 0.05$). It is precisely in the pregnant of the main group that there is a significant exhaustion of the compensatory and adaptive possibilities of the placenta with the development of such disorders as intrauterine growth retardation syndrome, extreme early and early preterm labor (Table 3).

Table 3

Average concentrations of lactogen in the serum of women of the main and control group in the 2nd and 3rd trimester (M \pm m)

	Lactogen, mg/l	
	22 – 23 weeks of gestation	32 – 33 weeks of gestation
Main group, (n=96)	4.92 ± 0.72 *	6.82 ± 0.65
Control group, (n = 39)	5.05 ± 0.33 *	7.01 ± 0.57

Note. * – difference is statistically significant as compared to control group, $p < 0.05$

Thus, the obtained data on PL in the examined groups of pregnant women are consistent with the general trend, which also reflects the state of tension of the hormone-producing placenta function, which is attributable to the initial stages of placental dysfunction.

The concentration of cortisol (C) in the blood serum of pregnant women in the main group according to the results of the conducted studies in the dynamics of pregnancy at 22-23 weeks was 229.46 ± 15.93 ng/ml, which is by 5.5% higher than the upper limit of the physiological norm and almost by 3.4% exceeds the similar finding in the control group (160.0 ± 14.99 ng/ml; $p < 0.05$). According to

I.A. Zhabchenko and co-authors (2016) [2], with the increase in the concentration of cortisol in the blood plasma by three times, its concentration in myometrium increases by nine times, therefore most of the complications during pregnancy against chronic stress should be associated with disorder in production of this hormone. Concentration of C in the blood serum of women in the main group during pregnancy progressively increased and at 32-33 weeks it was 233.19 ± 7.26 ng/ml, which exceeds the upper limit of the physiological norm by 7.3% and by 17.9% – average gestation finding in the control group (197.86 ± 12.14 ng/ml; $p < 0.05$) (Table 4).

Table 4

Average concentrations of cortisol in the serum of women of the main and control group in the 2nd and 3rd trimester (M±m)

	Cortisol, ng/ml	
	22 – 23 weeks of gestation	32 – 33 weeks of gestation
Main group, (n=96)	229.46 ± 15.93 *	233.19 ± 7.26 *
Control group, (n = 39)	160.0 ± 14.99	197.86 ± 12.14

Note. * – difference is statistically significant as compared to control group, $p < 0.05$

Thus, in pregnant women of the main group gestation course occurs against significant increase in the concentration of C, which is the biochemical basis of persistent stress in women of this group. Increasing concentration of precisely C triggers the mechanism of functional changes in the system of the hippocampus-hypothalamus-pituitary-adrenal glands, which results in the increase in blood pressure, the risk of development of insulin resistance in the fetus. According to S.I. Zhuk and co-authors (2017) [3], there is a system of "fetal programming" – manifestation of disorders that occurred during intrauterine state of the fetus already in adult age, because high concentration of C contributes to the change in the number of steroid

receptors in the neuroendocrine system of the unborn child, resulting in increased biosynthesis of the hormone to the action of any causative agent from the outside in the future. Thus, a "false circle" is formed, which is the cause of a sustained increase in basal and stress-induced glucocorticoid content in the future in the adult person. The effect of glucocorticoids on the fetus changes the expression of genes that are responsible for the metabolism of glucose and lipids in the liver, which in adult age increases the possibility of metabolic disorders in the form of hyperlipidemia, glucose tolerance and hyperglycemia [3, 11].

At the same time, prolactin (PRL) concentration increases in the majority of pregnant women.

Table 5

Average concentrations of prolactin in the serum of women of the main and control group in the 2nd and 3rd trimester (M±m)

	Prolactin ng/ml	
	22 – 23 weeks of gestation	32 – 33 weeks of gestation
Main group, (n=96)	326.31 ± 11.29 *	400.42 ± 5.35 *
Control group, (n = 39)	271.16 ± 7.13	362.28 ± 6.28

Note. * – difference is statistically significant as compared to control group, $p < 0.05$



Already in the second trimester, the content of this hormone exceeded the upper limit of gestational norm by 13.3% (326.31 ± 11.29 ng/ml), and compared with the index of this hormone in the pregnant of control group (271.16 ± 7.13 ng/ml, $p < 0.05$) – by 20.3%. In the third trimester, the concentration of PRL in both groups was within the normal range, but in the main group this figure was higher by 10.5% (400.42 ± 5.35 ng/ml and 362.28 ± 6.28 ng/ml; $p < 0.05$ respectively (Table 5).

Thus, the presence of persistent long-term stress, increased concentrations of PRL and C in pregnant women – IDP is obvious. At the same time, the role of hyperprolactinemia in the pathogenesis of the deficiency of the yellow body in the early stages of gestation and threat of abortion associated with it is assured. Thus, hyperprolactinemia also contributes to the progression of placental dysfunction, which is accompanied by an imbalance of placental hormones, circulatory disorders in the utero-placental and placental-fetal cortex, pathological changes in the placenta [4, 10] with the development of placenta-associated gestational complications.

CONCLUSION

Thus, for pregnant women from a group of displaced persons the following is characteristic:

1. Placental dysfunction with the disturbance of balance of the main placental hormones: increased estradiol concentration and the relative reduction of progesterone and placental lactogen, shift of estrogen-progesterone equilibrium towards relative hyperestrogenemia.
2. Increased concentration of stress-associated hormones – cortisol and prolactin.
3. The revealed hormonal-metabolic disorders in pregnant women – internally displaced persons are biochemical markers of placental dysfunction, which testify to the expediency of a comprehensive pre-conceptional preparation with the involvement of a psychologist and the inclusion of preventive measures in the form of long-term progesterone support during pregnancy in the program of antenatal observation of such women.

REFERENCES

1. Astahov VM, Bacyleva OV, Puz IV. [Psychological support of pregnant women in modern conditions]. *Zdorove zhenschiny*. 2014;4(90):58-61. Russian.
2. Zhabchenko IA, Oleshko VF, Bondarenko OM, Syudmak OR. [Features of hormonal homeostasis in pregnant women with functional disorder of the obstructive function of the cervix]. *Reproduktivnaya endokrinologiya*. 2016;5(31):85-89. Ukrainian. doi: <https://doi.org/10.18370/2309-4117.2016.31.85-89>.
3. Zhuk SI, Shurevskaya OD. [Stress fetal programming]. *Zdorove zhenschiny*. 2017;1(117):116-9. Ukrainian.
4. Larina AA, Grigoryan OR, Andreeva EN, Dzernova LK. [Hyperprolactinemia and pregnancy - review of literature]. *Problemy reproduktsii*. 2013;3:13-17. Russian.
5. Malgozhata Zyigmunt, Yatsek Sapa. [Progesterone – a new look at an old drug]. *Reproduktivnaya endokrinologiya*. 2017;1(33):17-25. Russian. doi: <https://doi.org/10.18370/2309-4117.2017.33.17-25>.
6. Malgina GB, Vetchanina EG, Pronina TA. [Perinatal problems associated with psychoemotional stress during pregnancy and their correction]. Materials of the All-Russian Conference with international participation «Perinatalnaya psihologiya i meditsina», Ivanovo, 2001;35-38. Russian.
7. [Order of the Ministry of Health of Ukraine dated July 15, 2011 N 417 “Methodological recommendations for the provision of ambulatory obstetric and gynecological care”]. Kyiv; 2011. Ukrainian.
8. Moskalenko VF. [Biostatistika]. Kyiv. 2009;184. Ukrainian.
9. 8 disturbances of high estrogen. Available from: <https://ukr.media/medicine/379194/>. Ukrainian.
10. Sebko TV, Heydar LA, Koneeva SS. [Hyperprolactinemia]. *Rossiyskiy meditsinskiy zhurnal*. 2016;22(5):250-9. Russian.
11. Tatarchuk TF. [Stress and reproductive function of women]. *Mezhdunarodnyi endokrinologicheskiy zhurnal*. 2006;3(5). Russian.
12. Trishkin AG. [The information content of the determination of placental lactogen and free estriol for the diagnosis of chronic placental insufficiency]. *Zhurnal akusherstva i zhenskih boleznay*. 2011;LX(2):63-67. Russian.
13. Trishkin AG, Novikova ON, Artymuk NV, Ushakova GA, Kiprina ES, Bikmetova ES. [Hormonal and metabolic characteristics of fetoplacental complex in women with fetal growth retardation]. *Mat i ditya v Kubasse* (Spetsvyipusk 1). 2012;59-63. Russian.
14. Katarzyna Zielniok, Małgorzata Gajewska, Tomasz Motyl. Molecular actions of 17β -estradiol and progesterone and their relationship with cellular signaling pathways. *Postepy Hig Med Dosw*. 2014;68:777-92. doi: <https://doi.org/10.5604/17322693.1108390>

СПИСОК ЛІТЕРАТУРИ

1. Астахов В. М., Бацилева О. В., Пузь И. В. Психологическое сопровождение беременных в современных условиях. *Здоровье женщины*. 2014. Т. 90, № 4. С. 58-61.
2. Жабченко І. А., Олешко В. Ф., Бондаренко О. М., Сюдмак О. Р. Особливості гормонального гомеостазу вагітних із функціональним порушенням обтураційної функції шийки матки. *Репродуктивна ендокринологія*. 2016. Т. 31, № 5. С. 85-89. DOI: <https://doi.org/10.18370/2309-4117.2016.31.85-89>
3. Жук С. І., Щуревська О. Д. Стрес-програмування плода. *Здоровье женщины*. 2017. Т. 117, № 1. С. 116-119.
4. Ларина А. А., Григорян О. Р., Андреева Е. Н., Дзеранова Л. К. Гиперпролактинемия и беременность: обзор литературы. *Проблемы репродукции*. 2013. № 3. С. 13-17.
5. Малгожата Зыгмунт, Яцек Сапа Прогестерон – новый взгляд на давно известное лекарство. *Репродуктивна ендокринологія*. 2017. Т. 33, № 1. С. 17-25. DOI: <https://doi.org/10.18370/2309-4117.2017.33.17-25>
6. Мальгина Г. Б., Ветчанина Е. Г., Проница Т. А. Перинатальные проблемы, связанные с психоэмоциональным стрессом при беременности, и их коррекция. *Перинатальная психология и медицина: материалы Всерос. конф. с междунар. участием (Иваново)*. 2001. С. 35-38.
7. Методичні рекомендації щодо надання амбулаторної акушерсько-гінекологічної допомоги: наказ МОЗ України від 15.07.2011 р. № 417. Київ, 2011.
8. Москаленко В. Ф. Біостатистика. Київ, 2009. 184 с.
9. 8 тривожних сигналів високого естрогену. 2018. URL: <https://ukr.media/medicine/379194/>
10. Себко Т. В., Хейдар Л. А., Конеева С. С. Гиперпролактинемия. *Рос. медицинский журнал*. 2016. Т. 22, № 5. С. 250-259.
11. Татарчук Т. Ф. Стресс и репродуктивная функция женщины. *Международ. эндокринолог. журнал*. 2006. Т. 5, № 3. URL: <http://www.mif-ua.com/archive/article/2107>
12. Тришкин А. Г. Информативность определения плацентарного лактогена и свободного эстриола для диагностики хронической плацентарной недостаточности. *Журнал акушерства и женских болезней*. 2011. Вып. LX. № 2. С. 63-67.
13. Тришкин А. Г., Новикова О. Н., Артымук Н. В., Ушакова Г. А. Гормонально-метаболические особенности фетоплацентарного комплекса при задержке роста плода. *Мать и дитя в Кузбассе*. 2012. С. 59-63.
14. Zielniok Katarzyna, Gajewska Małgorzata, Motyl Tomasz. Molecular actions of 17β-estradiol and progesterone and their relationship with cellular signaling pathways. *Postepy Hig Med Dosw*. 2014. N 68. P. 777-792. DOI: <https://doi.org/10.5604/17322693.1108390>

The article was received
2019.03.15

