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PATHOPHYSIOLOGY OF POSTPARTUM AFFECTIVE DISORDERS: CLASSIFICATION, CURRENT CONCEPTS

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Abstract. This literature review is devoted to the issue of studying the pathophysiological mechanisms of postpartum affective disorders, one of which is postpartum depression. The difficulties of classifying mental disorders of pregnancy and after childbirth are considered, in particular, the presence of postpartum obsessive-compulsive disorder, postpartum panic disorder, posttraumatic stress disorder associated with pregnancy and childbirth is reported, the term “perinatal grief”, “posttraumatic growth”, “posttraumatic potential of reproductive losses” and various other terms and concepts are considered, which indicates the complexity and ambiguity of classifying mental disorders of pregnancy and after childbirth. Data from various studies on changes in hormone levels as one of the leading mechanisms for the development of mental disorders in the postpartum period are presented. The influence of oxytocin and its anxiolytic effect, as well as the effect of the oxytocin receptor on the development of postpartum affective disorders are considered. Information is provided on the influence of reproductive hormones on the development of postpartum depression, the role of the brain-derived neurotrophic factor BDNF is studied. The influence of proinflammatory and anti-inflammatory cytokines is considered, for example, it is shown that the levels of IL-1β, IL-6, TNFα are increased in patients suffering from depression, the role of neuroactive steroids is discussed. Studies on the genetic aspect of postpartum affective disorders, the relationship between the serotonin transporter gene and the development of postpartum depression are discussed, the role of the estrogen receptor in the development of postpartum affective disorders is considered. Data are provided on changes in the central nervous system during pregnancy and after childbirth, in particular, changes in brain structures that affect maternal behavior towards offspring, the medial preoptic area (mPOA), which controls care and care for offspring, transformations in synapses are considered, and data on changes in the volume of gray matter of the brain during pregnancy and after childbirth are provided. Considerable attention is paid to the relationship between sleep disorders and circadian rhythms as a provoking factor in the occurrence of mental disorders during pregnancy and after childbirth.

Keywords: postpartum depression, postpartum psychosis, pathophysiology of postpartum affective disorders, oxytocin, allopregnanolone, neuroactive steroids, thyroid hormones, gamma-aminobutyric acid, GABA, BDNF, sleep disorders

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ПАТОФИЗИОЛОГИЯ ПОСЛЕРОДОВЫХ АФФЕКТИВНЫХ РАССТРОЙСТВ: КЛАССИФИКАЦИЯ, СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ

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Резюме. Данный обзор литературы посвящен вопросу изучения патофизиологических механизмов послеродовых аффективных расстройств, одним из которых является послеродовая депрессия. Рассматриваются сложности классификации психических расстройств периода беременности и после родов, в частности, сообщается о наличии послеродового обсессивно-компульсивного расстройства, послеродового панического расстройства, посттравматического стрессового расстройства, связанного с беременностью и родами, рассматривается термин «перинатальное горе», «посттравматический рост», «посттравматический потенциал репродуктивных потерь» и другие различные термины и понятия, что говорит о сложности и неоднозначности классификации психических расстройств периода беременности и после родов. Приводятся данные различных исследований об изменении уровня гормонов как одном из ведущих механизмов развития психических расстройств послеродового периода. Рассматривается роль окситоцина и его анксиолитического эффекта, а также влияние окситоцинового рецептора на развитие послеродовых аффективных расстройств. Изложена информация о влиянии репродуктивных гормонов на развитие послеродовой депрессии, изучается роль мозгового нейротрофического фактора BDNF. Рассматривается влияние провоспалительных и противовоспалительных цитокинов, например, показано, что повышены уровни IL-1β, IL-6, TNFα у пациентов, страдающих депрессией, обсуждается роль нейроактивных стероидов. Обсуждаются исследования, посвященные генетическому аспекту послеродовых аффективных расстройств, взаимосвязь между геном переносчика серотонина и развитием послеродовой депрессии, рассматривается роль эстрогенового рецептора в развитии послеродовых аффективных расстройств. Приводятся данные об изменении центральной нервной системы в процессе беременности и после родов, в частности изменения мозговых структур, влияющие на материнское поведение по отношению к потомству, медиальной преоптической области (mPOA), контролирующей заботу и уход за потомством, рассматриваются преобразования в синапсах, а также приводятся данные об изменении объема серого вещества головного мозга в процессе беременности и после родов. Значительное внимание уделяется взаимосвязи нарушений сна и циркадных ритмов как провоцирующему фактору возникновения психических расстройств периода беременности и после родов.

Ключевые слова: послеродовая депрессия, послеродовый психоз, патофизиология послеродовых аффективных расстройств, окситоцин, аллопрегнанолон, нейроактивные стероиды, гормоны щитовидной железы, гамма-аминомасляная кислота, ГАМК, BDNF, нарушения сна

Currently, active research into postpartum affective disorders is ongoing. For a more detailed understanding of this nosology, it is necessary to discuss the main postpartum affective disorders, their prevalence, and clinical picture [2, 3, 26]. The main classification of postpartum affective disorders is represented by three nosologies: postpartum depression, postpartum psychosis, and postpartum blues.

"BABY BLUES"

Postpartum blues, also known as baby blues and maternity blues is the most common and widespread affective postpartum disorder. According to various sources, 30 to 70% of women experience postpartum blues. The clinical symptoms of baby blues are mild and manifest as emotional lability, irritability, feelings of fatigue, mood swings, increased sensitivity, tearfulness, decreased concentration, and sleep and appetite disturbances. This condition usually begins 3–4 days after giving birth. Postpartum blues can last for several hours or days, but usually lasts no more than two weeks, resolves on its own, and does not require specific intervention or medication. To reduce the symptoms of postpartum blues, it is necessary to create a comfortable environment for a mother. A woman should feel cared for, supported, and compassionate [115].

POSTPARTUM DEPRESSION

Postpartum depression is another condition among postnatal affective disorders that is more dangerous for a mother and her infant. It is defined as a major depressive episode with a perinatal onset. Affective symptoms appear 4–6 weeks after delivery [87]. According to a number of authors, it is necessary to extend the onset of affective symptoms to 1 year after delivery in clinical practice [28]. It occurs, according to various data, in 10–15% of women and on average in 26% of those who gave birth during adolescence [5, 11, 87, 115]. Postpartum depression can be a continuation of prolonged baby blues with intensified clinical symptoms, or it can develop after a period of clinical well-being and absence of affective symptoms. Clinically, it manifests itself as emotional lability, feelings of guilt, tearfulness, loss of appetite, suicidal thoughts, sleep disturbances, fatigue, irritability, feelings of inferiority, and an inability to adequately care for a child. These symptoms must be present continuously for two weeks and interfere with the woman's daily life [7, 12, 32, 33, 36, 40, 43, 71, 92, 104, 105, 129, 131].

POSTPARTUM PSYCHOSIS

One of the rarest postpartum affective disorders is postpartum psychosis. There are 1–2 episodes of postpartum psychosis per 1,000 births. The first clinical symptoms appear 48–72 hours after delivery and can develop within two weeks after delivery. Clinically, it manifests with hallucinatory and delusional experiences, pronounced behavioral disorders, and mood swings from markedly depressed to elated and vice versa. Such patients require hospitalization in a psychiatric ward and treatment, since this condition is very dangerous for a mother and her infant. In case of timely treatment, clinical symptoms are relieved, and the woman returns to her normal life. However, endogenous mental illnesses, such as bipolar affective disorder or schizophrenia, may develop in future [115]. Episodes of postpartum psychosis are often associated with the manifestation of bipolar affective disorder. The biological nature of this condition is being examined at the moment [1, 8, 16, 29, 74].

OTHER TYPES OF POSTPARTUM AFFECTIVE DISORDERS. CURRENT TERMINOLOGY

Other postpartum affective disorders include postpartum obsessive-compulsive disorder, eating disorders, postpartum panic disorder, and post-traumatic stress disorder associated with pregnancy and childbirth [93, 95, 126]. The literature also mentions the term "perinatal grief" — the parental experience associated with the loss of a child as a result of miscarriage, neonatal loss, or termination of pregnancy for medical reasons, as well as posttraumatic growth (Posttraumatic Growth) or post-traumatic potential for reproductive loss, which is understood as a woman's adaptation after perinatal loss, acceptance of the loss and the beginning of a new stage in life, a combination of positive cognitive and behavioral changes [44, 83]. "Perinatal grief" is a predictor of the risk of developing post-traumatic stress disorder associated with pregnancy and childbirth [44]. There is a separate group of anxiety disorders associated with pregnancy and childbirth [49].

Concepts such as postpartum posttraumatic stress (PTS) are also described, which is subdivided into postpartum posttraumatic stress associated with childbirth (PTS related to childbirth — PTS-C) and postpartum posttraumatic stress associated with other events (PTS related to other stressors — PTS-O), as well as postpartum post-traumatic stress disorder (PP-PTSD) [9, 57, 87].

N. Helle et al. comducted a study devoted to interaction between post-traumatic stress disorder in parents and the birth of a premature baby. They report acute stress

disorder (ASD) and distinguish post-traumatic stress symptoms (PTSS) separately from post-traumatic stress disorder [58].

Some researchers distinguish posttraumatic stress disorder in the postpartum period, posttraumatic stress disorder associated with traumatic childbirth, and posttraumatic stress disorder in pregnant women, which has been studied less than manifestations of postpartum posttraumatic stress disorder [31].

There is a term “peripartum onset” that refers to the beginning of a major depressive episode during pregnancy and/or after childbirth [45].

Currently, it is recommended to take into account not only mental disorders that arise in the postpartum period, but also throughout pregnancy [45]. A number of authors recommend considering not only the first months after childbirth as postpartum mental disorders, but also the period up to 1 year . They also recommend paying attention to the mental state of women throughout pregnancy, since postpartum depression is often undiagnosed during pregnancy, or a depressive episode could have occurred before pregnancy.

PATHOPHYSIOLOGICAL ASPECTS OF POSTPARTUM AFFECTIVE DISORDERS

Postpartum mental disorders are conditions with a known risk factor, which suggests a strong influence of biological and genetic factors. However, currently there are no clearly identified factors that are responsible for the development of postpartum affective disorders and affective disorders during pregnancy. Therefore, consideration of this nosology requires a comprehensive analysis of all known factors, both biological and social ones (Fig. 1).

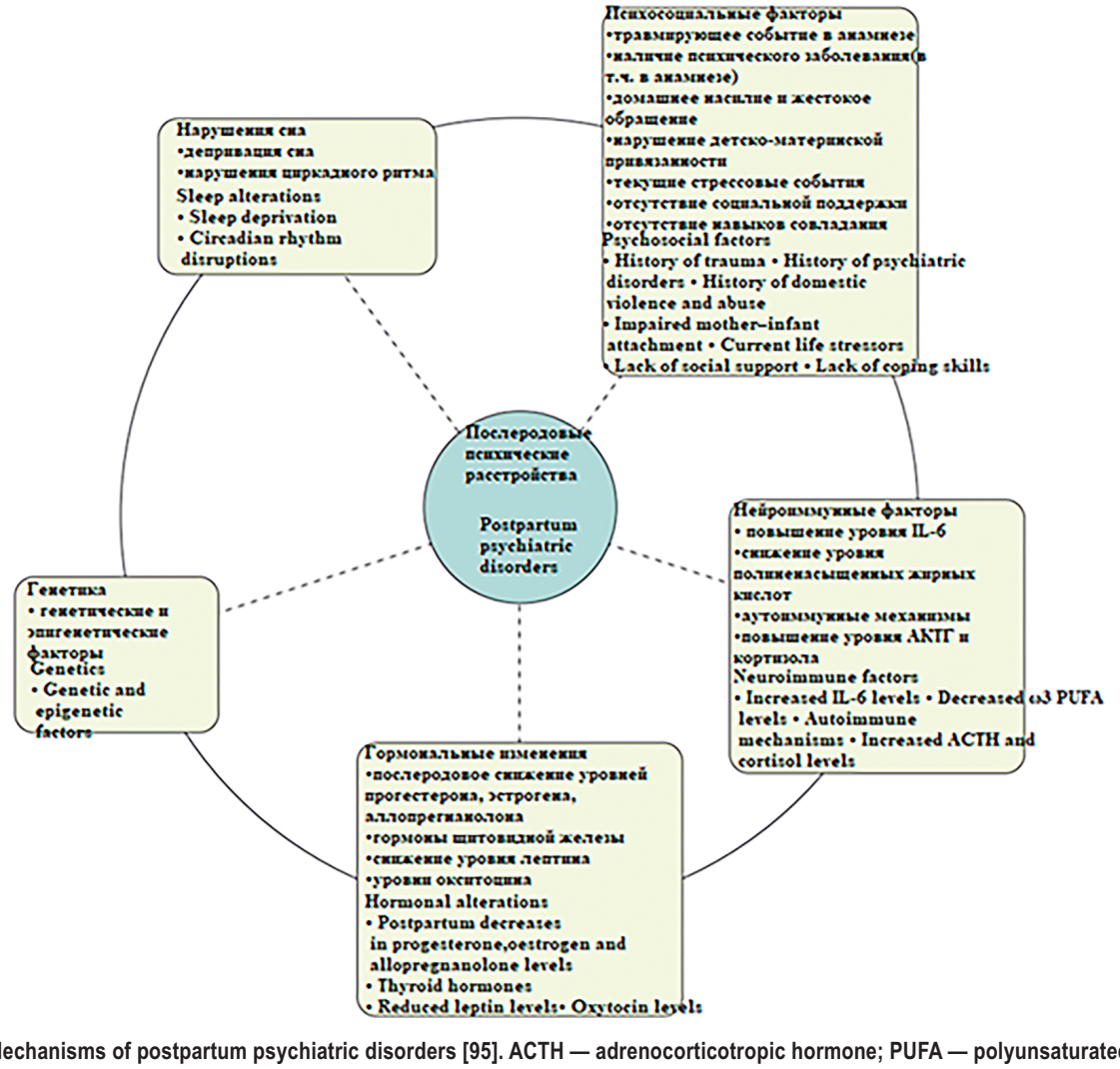

Fig. 1. **Mechanisms of postpartum psychiatric disorders [95]. ACTH — adrenocorticotropic hormone; PUFA — polyunsaturated fatty acid**

Рис. 1. **Механизмы послеродовых психических расстройств [95]. АКТГ — адренокортикотропный гормон; ПНЖК — полиненасыщенные жирные кислоты**

Postpartum mental disorders are reinforced by hormonal and neurotransmitter changes associated with childbirth [8]. Women with chronic post-traumatic stress disorder have changes in the hypothalamic-pituitary-adrenal axis, and further changes occur during pregnancy and childbirth [30]. In addition, postpartum affective disorders, including post-traumatic stress disorder associated with pregnancy and childbirth, may also arise due to an increase and later sharp decrease in estrogen, progesterone, and cortisol, which have neuroactive properties. [30, 54, 73, 98, 128, 132, 136].

CHANGES IN THE NERVOUS SYSTEM DURING PREGNANCY

Animal studies show that changes in the female brain develop during pregnancy and after childbirth. Brain structures that influence maternal behavior toward offspring change, such as the medial preoptic area (mPOA), which controls care and nurturing of offspring. Remodeling processes occur in the synapses, the length of dendrites changes, and the density of spines and astrocytes changes.

There is evidence that firs-time-mothers show a symmetrical pattern of extensive reduction in gray matter (GM) volume. There is also evidence for a decrease in gray matter volume in the brain associated with an increase in endogenous and exogenous sex steroid levels unrelated to pregnancy, for example, during adolescence and when exogenous sex steroids are taken.

Moreover, there are data regarding an increase in gray matter in the hypothalamus, substantia nigra, and amygdala in the maternal brain when there is a positive perception of an infant. Some researchers report an increase in gray matter in the midbrain, prefrontal cortex, and parietal lobe between 2–4 weeks and 3–4 months after giving birth, while others report no changes in gray matter in the early postpartum period. Animal experiments have shown that visual and auditory stimuli received from offspring activate the medial preoptic area (mPOA) and the nucleus of the terminal strip, which are projected into the ventral tegmental area and the retrorubral field, thereby activating the mechanism of positive response to offspring, the so-called reward circuit, promoting the release of dopamine. The dorsal striatum, substantia nigra, amygdala, and hippocampus are also involved in the mechanism of positive response to offspring, with a child's smile being a particularly strong stimulus [13, 100].

There are studies showing that women with postpartum depression have weaker activation of the areas responsible for positive perception of offspring (reward areas): the thalamus, the adjacent nucleus, the caudate nucleus, as well as the lateral and orbitofrontal cortex, which are responsible for regulating emotions [10].

Magnetic resonance imaging (MRI) revealed a reduction in the prefrontal cortex, orbitofrontal cortex, cingulate gyrus, hippocampus, corpus callosum, white matter abnormalities, and a high prevalence of right occipital lobe curvature in patients with major depressive disorder. A reduction in hippocampal volume was also noted in patients with frequent relapses of depression and poor response to antidepressant therapy [46]. However, some studies do not reveal changes in white matter structure. A number of researchers have shown that despite a reduction in brain structures and gray matter volume (considered signs of aging), the maternal brain appears younger 4–6 weeks after delivery compared to 1–2 days after delivery. E. Hoekzema et al. showed that the decrease in gray matter volume persists up to 2 years after giving birth, and the hippocampus returns to its original volume 2 years after giving birth [91]. In contrast, some studies report an increase in gray matter volume in the inferior prefrontal cortex, parietal lobe, limbic and cerebellar structures from 2–4 weeks to 3–4 months after giving birth, which has been linked to a more positive perception of one's child. Luders et al. showed an increase in gray matter volume in the prefrontal cortex, middle occipital gyrus, and caudate nucleus, which was also associated with the development of adaptive maternal behavior [91].

Studies using magnetic resonance spectroscopy (MRS) have revealed a decrease in the concentration of gamma-aminobutyric acid (GABA), glutamate, and glutamine in the occipital, prefrontal, and cingulate cortex in patients with major depressive disorder. Thus, the hypothesis of glutamatergic insufficiency is important for clinical practice and requires further study [46]. There are studies using MRI in patients with postpartum depression, but the data are ambiguous and require further study.

It has been shown that MRI or positron emission tomography (PET) (e.g., measurement of brain monoamine oxidase type A) can be used to observe altered activity in cortical and subcortical regions in women suffering from postpartum affective disorders [38, 95].

These data are ambiguous and require further study to better understand morphological changes in the brain in patients with postpartum affective disorders and affective disorders during pregnancy [41, 114].

GENETIC FACTORS

A number of authors describe an increased risk of inheriting postpartum depression [95]. It has been proven that postpartum psychosis is related to the familial form of bipolar disorder, and that postpartum triggers of bipolar disorder are

also hereditary [95]. Stressful events, as well as adverse events in early life, lead to pathophysiological changes and altered gene expression due to increased allostatic load. Mechanisms that modify gene expression include epigenetic modification, such as DNA methylation and histone modification, which alters DNA accessibility and chromatin structure, changes in transcriptional control of stress-responsive pathways, and shortening of telomere length [95]. For example, epigenetic changes have been found in the *HP1BP3* and *TTC9B* genes, which have different methylation patterns in women suffering from postpartum depression, depending on the time of symptom onset [95].

Studies show that 25% of genetic factors are associated with the variability of depressive disorders. Women whose mothers experienced depressive symptoms during the perinatal period are at greater risk of developing the same symptoms. The risk is especially high if the depressive symptoms developed during the postpartum period [45]. A correlation has been found between a family history of recurrent depressive disorder and depressive symptoms that occur in the first 4 weeks of the postpartum period [45].

5-HTT is a serotonin transporter gene that is frequently studied when inherited depressive disorders, including those with perinatal onset, are examined [45]. Numerous studies confirm the relationship between the serotonin transporter gene and the development of postpartum depression. A link has been found between the genotype with high *5-HTT* expression and postpartum depression, although no major depressive episode was detected. It has been found that female carriers of the long *5-HTT* allele experience more severe depressive episodes during pregnancy than carriers of the short allele. However, there are studies showing the contrary. They suggest that short allele carriers are at risk for developing postpartum depression. It has also been shown that a genotype with low *5-HTT* expression is associated with the development of depressive symptoms during the first 6 months after childbirth. In a large group of women, it was shown that low *5-HTT* expression, combined with unfavorable external factors such as low socioeconomic status, increased the risk of developing depressive symptoms during pregnancy and during the first year after childbirth. Currently, the most promising areas of research are genome-wide association studies (GWA) and epigenetic studies to identify the hereditary nature of depressive disorders during pregnancy and the postpartum period [45, 61, 69, 96].

A study by Guintivano et al. demonstrated that DNA methylation changes after estrogen administration. CpG methylation differences were also observed in the promoter regions of the *HP1BP3* and *TTC9B* genes, which are associated with estrogen signaling. These biomarkers predicted the onset of postpartum depression symptoms with an accuracy of more than 80% [45].

Metha et al. evaluated gene expression from the first trimester to the seventh week after delivery. They identified 116 transcripts with varying degrees of expression in the third trimester, which predicted the risk of postpartum depression with 88% accuracy. The authors then compared women with symptoms of depression and women without depressive symptoms and found differences in 42 expressed transcripts in the third trimester, none of which overlapped with the 116 transcripts, which probably indicates the specificity of this biomarker for postpartum depression [6, 45]. Thus, there is likely a period during which women are most vulnerable to genetic factors and epigenetic changes.

Numerous studies confirm the relationship between genetic factors and adverse environmental factors, including stress, which together contribute to the development of mental disorders during pregnancy and after childbirth.

It is believed that the increased risk of postpartum depression may be associated with increased sensitivity to estrogen-mediated epigenetic reprogramming [45]. Thus, estrogen may be a trigger for changes in gene expression.

The estrogen receptor gene (ESR1) mediates hormonal changes, which may also be a cause of postpartum depression. There is evidence that polymorphism (ESR1) is associated with symptoms of postpartum depression [107]. The possible influence of polymorphisms in the gene encoding monoamine oxidase type A (MAOA) is also discussed as a possible factor in the development of postpartum depression. Monoamine oxidase is involved in the oxidative deamination of dopamine, norepinephrine, and serotonin. It has been found that women with genetic and epigenetic changes in MAOA, when exposed to adverse life factors, had an increased risk of developing postpartum depression and increased cortisol levels [106]. There are also studies showing that polymorphisms in the catechol-O-methyltransferase (COMT) gene, which breaks down adrenaline, noradrenaline, and dopamine, correlate with the level of depressive symptoms in the early postpartum period [107].

There were found interesting evidence regarding the relationship between postpartum depression and the presence of polymorphisms of the tryptophan hydroxylase 2 (*TPH2*) gene, which catalyzes the first stage of serotonin synthesis. Thus, the presence of polymorphisms in the promoter region is associated with the development of depressive symptoms during pregnancy and up to 6–8 months after childbirth, while polymorphisms in intron 8 were associated with the development of depressive symptoms during pregnancy, but not in the postpartum period. It is also worth noting that *TPH2* gene expression is negatively regulated

by glucocorticoid receptors, which requires further study for the mechanisms of postpartum depression [42, 107].

A polymorphism in the gene involved in allopregnanolone aldoketoreductase family 1 C2 (*AKR1C2*) synthesis is associated with decreased allopregnanolone levels and increased depressive symptoms during pregnancy [107].

Thus, genetic research data contribute to the understanding of postpartum affective disorders, as well as mental disorders during pregnancy, however, they require further study [34, 35, 65, 66, 75, 86, 94, 97, 123, 127].

SLEEP DISORDERS

Sleep and circadian rhythm disorders can trigger mental disorders, such as episodes of mania, and can be a predictor of postpartum depression [48]. Pregnant women have longer periods of wakefulness, lower sleep quality, and more transitions between sleep and wakefulness. There is evidence of blunted melatonin amplitude in women in the postpartum period, as well as clinically significant phase shifts in circadian rhythms in women with postpartum depression. The manifestation of post-traumatic stress disorder associated with pregnancy and childbirth is exacerbated in women who experience sleep deprivation and fatigue, partly due to nighttime feedings, particularly in the presence of insomnia 8 weeks after giving birth [15, 30, 87]. Studies show that sleep quality impairment is already observed in the first trimester, progressively worsens throughout pregnancy, and significantly worsens in the first month after delivery. Elevated progesterone levels are associated with daytime sleepiness and shorter sleep-onset latency (SOL). Physical discomfort associated with physiological changes also significantly impairs sleep quality throughout pregnancy [17]. A major factor contributing to sleep disturbances in the postpartum period is the need for constant care for a newborn, especially if an infant has conditions that require increased attention or has a difficult temperament [17]. There are studies showing that sleep is worse after a cesarean section than after a natural birth, which is associated with surgical intervention [17]. Studies confirm that women with clinically significant postpartum depression reported poorer sleep quality, early awakenings, and increased daytime sleepiness, which is characteristic of the clinical picture of depressive states [4, 15]. Two years after giving birth, insomnia symptoms may remain prominent in persistent post-traumatic stress disorder associated with pregnancy and childbirth [30]. It has been shown that the circadian activity rhythm (CAR) decreases from the beginning of pregnancy to the postpartum period and increases gradually 10–13 weeks after childbirth, with greater variability compared to the period before pregnancy [48].

Research is currently ongoing on improving sleep quality through the use of light therapy. A study by Lee et al. examined the effect of light therapy on depressive symptoms and sleep in mothers whose infants were born with low birth weight and were in the intensive care unit [48]. The condition of the child and his or her stay in the intensive care unit affected the mother's circadian rhythms, as stress factors led to poor sleep, which was exacerbated by hospital lighting. Mothers who received 30 minutes of bright light therapy daily experienced a reduction in depressive symptoms and improved sleep quality.

Thus, sleep disturbances are a risk factor for postpartum affective disorders, and poor subjective sleep quality is a predictor of depressive symptoms in the perinatal period. An increased duration of daytime sleep is linked to mood disorders in the third trimester and one week after delivery [17, 60, 84, 90].

OXYTOCIN

Oxytocin acts as both a hormone and a neurotransmitter. Oxytocin levels are normally relatively stable, without significant fluctuations. During pregnancy and childbirth, oxytocin levels change. Oxytocin levels also vary in parent-child relationships.

Oxytocin promotes stable social interaction by acting as a neurotransmitter in the central nervous system through its effects on the hippocampus, amygdala, nucleus accumbens, and limbic system.

In women, oxytocin plays an important role during labor, ensuring calcium penetration into myoepithelial cells to contract muscle fibers, and also contributes to the process of breastfeeding.

It has been shown that intranasal administration of oxytocin increases trust in strangers, reduces cortisol levels during family conflicts, and increases communication. In an experiment by Cardoso et al., intranasal administration of 24 IU of oxytocin increased the need for interaction during social stress by increasing trust in other people [28].

During pregnancy, oxytocin levels increase, raising maternal attachment, reducing amygdala activation, thereby reducing aversion and anxiety, and promoting responsiveness to a baby's cries. Oxytocin stimulates the insula and inferior frontal gyrus, which are responsible for empathy, promoting child-parent attachment.

When the mother and/or child are in favorable circumstances, oxytocin promotes increased social interaction, as opposed to, for example, the presence of strangers nearby. It has been shown that maternal childhood trauma can disrupt normal oxytocin regulation, contributing to affective disorders and impaired parent-child relationships.

Regulation of oxytocin during pregnancy is closely linked to other hormones. Estrogens increase the number of oxytocin receptors and its transcription, thereby increasing the density of oxytocin receptors in the uterus, brain, and breast tissue. Adverse or stressful factors activate the paraventricular nuclei of the hypothalamus and the amygdala, which are responsible for the anxiety response. The hypothalamus promotes corticotropin-releasing hormone production. As a result, adrenocorticotropic hormone is released, catecholamines and cortisol are secreted from the adrenal glands, and at the same time, the sympathetic nervous system is activated. Thus, the body is ready to respond to danger. Oxytocin inhibits the hypothalamic-pituitary system, thereby exerting a significant anxiolytic effect [37].

Elevated cortisol levels and large fluctuations in cortisol levels have been found in 40–60% of women with postpartum depression. Lower oxytocin levels have been shown in patients with depression with comparable cortisol levels in the main and control groups. Thus, women with low oxytocin levels are at risk for developing postpartum depression, regardless of cortisol levels. The action of oxytocin depends on the number of oxytocin receptors (OXTR). It has been shown that epigenetic changes in the oxytocin receptor gene increase the manifestations of anger and fear reactions due to the activation of the amygdala. DNA methylation of the OXTR gene is possible in dangerous and stressful situations, especially during childhood, which reduces the transcription of the latter. It has also been proven that certain polymorphisms of the oxytocin and OXTR genes contribute to manifestations of postpartum depression (Fig. 2).

Oxytocin is used therapeutically either intranasally, due to its effect on the central nervous system, or intravenously, due to its effect on the uterus. The intranasal route of oxytocin administration has been shown to be the safest. Psychiatry is investigating the positive effects of intranasal oxytocin administration in schizophrenia, phobic disorders, post-traumatic stress disorder, and addictions, and significant behavioral changes have been shown in autism. Numerous studies have shown that oxytocin is

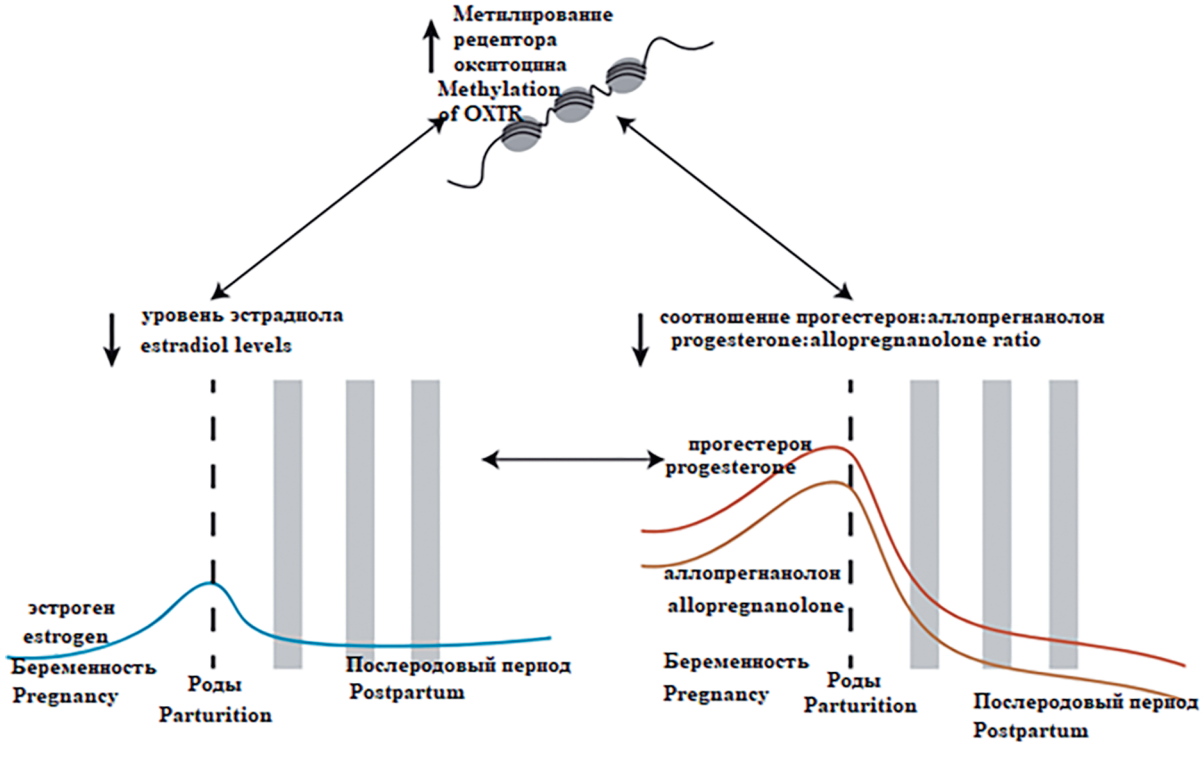

Fig. 2. **Epigenetic regulation of *OXTR* and hormonal abnormalities associated with postpartum depression. Variations in DNA methylationof the *OXTR* gene in women with postpartum depression is negatively correlated with serum estradiol levels (left panel). Asignificant interaction between estradiol, *OXTR* DNA methylation, and the ratio of allopregnanolone to progesterone was alsoobserved in women with postpartum depression [107]**

Рис. 2. **Эпигенетическая регуляция *OXTR* (рецептор окситоцина) и гормональные нарушения, связанные с послеродовой депрессией. Изменения в метилировании ДНК гена *OXTR* (рецептор окситоцина) у женщин с послеродовой депрессией отрицательно коррелируют с уровнем эстрадиола в сыворотке крови (левая панель). Значительное взаимодействие между эстрадиолом, метилированием ДНК *OXTR* и соотношением аллопрегнанолона и прогестерона также наблюдалось у женщин с послеродовой депрессией [107]**

ineffective in depressive disorders, sometimes even contributing to an increase in symptoms. Patients suffering from depression experienced anxiogenic reactions when oxytocin was administered intranasally. In contrast, a comparison group of healthy individuals experienced an anxiolytic effect when oxytocin was administered intranasally. In women with postpartum depression, oxytocin administration enhances defensive reactions and contributes to an anxiogenic effect. Women with postpartum depression have lower levels of oxytocin in plasma and saliva, and those with depressive symptoms during pregnancy have low levels of oxytocin in the postpartum period. According to one hypothesis, exogenously administered oxytocin affects the central nervous system, promoting the production of endogenous oxytocin. At present, there is no clear data showing a correlation between the exact amount of oxytocin administered and the response of the central nervous system. However, some studies suggest that such a correlation exists. For example, repeated intranasal administration of 200 IU of oxytocin did not reduce cortisol levels in primates, while administration of 50 IU contributed to a decrease in cortisol levels. It is suggested that these phenomena may be caused by binding of oxytocin to vasopressin receptors, which enhances stress responses [63, 64, 80, 110, 118, 130, 134].

The hypothesis of the central action of oxytocin when administered peripherally raises unresolved questions. There are issues with crossing the blood-brain barrier, since oxytocine is hydrophilic and only a small part of intravenously administered oxytocin can cross the blood-brain barrier. As the blood-brain barrier has systems for transporting hydrophilic molecules, a hypothesis has been proposed. It has been suggested that oxytocin and vasopressin may be actively transported from the blood into the cerebrospinal fluid, but there is no precise data if oxytocin can pass through the blood-brain barrier. According to another hypothesis, there is a negative feedback mechanism whereby exogenously administered oxytocin binds to oxytocin receptors and reduces endogenous oxytocin levels [76, 78].

It has been reported that women who experience high levels of stress during pregnancy and eight weeks after giving birth have high levels of oxytocin and less pronounced depressive symptoms. This fact can be explained by endogenous oxytocin effects, which protect the mother and child frostress, reduces the risk of postpartum depression, and promotes maternal attachment and harmonious mother-child relationships. Currently, there is no clearly identified relationship between the level of endogenous oxytocin, exogenous oxytocin, and symptoms of postpartum depression. A number of studies link intravenous administration of oxytocin during childbirth with the development of symptoms of postpartum depression, which requires further study [18, 28, 20–22, 24, 27, 39, 53, 64, 72, 85, 112, 113, 116, 122].

PSYCHONEUROIMMUNOLOGY OF POSTPARTUM DEPRESSION

Various pathological conditions activate the innate immune response to limit the spread of infection and reduce tissue involvement. The innate immune response is carried out through the production of pro-inflammatory and anti-inflammatory cytokines. Since a continuous inflammatory response causes undesirable effects in the body, anti-inflammatory cytokines are produced, which inhibit the production of pro-inflammatory cytokines. If this balance is disturbed, mental illnesses, including depression, may develop. Prolonged or enhanced activation of the pro-inflammatory immune response may contribute to the development of depression. Patients with depression have elevated levels of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNFα. The hypothalamic-pituitary-adrenal axis also influences the immune response. Normal functioning of the hypothalamic-pituitary-adrenal system is necessary to protect against excessive exposure to glucocorticoids, such as immunosuppressive, lipogenic, and catabolic effects. When exposed to stressors, the hypothalamic-pituitary-adrenal axis releases large amounts of cortisol compared to normal basal levels. Stressors also provide additional energy through gluconeogenesis, thereby suppressing the immune response. After exposure to a stress factor, the hypothalamic-pituitary-adrenal axis gradually returns to normal functioning, but if the stress factor continues and becomes chronic, the hypothalamic-pituitary-adrenal system ceases to function normally, becoming hyperactive or hypoactive [77, 111].

Hyperactivation of the hypothalamic-pituitary-adrenal axis is associated with melancholic depression, anorexia nervosa, and attachment disorders in childhood. Hypofunction, in turn, is associated with seasonal and atypical depression, fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome. A number of authors also include postpartum depression in this group. Constantly elevated levels of pro-inflammatory cytokines reduce the function of glucocorticoid receptors in the central nervous system, thereby reducing the sensitivity of the hypothalamus to increased cortisol levels and reducing the normal response of the hypothalamus through a negative feedback mechanism. Hyperactivation of the hypothalamic-pituitary-adrenal axis contributes to a pronounced inhibitory effect on the inflammatory and/or immune response by blocking the stages of the

pro-inflammatory process. A bidirectional relationship has been demonstrated between the innate immune response, the hypothalamic-pituitary-adrenal axis, and postpartum depression (Fig. 3).

Figure 4 shows the normal responses of the immune system and the hypothalamic-pituitary-adrenal axis that contribute to normal postpartum emotional regulation.

It has been shown that pregnancy increases the level of anti-inflammatory cytokines, contributing to pregnancy maintenance and immunosuppression, while the level of pro-inflammatory cytokines decreases during pregnancy. After the birth of the baby and placenta, the anti-inflammatory background changes to pro-inflammatory within a few hours, as the involution processes in the uterus are characterized by ischemia, phagocytosis, and autolysis involving inflammation and cytokines. In addition, perineal tissue is often damaged during childbirth, which contributes to the development of an inflammatory response, as does the process of childbirth itself, accompanied by physical, painful, and emotional stress. Women who do not suffer from postpartum depression experience an increase in pro-inflammatory cytokines during the postpartum period due to their innate immune response. Several months after giving birth, the inflammatory reactions cease. After delivery, the hypothalamic-pituitary-adrenal axis becomes hyporeactive and returns to its pre-pregnancy level at around 12 weeks, limiting inflammatory responses and ensuring balanced emotional regulation. It is believed that women with postpartum depression have an enhanced inflammatory response after childbirth and/or insufficient suppression of the hypothalamic-pituitary-adrenal axis. At present, data on hypoactivation and hyperactivation of the hypothalamic-pituitary-adrenal axis, as well as data on pro-inflammatory and anti-inflammatory immune responses in postpartum depression and other affective disorders, require clarification for further application in clinical practice [19, 25, 51, 125, 137, 117].

REPRODUCTIVE HORMONES

Numerous data indicate that changes in reproductive hormone levels in the postpartum period influence the development of postpartum affective disorders (Fig. 5). Estrogen and progesterone are produced in large quantities during pregnancy and decrease sharply after childbirth. Estrogen and progesterone receptors are expressed throughout the brain and can modulate neurotransmission and neuroplasticity through both genomic and non-genomic mechanisms. For example, levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and forebrain of rodents decrease with ovariectomy and increase with estradiol administration. Brain-derived neurotrophic factor levels decrease with depressive symptoms and stress in patients and increase after taking antidepressants [95]. Thus, a rapid drop in reproductive hormone levels can cause a decrease in brain-derived neurotrophic factor levels, thereby contributing to the risk of developing postpartum affective disorders [95]. Progesterone has also been shown to play an important role in the release, regulation of synthesis, and transport of neurotransmit-

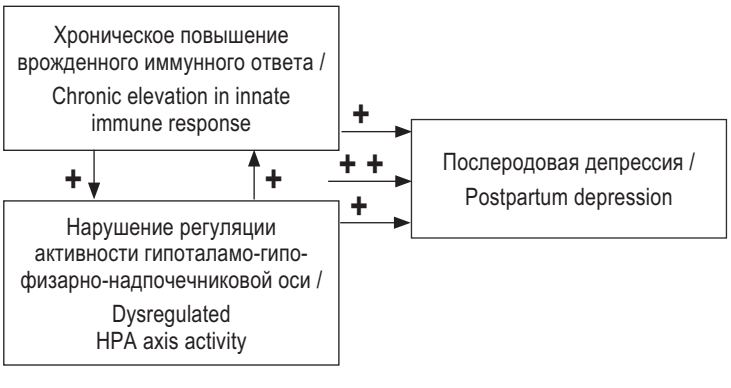

Fig. 3. Conceptual framework for the proposed study, depicting dysregulated relationships among the HPA (hypothalamic-pituitary-adrenal) axis, the inflammatory response, and PPD (postpartum depression) [32]

Рис. 3. Концептуальная основа предлагаемого исследования, иллюстрирующая нарушенную регуляцию взаимоотношений между осью HPA (гипоталамо-гипофизарно-надпочечниковая ось), воспалительной реакцией и PPD (послеродовая депрессия) [32]

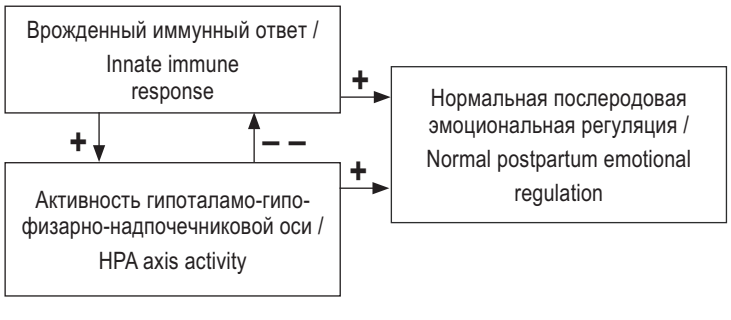

Fig. 4. Conceptual framework depicting normal relationship between the inflammatory response and the HPA axis [32]

Рис. 4. Концептуальная схема, иллюстрирующая нормальную взаимосвязь между воспалительной реакцией и осью HPA [32]

ters, as well as to increase the expression of brain-derived neurotrophic factor in the hippocampus and cerebral cortex in rodent models [95]. Apparently, women with postpartum depression have different sensitivities to changes in hormone levels. Thus, it has been shown that the administration of supraphysiological doses of progesterone and estradiol exacerbates the symptoms of depression in patients with a history of postpartum depression [18, 52, 88, 107, 119].

It has been shown that women with postpartum depression had low serum prolactin levels and were less likely to breastfeed. Reduced prolactin levels are also observed in women with severe symptoms of postpartum depression, as well as in women at increased risk of developing postpartum depression. It has been hypothesized that there is an interrelated pathophysiological mechanism between postpartum depression and lack of lactation [107, 120, 121].

THE ROLE OF NEUROACTIVE STEROIDS AND GAMMA-AMINOBUTYRIC ACID

There is some evidence of an association between postpartum depression and neuroactive steroids and GABA. Levels of neuroactive steroids increase in the CNS during pregnancy and rapidly decrease after childbirth. Impaired regulation of neuroactive steroid metabolism, as well as impaired interaction with GABA and insufficient activation of GABA receptors, are associated with the development of postpartum depression [47, 55].

The main metabolite of progesterone is the neurosteroid allopregnanolone, a positive allosteric modulator of synaptic and extrasynaptic gamma-aminobutyric acid type A (GABA A) receptors (Fig. 6). Animal models have shown that intravenous administration of allopregnanolone significantly reduces symptoms of anxiety and depression. Allopregnanolone levels peak in the third trimester of pregnancy and decline rapidly after childbirth. Thus, it is assumed that the trigger for postpartum affective disorders, including depression, is the inability of GABA receptors to quickly adapt to the sharp decline in allopregnanolone levels after childbirth [95]. This hypothesis is being studied for the possible treatment of postpartum depression with Brexanol, a patented formula of synthetic intravenous allopregnanolone, a GABA receptor modulator that has been shown to rapidly relieve the clinical symptoms of postpartum depression in placebo-controlled randomized clinical trials compared to antidepressant therapy [95, 70]. Brexanolone was approved by the US Food and Drug Administration (FDA) for the treatment of postpartum depression in 2019, as an intravenous form of allopregnanolone for continuous

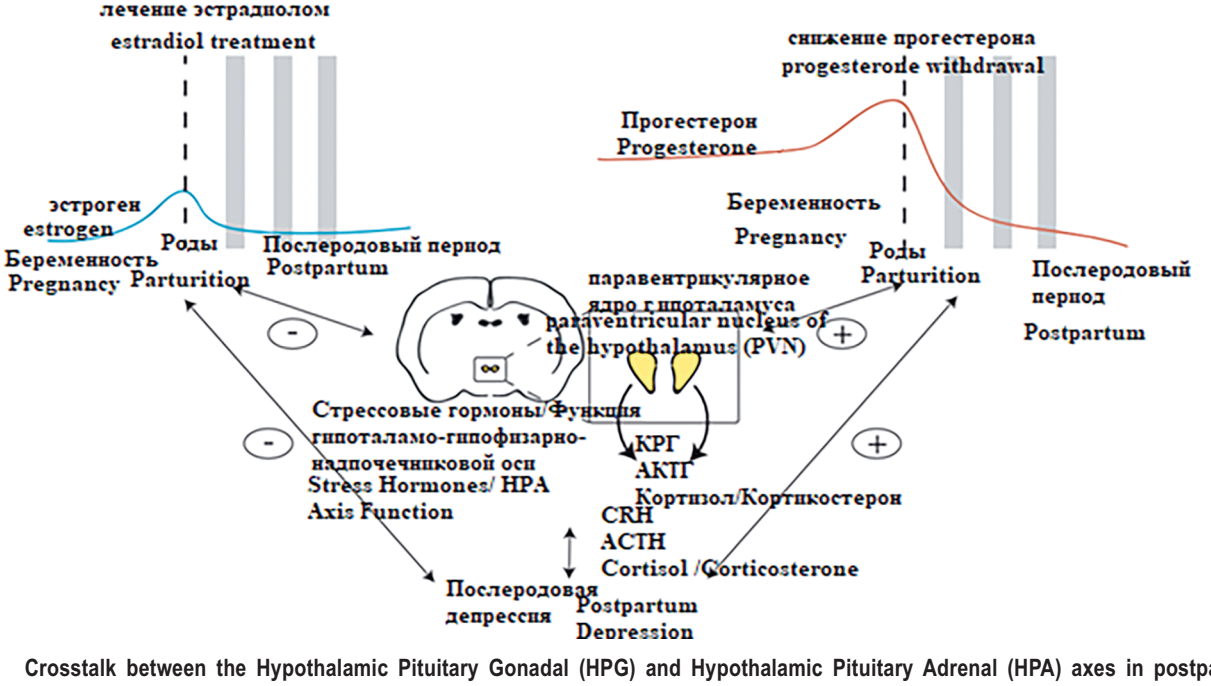

Fig. 5. **Crosstalk between the Hypothalamic Pituitary Gonadal (HPG) and Hypothalamic Pituitary Adrenal (HPA) axes in postpartum depression. Reproductive hormones have been shown to impact HPA axis function and vice versa [107]**

Рис. 5. **Перекрест между осями гипоталамо-гипофизарно-гонадной (HPG) и гипоталамо-гипофизарно-надпочечниковой (HPA) системами при послеродовой депрессии. Было показано, что репродуктивные гормоны влияют на функцию оси HPA и наоборот [107]**

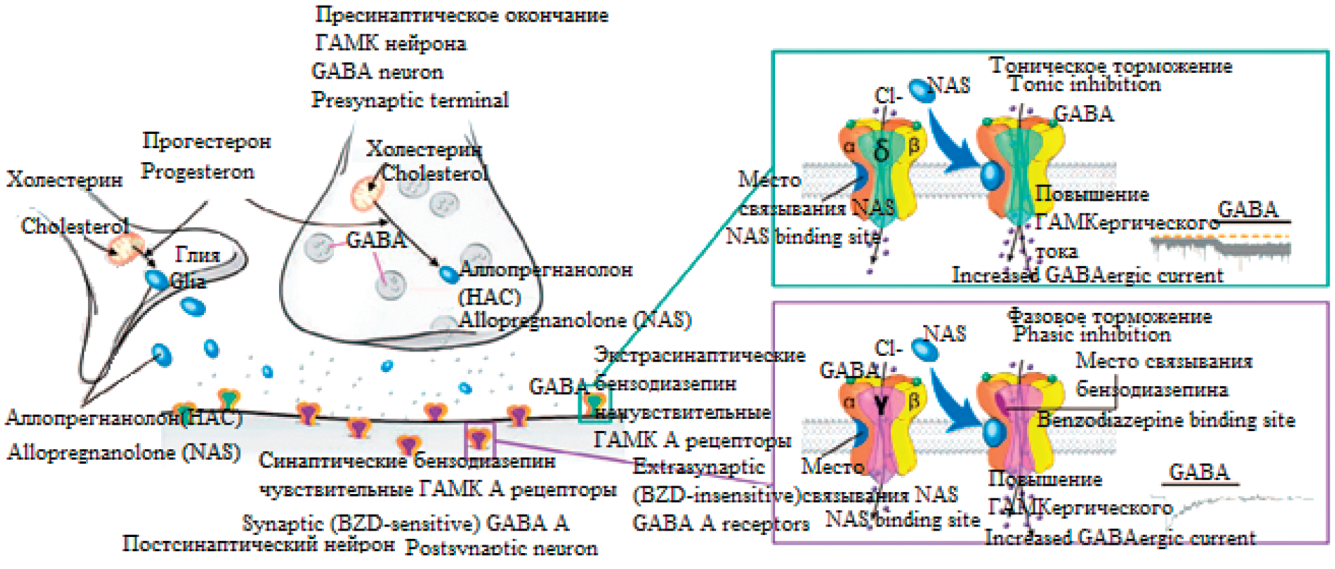

Fig. 6. **Mechanism of action of the positive allosteric modulator allopregnanolone on synaptic and extrasynaptic GABA A receptors. Allopregnanolone binds both synaptic and extrasynaptic GABA A receptors, acting as a positive allosteric modulator to increase the frequency and duration of channel opening, thus increasing hyperpolarizing GABAergic current [55]. BZD — benzodiazepine; GABA — gamma-aminobutyric acid; GABA A — gamma-aminobutyric acid type A; NAS — neuroactive steroid**

Рис. 6. **Механизм действия положительного аллостерического модулятора аллопрегнанолона на синаптические и экстрасинаптические ГАМК-рецепторы. Аллопрегнанолон связывает как синаптические, так и экстрасинаптические ГАМК-рецепторы, действуя как положительный аллостерический модулятор, увеличивая частоту и продолжительность открытия каналов, что увеличивает гиперполяризующий ГАМК-эргический ток [55]. BZD — бензодиазепин; GABA — гамма-аминомасляная кислота; GABA A — гамма-аминомасляная кислота типа А; NAS — нейроактивный стероид**

infusion over 60 minutes [55]. SAGE-217 (zuranolone) is an oral analogue of allopregnanolone that has also shown good results in the treatment of postpartum depression. Ganaloxon, a 3β-methylated synthetic analogue of allopregnanolone, is also being considered for the treatment of postpartum depression in both oral and intravenous forms [47]. Preclinical studies show that allopregnanolone plays an important role in suppressing the hypothalamic-pituitary-adrenal axis response to stress during pregnancy [14, 20, 21, 47, 56, 121].

THYROID HORMONES

The concentration of thyroxine-binding globulin increases during pregnancy and may be an indicator of sensitivity to elevated estrogen levels. Some studies suggest that a decrease in thyroxine-binding hormone is a predictor of postpartum depression. In addition, comorbidity of postpartum autoimmune thyroid diseases and postpartum affective disorders has been noted, which coincides with the phenomenon of postpartum rebound of the maternal immune system [95]. Women with elevated levels of antibodies to thyroid peroxidase during pregnancy have an increased risk of developing postpartum affective disorders.

A number of authors compare postpartum depression with autoimmune diseases, comparing possible similar mechanisms, such as the influence of maternal-fetal microchimerism, as well as considering the course of autoimmune diseases during pregnancy and after childbirth [50, 108, 109].

NEUROIMMUNE PATHWAYS

During the transition from pregnancy to childbirth and the postpartum period, there is an enhanced immune response associated with both pro-inflammatory and anti-inflammatory mediators. Women with postpartum depression have elevated IL-6 levels and reduced leptin levels. Reduced leptin levels during childbirth may be a marker for the risk of developing postpartum depression. A decrease in uteroglobin, known as the endogenous anti-inflammatory compound CC16, is also associated with the risk of developing postpartum affective disorders. According to the literature, a decrease in polyunsaturated fatty acids may also be associated with the risk of developing postpartum mental disorders. It has been noted that episodes of mental illness occur more frequently during the first pregnancy, which may be associated with dramatic changes in neuroendocrine regulation during the first pregnancy compared to subsequent pregnancies, as well as a potentially higher risk of

developing preeclampsia during the first pregnancy. Preeclampsia and postpartum psychosis are associated with immune dysregulation, which is confirmed by the comorbidity of autoimmune thyroiditis after childbirth and changes in the level of autoimmune antibodies in the central nervous system in patients with postpartum psychosis. Monocytosis was also detected in patients with postpartum psychosis, with no increase in T-lymphocytes after childbirth and impaired tryptophan cleavage [62].

Fluctuations in corticotropin-releasing hormone during pregnancy and after childbirth can also disrupt the functioning of the hypothalamic-pituitary-adrenal axis and contribute to the development of postpartum affective disorders [95].

Thus, there is a further need to study biological predictors and markers of postpartum affective disorders in detail in order to ensure intervention in case of mental impairments in the postpartum period as early as possible [95, 135].

Disruptions in the kynurenine pathway, namely increased kynurenine levels, are associated with the development of postpartum depression. There is a hypothesis that high levels of kynurenine contribute to inflammation-induced destruction of tryptophan, which reduces serotonin production and causes the development of postpartum depression [89, 107, 124, 133].

Other possible factors in the development of postpartum depression include low levels of omega-3 unsaturated fatty acids and decreased vitamin D levels. However, these data require further consideration [107].

CONCLUSION

It is necessary to further explore the pathophysiological mechanisms of affective disorders associated with pregnancy and childbirth, as well as to differentiate the periods of pregnancy and postpartum. There is also a need to understand mechanisms associated with these time periods in detail, as mental disorders during pregnancy and postpartum may differ in their pathophysiological patterns and represent different conditions in terms of inflammation, endocrine changes, and other pathological processes (Figs. 7, 8) [102]. Questions remain as to whether stem cells can be used to treat postpartum depression [103]. Further study of mental disorders associated with pregnancy and childbirth is also required in relation to the central serotonin system and the use of selective serotonin reuptake inhibitors [67, 68, 79, 81, 82, 101, 105]. Genetic and epigenetic research is actively developing in terms of mental disorders. It is assumed that there are certain genetic markers that can predict the risk of developing depressive disorders during

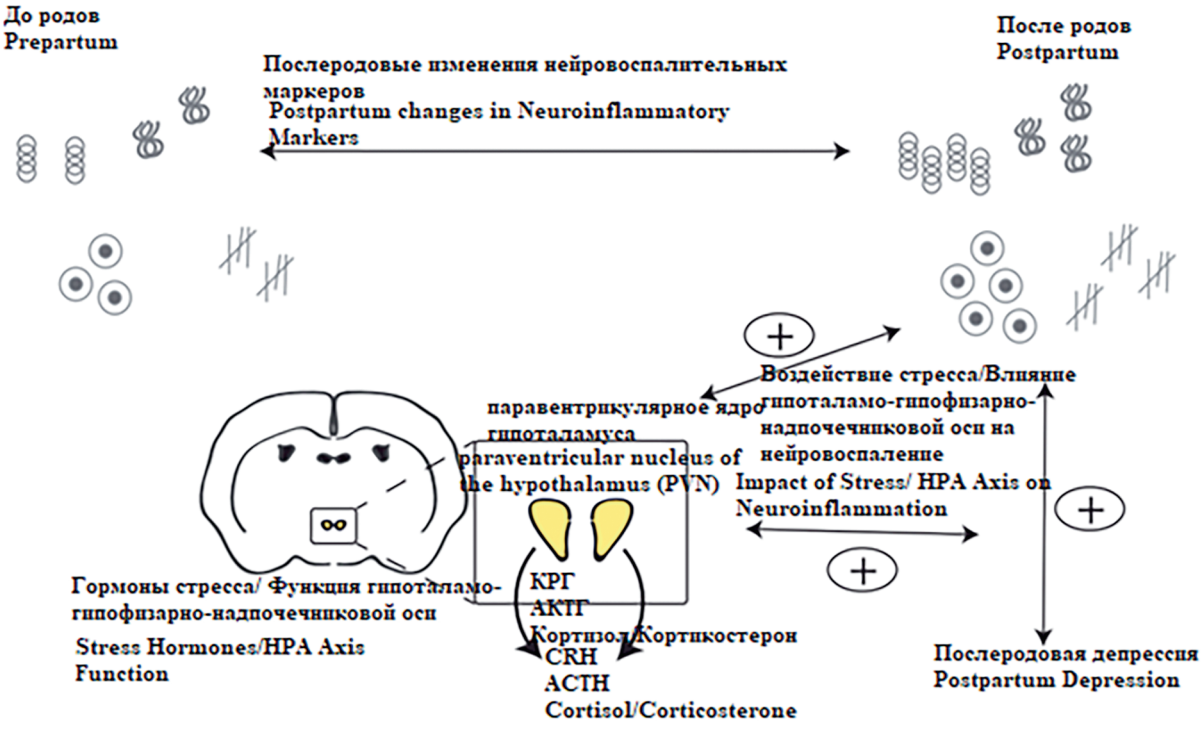

Fig. 7. Stress hormones and inflammation in postpartum depression [107]

Рис. 7. Гормоны стресса и воспаление при послеродовой депрессии [107]

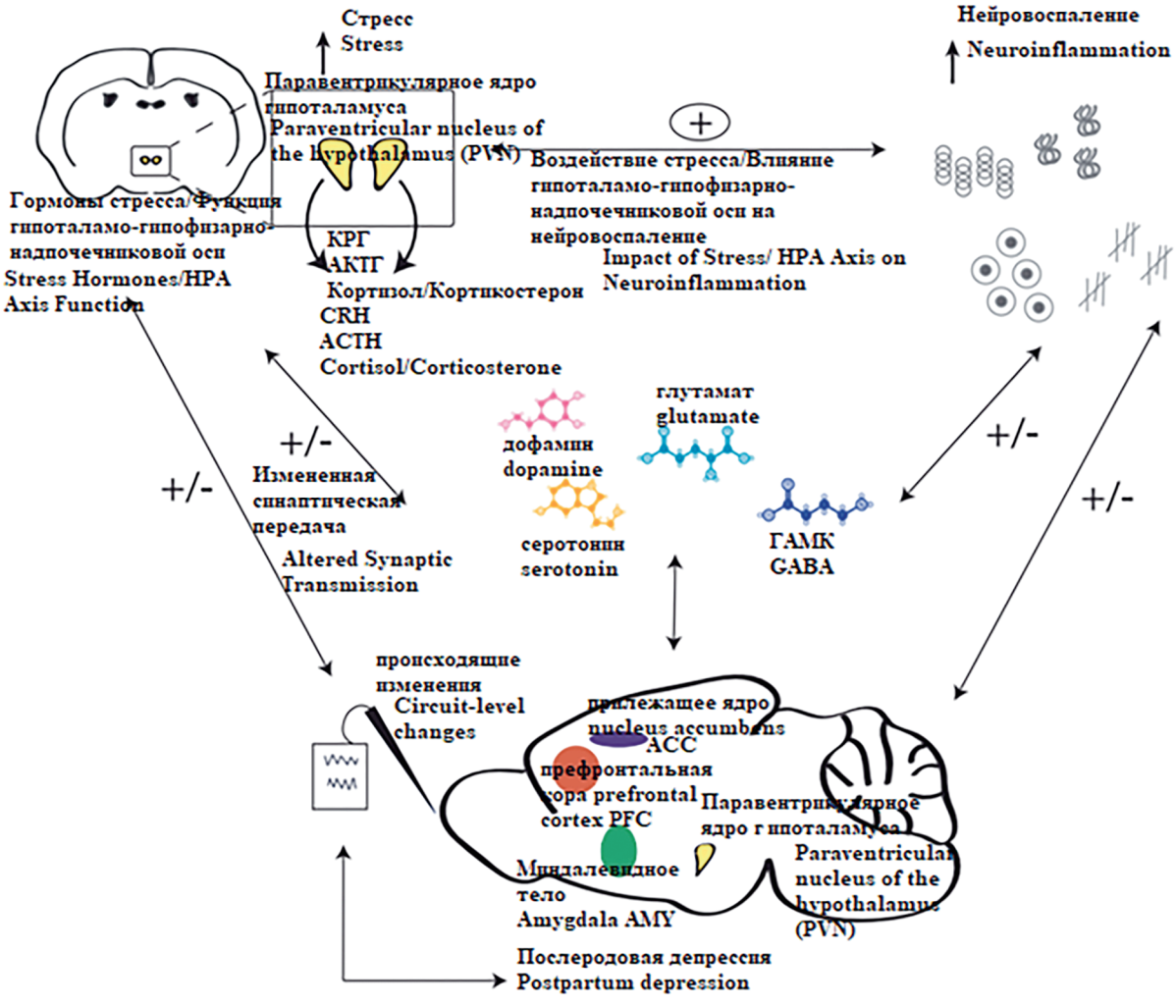

Fig. 8. Environmental impacts on synaptic transmission and circuit function in postpartum depression [88]

Рис. 8. Воздействие окружающей среды на синаптические функции передачи и цепи при послеродовой депрессии [88]

pregnancy and childbirth [107]. Thus, to date, there are no clearly identified markers that accurately predict the development of mental disorders, but sufficient diverse data has been obtained which, when taken together, can partially explain the development of mental disorders during pregnancy and after childbirth. Maternal mental disorders are currently explained by adverse external factors affecting a biologically and genetically predisposed basis. Post-traumatic stress disorder associated with pregnancy and childbirth requires separate detailed consideration [30, 59, 99].

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