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# COGNITIVE FUNCTION OF PREGNANT WOMEN: THE PROBLEM OF POSTOPERATIVE COGNITIVE DYSFUNCTION IN WOMEN AFTER LABOR

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▪ The problem of postoperative cognitive dysfunction is relevant in obstetrics due to the initial psychophysiological state of a pregnant woman and the high frequency of abdominal delivery everywhere. When choosing the optimal method of anesthesia for a cesarean section, which would minimally affect cognitive functions, it is necessary to consider the impact of anesthesia on the memory and attention of puerperas, as well as their initial cognitive status. To assess memory and attention in women of reproductive age, in our opinion, the most appropriate tests are the MoCA-test, Benton test, Wechsler test, hospital anxiety and depression scale, and a self-assessment questionnaire. These tests are recommended by psychophysiologists and have proven themselves to be well applied in daily clinical practice. Standard test kits with a formalized (quantitative) evaluation of the results allow a rapid assessment of several cognitive functions in a limited time. This review article presents the problem of the cognitive function of pregnant women and postoperative cognitive dysfunction during pregnancy.

▪ **Keywords:** women of childbearing age; pregnancy; cognitive function; memory; attention; caesarean section; general anesthesia; regional anesthesia.

# ОСОБЕННОСТИ КОГНИТИВНОЙ ФУНКЦИИ БЕРЕМЕННЫХ. ПРОБЛЕМА ПОСЛЕОПЕРАЦИОННОЙ КОГНИТИВНОЙ ДИСФУНКЦИИ У РОДИЛЬНИЦ

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▪ Проблема послеоперационной когнитивной дисфункции актуальна в акушерстве в связи с исходным психофизиологическим состоянием беременной и высокой частотой абдоминального родоразрешения во всех странах. При выборе оптимального метода анестезии при операции кесарева сечения, который бы в минимальной степе-

ни затрагивал когнитивные функции, следует учитывать влияние анестезии на память и внимание родильниц, а также их исходный когнитивный статус. Для оценки памяти и внимания у женщин репродуктивного возраста, по нашему мнению, наиболее приемлемы MOCA-тест, тест Бентона, тест Векслера, госпитальная шкала тревоги и депрессии, анкета самооценки состояния. Данные тесты рекомендованы психофизиологами и хорошо показали себя в ежедневной клинической практике. Стандартные тестовые наборы для формализованной (количественной) оценкой результатов позволяют провести экспресс-оценку нескольких когнитивных функций в условиях ограниченного времени. В обзоре представлены состояние проблемы когнитивной функции, а также проблема послеоперационной когнитивной дисфункции у беременных.

▪ **Ключевые слова:** женщины детородного возраста; беременность; когнитивная функция; память; внимание; кесарево сечение; общая анестезия; регионарная анестезия.

Changes in the cognitive sphere after surgical interventions are one of the urgent problems in medicine [1]. Close attention to this issue is primarily associated with a high frequency of postoperative cognitive disorders and an increase in the number and size of legal lawsuits [2]. General anesthesia can cause such damage to the higher nervous function in the perioperative period as mental disorders, delirium, convulsive syndrome, opisthotonus, postoperative cognitive dysfunction (POCD), sleep–wakefulness imbalance, coordination disorders, choreoathetosis, stroke, acute sensorineural hearing loss, spastic paraplegia, and malignant hyperthermia [3].

POCD is a cognitive disorder that develops in the early postoperative period. It appears clinically in the form of memory disorders, difficulty concentrating (concentration) attention, and other cognitive function imbalances (thinking, speech, etc.) and is verified according to neuropsychological testing — a decrease in testing indicators in the postoperative period by at least 10% of the preoperative level [4]. Cognitive dysfunction becomes particularly important after operations and anesthesia for women of reproductive age, who need not only to quickly adapt socially but also to care for a child. A pregnant woman develops several physiological phenomena specific to this state of the body. Two independent studies examined the effects of hormonal changes during pregnancy on the development of neurological symptoms associated with memory and cognitive impairment.

Estrogen and progesterone significantly affect brain function by affecting different types of neurons. Regardless of changes in brain cells during pregnancy, women often report increased forgetfulness and distraction. Pregnancy is a critical period for the central nervous system (CNS) because during this time, a woman is exposed to massive effects of significant hormonal fluctuations. Perhaps the sex hormones estrogen and progesterone perform a protective function, preparing the woman's brain for motherhood, when all attention should be focused on the needs of the newborn. So, attacks of hot flashes can be associated with the development of degenerative or age-related changes in some brain structures, with the most expressed changes in the hippocampus, which is responsible for memory functions and mental activity. This indicates a possible effect of hormones on spatial memory during pregnancy, which manifested in everyday distraction and forgetfulness [5].

During pregnancy, women are seized with thoughts about the upcoming changes in their life associated with the birth and care of a child. A preoccupation that is accompanied by a certain physical and mental strain can be explained from an evolutionary perspective. Scientists from the University of Leiden in the Netherlands have suggested that memory loss during pregnancy is a psychophysiologically appropriate mechanism that contributes to focusing on child care and suppressing the significance of secondary stimuli (Leiden Psychology Blog). Probably, during this period, the intuition acquires protective qualities that encourage a woman to ignore any aspects of life that do not concern the child. The widespread view of certain mental disorders in pregnant women has been reinforced by a wealth of empirical data based on observation of pregnant women. According to experts from the Mayo Clinic in Rochester (USA), pregnant and nursing mothers often complain of forgetfulness and absent-mindedness. Generally, pregnant women may mistakenly attribute all mental abnormalities to pregnancy because at this time, their thoughts are focused on a more important state for them. Simultaneously, a lack of

sleep can neutralize the positive cognitive effects of pregnancy and appear in an impaired memory or cognitive functions [5]. Many women reported that they suffered from inattention during pregnancy, had difficulty concentrating and planning, and made many mistakes when performing tasks that were not difficult for them before pregnancy. Thus, there is an opinion that the cognitive status of pregnant women is reduced. There are many reasons that pregnancy can lead to decreased cognitive function, including hormonal changes, mood changes, special responsibility awareness in connection with carrying a child, and other factors [6].

Parsons et al. (2004) found that pregnant women are characterized by forgetfulness, disorientation, reading difficulties, and "confusion in thoughts." Buckwalter et al. (1999), systematically checking cognitive functions and hormone levels during pregnancy, found that cognitive deficits that develop during pregnancy were manifested not only by temper tantrums but also by more complex processes such as impaired verbal learning and difficulties in solving cognitive tasks that require high speed [7].

Crawley et al. in 2003 studied verbal memory and attention in nonpregnant and pregnant women in the second and third trimesters, in 6 weeks, and in a year after giving birth. The authors found no differences between pregnant and nonpregnant women. Simultaneously, pregnant women themselves indicated a decrease in these functions from the second trimester. The same authors believed that the perception of pregnant women may be reduced the second time because of mood disorders. Henry and Sherwin in 2012 have shown that hormonal changes (estradiol, cortisol, and prolactin levels) during pregnancy can affect individual cognitive functions [8].

Volkov and Kligunenko (2013) found that pregnancy forms mild cognitive disorders such as absent-mindedness, dyspraxia, some memory loss, and a slight lack of control functions. Cognitive dysfunction occurs in the first trimester of pregnancy in every fourth woman. As pregnancy progresses, their frequency increases with the probability of occurrence in every second woman, and the appearances increase and continue until the end of pregnancy. Age and education level do not significantly affect the development of cognitive disorders during pregnancy. Volkov (2014) believed that cognitive dysfunction during pregnancy is associated with high estradiol and progesterone levels. Meanwhile, albumin, hemoglobin, and serum iron levels do not affect cognitive functions during pregnancy [9].

## Changes in the CNS of pregnant women with preeclampsia

Preeclampsia is a frequent and dangerous complication of pregnancy and one of the main causes of maternal mortality and perinatal losses [10]. This pathology is detected in 6–8% of pregnant women in developed countries and more than 20% of patients in developing countries. In Russia, Belarus, and Ukraine, the frequency of preeclampsia increases from year to year and reaches 16–22% and up to 28–30% in specialized high-risk hospitals [11].

The CNS, which is in close interaction with the immune and endocrine systems, ensures the maintenance of homeostasis during pregnancy. Having the properties of integrativity and plasticity, the nervous system coordinates the adaptation processes, which are crucial for the physiological course of the gestation process [12].

A CNS function imbalance, along with immunological shifts, disrupts the adaptation mechanisms and appearance of pregnancy complications including preeclampsia. Severe forms of preeclampsia can lead to maternal and perinatal mortality [13]. The frequency of severe forms of preeclampsia can be reduced by four times, and their death rate can decrease by three times if preventive treatment is made in advance in groups of pregnant women who have a high probability of developing this complication [14]. Some authors consider preeclampsia to be immunopathologic, although it is known that the nervous system significantly affects various links of general and local immunity and the occurrence of pregnancy complications.

Nowadays, adaptive changes in homeostasis indicators in physiological pregnancy, that is, the "pregnancy norm," have been studied. Each trimester of pregnancy corresponds to its own indicators of homeostasis norms. However, the scientific literature does not contain data on a comprehensive study of the state of the nervous system, which characterizes each trimester of

physiological pregnancy. A few published studies revealed a bioelectric activity of the brain without regard to the trimester of pregnancy, the autonomic nervous system [15, 16], and some hemodynamic parameters in pregnant and parturient women [17].

Mechanisms of CNS damage in severe forms of preeclampsia have not been studied sufficiently. Most of the work is devoted to the study of the state of the autonomic nervous system and changes in the mental status. It is shown that preeclampsia is caused by the pathology of the suprasegmental division of the autonomic nervous system, which appeared as a syndrome of autonomic dysfunction and psychovegetative disorders. These disorders in preeclampsia develop in approximately 90% of pregnant women and are polysystemic in nature. Patients usually complain of periodic headaches, dizziness, heart failure, palpitations, lack of air sense, sweating, stuffy room intolerance, meteotropnost, sleep–wakefulness imbalance, increased fatigue, emotional disorders in the form of irritability, sharp mood changes, anxiety feelings, and fear [18].

## Effect of anesthesia on CNS functions

Disorders of CNS function vary depending on the type of anesthesia, the patient's somatic and neurological status in the preoperative period, age, and many other factors. Because of these reasons, it is not possible to conclude that general anesthesia causes any particular type of damage. In most studies on this problem, there is evidence of some general depression of the functional CNS state in the postoperative period that is expressed as a decrease in memory, reactivity, and attention, which are more often found in POCD. In fact, cognitive (informative) functions are unfavorably affected by all known anesthetics. Thus, data are presented on the negative impact of moderate doses of general anesthetics and narcotic analgesics, including morphine, fentanyl, amphetamine, halotane, sodium oxybutyrate, hexenal, ketamine, nembutal, and propofol, in the CNS. Last year, the question of the damaging effect of anesthesia on the brain with controlled hypotension has been raised.

Not long ago, it was believed that the development of POCD is possible only for elderly patients with initial dementia and delirium, often observed after cardiothoracic operations using artificial blood circulation and after intraoperative cerebral desaturation [19]. The practical significance of neuropsychological testing for patients before planned surgeon and neuropsychological status assessment in the early postoperative period is the possibility of predicting the degree of postoperative cognitive delirium, determining preventive neuroprotective therapy [20], and choosing the correct anesthesia method that least affects cognitive functions.

Cobum (2010) showed that anesthesia-induced neurodegeneration can occur in young people and even children. Surgeries, both large and small, are often associated with cognitive changes such as memory loss and distraction.

The use of long-term epidural analgesia for pain relief during natural birth canal delivery decreases the frequency of postpartum depression 6 weeks after delivery compared with patients who were not given pain relief. No effect of the delivery method on the incidence of postpartum depression was found [21].

Radavanovic et al. (2011) reported that intraoperative awakening during general anesthesia leads to post-traumatic stress disorders, including cognitive dysfunction, in 33–56% of patients. In obstetrics, this factor is associated with surface anesthesia before fetal extraction. In terms of the frequency of intraoperative awakening, Cesarean operation ranks third, reaching 0.9% [22].

The degree of POCD severity varies widely in children and adults. Several authors consider general anesthesia as a determinant or risk factor of accelerated age-related cognitive decline, but this question is currently open. As a rule, superficial general anesthesia in the first minute of abdominal delivery (before the fetal extraction) further affects the development of memory and attention problems, which is especially significant in emergency delivery under general anesthesia [23].

POCD due to its prevalence and multifactorial nature is an urgent multidisciplinary problem that requires the participation of many specialists — anesthesiologists, neurologists, clinical neurophysiologist, pathophysiologists, and medical psychologists.

Gynecological patients after uterine amputation experience severe psychological stress, which leads to emotional problems. According to Russian researchers, the frequency of cognitive disorders after such operations ranges from 6% to 50% [24].

## Methods for evaluating POCD

Diagnosis of cognitive and psychoemotional disorders is based on the collection of complaints and anamnesis of the disease, including interviews with patients' relatives, data from neuroimaging studies, and parallel research of the cognitive and psychoemotional sphere. Self-esteem of cognitive disorders is closely related to the emotional state. Patients usually tend to exaggerate the severity of imbalances. However, patients with cognitive disorders, due to reduced criticism of themselves, cannot complain about forgetfulness. Relatives of patients may also underestimate the significance of cognitive disorders because of subjective reasons. In this regard, the most reliable way to objectify the state of cognitive functions is neuropsychological testing [25].

While working on this problem, the authors focused on the following tests for the rapid assessment of the cognitive status of obstetric patients.

The Montreal Cognitive Assessment (MoCA) test allows you to evaluate various aspects of a cognitive activity: memory, "frontal" functions (the test of connecting letters and numbers, speech fluency, generalization, etc.), nominative speech function (naming animals), and visual–spatial praxis (cube and clock). This is why the technique can be used to diagnose both vascular and primary degenerative cognitive disorders. The sensitivity of the MoCA test is high; for this reason, the Montreal cognitive scale is suitable for detecting both severe and moderate cognitive disorders. At the same time, the formalized assessment system of the MoCA test does not provide gradation by severity of imbalances depending on the points scored. The basis for determining the severity of cognitive impairment is the degree of functional restriction in everyday life, which is mostly established when talking with relatives. The test is presented in the form of a table that must be filled in with a doctor during testing.

The hospital anxiety and depression scale is designed for primary detection (screening) and determination of the severity of depression and anxiety in the general medical practice of adults. The measured variables are psychological appearances of anxiety and depression. The questionnaire consists of 14 questions corresponding to two subscales, namely anxiety and depression. For each statement, there are four response options that reflect the gradation of the severity of the sign and are encoded by increasing the severity of the symptoms from 0 (absent) to 4 points (maximum severity). To ensure the spontaneity of the patient's response, it is desirable to set a clear framework for answering questions and filling in the scale (about 20–30 min). When interpreting the data, the total index for each subscale (anxiety and depression) is taken into account, and three areas of values are distinguished: 0–7 points, normal; 8–10 points, subclinically expressed anxiety/depression; and 11 points and higher, clinically expressed anxiety/depression.

The self-assessment questionnaire was developed by the staff of the Military Medical Academy and is designed to study the subjective state of health and identify somatic complaints of students. The survey was conducted using special registration forms. The respondent is offered seven pairs of polar statements that characterize a certain state. The patient must evaluate the severity of each of them on a special scale. In addition, the method includes a list of 19 complaints that allow you to obtain detailed information about the features of your health status. You can fill out the questionnaire multiple times during the day, which is especially important when studying the dynamics of the state during activity. This technique can be used not only for students but also for patients of various profiles [26].

The Benton test has proven its sensitivity in detecting hyperkinetic syndrome, and it is effective in Alzheimer's disease, traumatic brain injury, and other intellectual and cognitive disorders. The Benton test is most often used in neuropsychological practice since it is the least time-consuming for the subject and easy to process for the experimenter. Its focus is visual short-term memory. The design feature is the reproduction (drawing) of figures that are presented as standards for a certain strictly fixed time. A set of geometrically relatively abstract shapes contains 10 series. It evaluates both the number of correctly reproduced tasks and the quality of errors. The overall low score of the test is typical for patients with diffuse organic brain damage accompanied by memory impairment [27].

The Wexler test (a subtest repetition of digital series) aimed to study memory and attention.

Performing its subtest requires a lot of concentration so its results are affected by both external and internal interferences, especially of an emotional nature. The imbalance of noise immunity is considered by many authors to be a sign of internal anxiety, which prevents you from focusing on the task. The test results are sensitive to cerebral pathology (especially temporal localization).

Along with neuropsychological testing, there is the concept of a biomarker of brain damage. The ideal biomarker has not yet been found since the criteria for its determination are high: clear biokinetic properties, rapid detection in accessible biological environments in the first hours after injury, high sensitivity and specificity for a damage to the brain substance, reflection of the dynamics of the disease and the effectiveness of a treatment, prediction of the functional outcome, and ease of identification and measurement using widely available, simple methods; the content of the biomarker in biological fluids should correlate with the severity of the injury and provide information about the nature of the injury (ischemic, hemorrhagic, or traumatic) [28].

Most of the biomarkers considered are proteins that are derived from astroglia or neurons. GFAP, PARK7, nucleoside diphosphate kinase, NR2A/2B antibodies, NR2A/2B protein, S-100 protein, neuron-specific enolase, natriuretic peptide, and matrix metalloproteinase 9 are the most well studied and commonly used.

There is a concept of biomarkers of apoptosis, which is a programed asynchronous cell death. Cathepsins are a group of proteases that can initiate and enhance apoptosis. Cytochrome C participates in the activation of caspase-9, which then activates caspase-3. Death receptors contain cytoplasmic death domains (DDs), which, by binding to the death ligand, attract adaptive proteins containing DD and the performer domain of death — death effector domain (DED). The interaction of DED and procaspase leads to the autoproteolytic and caspase cascade activation. A family of intracellular proteases called caspases 1, 3, 8, and 9 represents the effector arm of the apoptotic pathway. The activity of caspases plays an important role in cell death after a stroke. In experiments, it was shown that the inhibition of caspase-1 reduced the volume of the affected stroke area by 40–50%. Physiological inhibitors of apoptosis include growth factors, extracellular matrix, CD40L, neutral amino acids, zinc, estrogens, and androgens. Cytokines both induce and prevent apoptosis. The same interleukin can be both an inducer and inhibitor of apoptosis [28].

## Cerebroprotection of pregnant women

The practical significance of the POCD concept is the possibility of timely diagnosis of cognitive disorders and an early initiation of neuroprotective treatment [29]. In preeclampsia, cerebroprotection should be performed at all stages of pregnancy and childbirth. The initial cognitive deficit of pregnant women with preeclampsia makes it necessary to take care of the issue of protecting the brain in advance. Unfortunately, the most effective drugs, namely Cytoflavin® and Tanakan®, are contraindicated in pregnant women.

To assess the cognitive status and choose intraoperative cerebroprotection, a neurologist's consultation is necessary [30]. One of the ways to medically protect the brain during the termination of blood flow through the aneurysm-bearing vessel is a significant deepening of drug-induced sleep with the help of noninhalation anesthesia before the appearance of the burst–suppression pattern on the electroencephalogram. This overly pronounced inhibition of a bioelectric brain activity may be an independent cause of POCD development. At the same time, other authors deny the negative impact of deep anesthesia on the state of higher mental functions [31].

For cerebroprotection, nootropic drugs are widely used, which specifically affect higher integrative brain functions, improve memory, facilitate the learning process, stimulate intellectual activity, increase resistance to damaging factors, and improve cortical–subcortical connections. They can improve cognitive (informative) functions for healthy people and especially for those with various cognitive disorders [32].

The most common approaches to general anesthesia for carotid endarterectomy are total intravenous anesthesia with propofol and inhaled anesthesia with sevoflurane. These anesthetics have cerebroprotective properties that can reduce cerebral blood flow and oxygen consumption and decrease the release of neuronal damage markers, including the pharmacological preconditioning mechanism. Studies comparing the effects of

propofol and sevoflurane on carotid endarterectomy outcomes are few and contradictory, ranging from the more favorable effects of propofol or the lack of significant differences between anesthetics to the benefits of inhaled anesthesia [33].

## Conclusion

Pregnant women are at risk of developing POCD. The conducting of a pregnant woman with preeclampsia is particularly difficult. This interdisciplinary problem requires joint efforts of obstetricians and gynecologists, neurologists, and anesthesiologists. In this case, the main goal of the anesthesiologist is to conduct anesthesia as carefully as possible, considering the recommendations of neurologists and obstetricians. The difficulties of a surgical intervention, and first of all the choice of an anesthetic aid to ensure adequate anesthesia before fetal extraction, put the doctor before the choice of mother–fetus. As a rule, surface anesthesia in the first minute of abdominal delivery leaves an imprint on memory and attention, which is especially important for an emergency delivery under general anesthesia. Otherwise, preference should be given to regional methods of anesthesia, which proves the need for research in the field of cognitive functions of pregnant women.

The clinical significance of conducting neuropsychological testing for patients before the planned surgery and evaluating the neuropsychological status in the early postoperative period is to assess the preoperative cognitive status with the possibility of preventive neuroprotective therapy and the optimal choice of anesthesia methods that at least affect cognitive functions.

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