THE IMPACT OF MATERNAL OBESITY AND DIABETES ON FETAL BRAIN DEVELOPMENT (MECHANISMS AND PREVENTION)

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The rise in the incidence of obesity and diabetes mellitus, particularly in patients of reproductive age, has become a serious concern worldwide, as this maternal pathology not only causes high perinatal morbidity and mortality but is also responsible for developing neuropsychiatric disorders in the subsequent years of descendants’ life [1–3]. Researchers are paying special attention on studying the adverse effects of gestational diabetes mellitus that complicate the course of pregnancy in overweight and obese women [4, 5], the count of which specifically among the population of reproductive-age women has increased to 70% in the United States, and 20%–27% in Europe [6]. In addition, an increase in the nervous system disorders among children and adolescents is also being registered worldwide [3, 7], therefore, the clarification on the mechanisms underlying their development and formulating the preventive measures thereby represent an urgent problem [8, 9].

Moreover, numerous epidemiological studies have shown that descendants of obese women have a 3.6-fold increased risk of impaired cognitive development [10], a 2.8-fold increased risk of attention-deficient hyperactivity disorder [11, 12], and a significantly reduced IQ index [9, 13, 14]. A relationship has been observed between the frequency of autism and the value of the mother’s body mass index [15–17], as well as between maternal obesity and the development of aggressive behavior, anxiety, depression, and schizophrenia in descendants [18–22].
Likewise, similar results were obtained when studying the effect of diabetes mellitus on the development of the central nervous system of the descendants.

While studies have disclosed and described disorders of cognitive functions, speech, and psychomotor development, attention has been paid to the high frequency of attention-deficit hyperactivity disorder and schizophrenia [23–26], especially when pregnancy is complicated by diabetes mellitus [27, 28]. It is emphasized that insufficient glycemic control can lead to pronounced speech and intellectual development disorders in descendants to a greater extent [29]. Consequently, if a pregnant woman has both obesity and diabetes mellitus, the adverse effect of the environment on the operation of genetic information and brain development increases significantly, which can have long-term consequences.

Based on the literature, in cases of obesity and gestational diabetes mellitus, there is a combination of hormonal and metabolic disorders in a single functional “mother–placenta–fetus” system [30]. The pregnant woman has hyperleptinemia, hyperinsulinemia, and hyperglycemia due to insulin resistance [31, 32]. The lipid profile of blood serum is abnormal, as the levels of triglycerides, cholesterol, low- and very low-density lipoproteins are increased and that of high-density lipoproteins are reduced [33]. Hyperglycemia, hyperlipidemia, hyperinsulinemia, and insulin resistance contribute to the activation of the synthesis of free oxygen radicals in the mitochondrial chain, an increase in nitric oxide production, a deterioration of the electron transport system and mitochondrial permeability, which results in the development of mitochondrial dysfunction which is the most significant factor in the initiation of pathological processes in almost all functional systems of the body (nervous, immune, endocrine, etc.) [34].

Moreover, the endothelial dysfunction occurs as the function of cellular membranes, receptors, enzymes, and intracellular structures, in particular the endoplasmic reticulum, is disrupted by the oxidative modification of proteins [35]. While the oxidative stress of the endoplasmic reticulum induces the activation of the inflammatory response, thereby inducing the secretion of interleukins (IL-1α, IL-1β, IL-6) in adipose tissue [36], the totality of pathological processes in the body of a pregnant woman affects negatively the morphofunctional formation of the placenta. Impairment of its trophic, metabolic, endocrine, and transport functions underlies the programming of perinatal and long-term pathology of descendants [37].

Further, in early ontogenesis, the child’s brain undergoes significant changes in both structural and functional organization, including the processes of neurulation, cell proliferation and migration in the antenatal period, and synaptogenesis in the postnatal period, as well as an increase in the size and complexity of the structure of the dendritic tree of most neurons. Myelination of neural processes and terminations also start at birth. The environment and the genetic apparatus interact at all stages of brain development. Interestingly, gene expression in brain cells can be varied across certain limits by selective activation or deactivation of DNA sections. In newborns from obese and diabetic mothers, abnormalities relating to the gene expression involved in the regulation of the development of brain structures, inflammation and immune signaling, carbohydrate and lipid homeostasis, and oxidative stress have been established [38, 39]. Epigenetic changes under the influence of unfavorable environmental factors determine the consequences of perinatal brain damage, which is studied intensively in the field of neurobiology in animals.

Moreover, several experimental studies have demonstrated that among the descendants of obese mothers and in patients with diabetes mellitus, the lipid peroxidation is increased in the hippocampus, neuronal proliferation and the formation of neural networks are impaired [40], the activity of receptors for insulin and insulin-like growth factor is suppressed [41], and the volume of the cerebral cortex is reduced [42]. Oxidative stress in the brain persists in the subsequent months of life, which affects the rearrangement of chromatin in the nuclei of cells and underlies cognitive impairment, increased excitability, convulsive syndrome, and depression [43].

Generally, in cases of obesity and gestational diabetes mellitus, the level of proinflammatory cytokines is increased in the blood of mothers, in the placenta, and in the fetus [44, 45], which disrupts microcirculation and oxygenation of brain
structures, activates the production of cytokines and free radicals by microglia cells, inhibits the maturation of oligodendrocytes and the process of myelination, and leads to the activation of peroxidation and damage to neuronal structures [46–48]. Subsequently, the child experiences mental retardation and autistic disorders develop [49]. Numerous experimental studies have confirmed that offspring of obese females are attention-deficit and have expressed neuronal and systemic inflammation, hyperactivity, and impaired cognitive ability [50, 51].

Inflammatory changes in adipose tissue and skeletal muscles of the fetus are known to contribute to insulin resistance and excessive production of insulin by the pancreas [52]. Insulin receptors are expressed significantly in the cortex and hippocampus, and synaptic insulin signaling plays a key role in learning and memory processes [53, 54]. In an experiment with maternal obesity and hyperinsulinemia, suppression of the expression of genes for insulin receptors and glucose transporters was registered in the hippocampus of the fetus, which had an unfavorable effect on the functional development of the central nervous system [55].

Hyperleptinemia and leptin resistance in pregnant women with obesity and gestational diabetes mellitus also represent a significant adverse factor in the sensitive period of fetal brain development, since the suppression of the expression of leptin receptor genes in the cortex, thalamus, and hypothalamus disrupts the differentiation of neurons, synaptic plasticity, and programs motormental retardation in a child [56, 57].

Further, an increase in the level of proinflammatory cytokines in the fetal brain has been noted to cause reduction in the density of serotonin axons, which affects negatively neuronal migration, cortical neurogenesis, promotes neuronal apoptosis, and ultimately leads to hyperactivity and anxiety in the offspring of experimental animals [55, 58].

In maternal obesity and gestational diabetes mellitus, not only the development of the serotoninergic but also the dopaminergic system of the fetal brain is impaired, which is involved in the regulation of various forms of behavior, including eating behavior [59–62]. In humans, the dopamine signaling is known to be impaired in the genesis of schizophrenia, autism, hyperactivity syndrome, and eating disorders [63]. It should be noted that the ability to restore and develop impaired functions in descendants is reduced due to suppressed expression of the brain-derived nerve growth factor gene in the cortex and hippocampus [64, 65]. The results of experimental studies have shown that this leads to a deficit in spatial memory and inability to learn not only in the first weeks of life but also in adult life of animals [66].

The data obtained in the last decade on the effect of maternal obesity and diabetes mellitus on the development of the child’s brain and the mechanisms that determine the adverse consequences have attracted the attention of researchers in order to develop methods for prevention and early diagnostics of pathology of the central nervous system. It has been established that the prohibition of a high-fat diet during pregnancy and lactation, together with physical activity, promotes normal development of hippocampal neurons, improved synaptic plasticity, and learning [67]. According to studies, prenatal administration of melatonin prevents the development of an inflammatory process in the brain of fetuses of pregnant rats with induced inflammation [68], as melatonin and its metabolites activate reparative processes and axonal growth that prevents the subsequent development of neurological disorders [69]. Additionally, under conditions of oxidative stress, melatonin has been observed to reduce the damage caused by hypoxia, improve the maturation of oligodendroglia, and suppress the activation of microglia, which contributes to the normalization of the myelination process in newborn animals [70]. In addition, in hyperglycemia during diabetic pregnancy in mice, it stimulated the proliferation of stem cells, suppressed apoptosis, and prevented malformations of the brain and spinal cord [71], therefore the authors recommended the use of melatonin in clinical practice for reprogramming disorders of brain development in the child’s perinatal life [72]. A serious indication is the absence of the circadian rhythm of maternal melatonin in obesity and diabetes, which plays a key role in the development of the fetal brain and in its protection from adverse environmental impacts [73].

Thus, neuropsychic diseases in the descendants of obese and/or diabetic women should be prevented...
even at the stage of family planning and should be aimed at sleep normalization, metabolism, antioxidant status of the body in combination with constant glycemic control, identification and treatment of concomitant pathology, with an individual selection of diet and physical activity [74]. Until the required health indicators are achieved, the specific methods of contraception are recommended [75]. Strict control over the state of glycemia, the use of folic acid, antioxidants, vitamins, polyunsaturated fatty acids during pregnancy, prevention of fetal hypoxia during childbirth, hypoglycemia of the newborn, and breastfeeding provide conditions for the normal development of the brain of children of sick mothers [76].

References


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