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Гестационный сахарный диабет — фактор риска развития нервно-психической патологии у потомства

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АННОТАЦИЯ

В обзоре обобщены современные представления о гестационном сахарном диабете как независимом факторе риска развития долгосрочных нервно-психических заболеваний у потомства. Рассмотрены закономерности генетической программы морфофункционального развития мозга во время внутриутробной жизни, обеспечивающие основу для краткосрочных и долгосрочных функций центральной нервной системы. Приведены результаты экспериментальных и клинических исследований, объясняющих патофизиологические механизмы вредного воздействия на мозг плода гипергликемии, гиперинсулинемии, гиперлептинемии, окислительного стресса и системного воспаления у матери при осложнении беременности сахарным диабетом. Обсуждены виды структурных аномалий мозга и нервно-психические последствия. Представленный материал обосновывает необходимость профилактики нервно-психических заболеваний у потомства от женщин с ожирением и другой сопутствующей патологией еще на этапе планирования семьи, а при наступлении беременности — целесообразность раннего скрининга и лечения гестационного сахарного диабета, а также нейропротекции в перинатальный период жизни ребенка.

Ключевые слова: гестационный сахарный диабет; плод; мозг; нервно-психическая патология.

Как цитировать

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Gestational diabetes mellitus as a risk factor for neuropsychiatric pathology in offspring

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ABSTRACT

This review article summarizes current ideas about gestational diabetes mellitus as an independent risk factor for long-term neuropsychiatric morbidity in offspring. Herein, we describe the genetic programming patterns of morphofunctional brain development during intrauterine life, which provide the basis for short- and long-term functions of the central nervous system. The results of experimental and clinical studies are presented that explain the pathophysiological mechanisms of the harmful effects on the fetal brain of hyperglycemia, hyperinsulinemia, hyperlepthyremia, oxidative stress, and systemic inflammation in the mother with pregnancy complicated by diabetes mellitus. We also discuss structural brain abnormalities and neuropsychiatric consequences. The article substantiates the need for the prevention of neuropsychiatric diseases in the offspring of women with obesity and other concomitant pathology at the stage of family planning, and at the onset of pregnancy, the expediency of early screening, treatment of gestational diabetes mellitus and neuroprotection in the perinatal period of the child's life.

Keywords: gestational diabetes mellitus; fetus; brain; neuropsychiatric pathology.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is characterized by hyperglycemia first detected during pregnancy but not meeting the criteria for a diabetes mellitus diagnosis. The prevalence of GDM varies by region: 7.1% in North America and the Caribbean, 7.8% in Europe, 10.4% in South and Central America, 14.2% in Africa, 14.7% in the Western Pacific, 20.8% in Southeast Asia, and 27.6% in the Middle East and North Africa [1]. In Russia, this indicator is estimated at 4.5%–9.2% [2]. GDM is a significant medical and social issue in Russia and worldwide [3]. This maternal condition is associated with high perinatal morbidity and mortality and is an independent risk factor for the development of long-term neuropsychiatric diseases in offspring [4–8]. Studies have described cognitive [9, 10, 11], speech [12], and psychomotor development [13] issues and anxiety and depression symptoms in children [14]. Moreover, studies have shown a high incidence of attention deficit hyperactivity disorder [15, 16], autism [6, 17, 18], and schizophrenia [19–22] resulting from adverse effects during intrauterine development of children born to mothers with GDM. Recent research has focused on elucidating the mechanisms that explain the harmful effects of maternal diabetes on the fetal brain and its relationship with neurodevelopmental disorders in offspring. Brain development during fetal life provides the foundation for short- and long-term central nervous system functions.

BRAIN DEVELOPMENT

Brain morphogenesis involves three stages: cortical histogenesis and synapse development (7–23 weeks of gestation), cortical morphogenesis and white matter development (20–40 weeks of gestation), and neuronal myelination (from 18 weeks of gestation to adulthood) [23].

Neuronal differentiation occurs along with synapse formation, myelin maturation, and new neurotransmitter synthesis, as well as vascular development [24, 25]. During the intrauterine period, brain volume increases, furrows form, the shape of the ventricles changes, and subarachnoid spaces decrease. The second half of pregnancy and the first 28 days of postnatal life are crucial for the development of brain structures and neuronal networks. During this time, neurotransmitters and neuromodulators play a fundamental role [26–28]. Serotonin is critical in neural crest stem cell regulation and plays a key role in nerve cell survival, growth, differentiation, migration, and synaptogenesis. This is due to the presence of serotonin receptors and transporters that precede the emergence of serotoninergic neurons [29, 30]. During brain development, there is a gradual transition from an early placental source of serotonin, which is vital for forebrain development, to a later endogenous source synthesized in the fetal brain. This endogenous source is involved in the formation of neuronal cortical networks [31]. Catecholamines (norepinephrine, adrenaline, and dopamine) are the neurotransmitters involved in embryonic development. Norepinephrine is essential for cortical maturation, and dopamine modulates ion channels, including calcium-ionized currents, in several vertebrate neurons [32]. During embryonic development, acetylcholine synthesized in neuronal cells becomes a crucial neurotransmitter, controlling inflammation and promoting normal cortical development. Furthermore, corticotropin-releasing hormone is significant in synapse formation, cell survival, and plasticity, particularly in the olfactory bulb [28].

During weeks 24–40 of gestation, the risk of brain damage increases because of extensive cell replication and differentiation. Several factors, including hypoxia, ischemia, inflammation, excitotoxicity, and oxidative stress, can disrupt normal brain structure development, leading to unfavorable long-term consequences. Thalamocortical and limbic pathways develop earlier during pregnancy, creating a window of vulnerability. Adverse effects during this period can lead to sensory, motor, and behavioral disturbances. Damage to later developing associative cortico-cortical connections may result in serious cognitive impairment.

DISRUPTION OF FETAL BRAIN DEVELOPMENT IN PREGNANCIES COMPLICATED BY DIABETES MELLITUS

Pregnant women with GDM and obesity exhibit hyperleptinemia, hyperglycemia, hyperinsulinemia, and insulin resistance. Additionally, their blood levels of insulin-like growth factors, triglycerides, cholesterol, low-density lipoproteins, and inflammatory factors, such as interleukin-6 and tumor necrosis factor alpha, are elevated [33]. Exposure to unfavorable factors can disrupt the trophic, metabolic, endocrine, and transport functions of the placenta and can induce neurological and psychiatric diseases in the offspring [34, 35]. Microstructural abnormalities of white matter were observed in various brain regions (i.e., corpus callosum, posterior part of the internal capsule, and thalamus) in children born to mothers with GDM. These abnormalities largely cause impaired neurocognitive development, indicating a direct effect of GDM on the offspring's brain [36]. Impaired tactile-sensory behavior has been observed in the offspring of mothers with GDM, along with the suppression of axonal development in the thalamic cortex [37]. Maternal hyperglycemia has been associated with increased width of the posterior lateral fetal ventricles, transparent cavity septum, large cisterna, and thalamus and transcerebellar diameter and dendrite growth retardation in the fetal brain [38–40]. These effects occur three times more frequently with inadequate diabetes control

(glycosylated hemoglobin level >7%) during organogenesis in the first trimester [41]. Impaired cognitive development is a consequence of hyperglycemia [42]. Increased maternal glucose intake can cause hyperinsulinemia, which stimulates oxidative metabolism and leads to fetal oxygen deficiency and adverse neurological consequences [43]. The authors reveal that earlier diagnosis of GDM is critical owing to increased glucose intake during the maturation of new brain structures and connections. Promptly implementing a maternal glycemic control strategy can be beneficial for fetal brain development [4].

Maternal hyperglycemia causes oxidative stress, which contributes to the development of diabetic embryopathy and fetopathy by promoting cell apoptosis and disrupting gene expression [44, 45]. GDM results in persistent epigenetic modifications through DNA methylation, histone acetylation, and microRNAs in genes that affect neuroendocrine functions, energy homeostasis, and metabolism [46–49]. Gene expression disorders result in changes in enzyme activity and dysregulation of cell differentiation and development. These changes lead to a decrease in cell number, an imbalance between different cell populations, and irreversible morphofunctional disorders [50]. For instance, the offspring of mothers with GDM had lower methylation levels in two regions, including the promoter of the gene associated with autism spectrum disorders [51].

Under conditions of increased oxidative stress and insufficient antioxidant protection in GDM, the levels of neurotrophins, particularly brain nerve growth factor, are altered. This factor contributes in neuronal differentiation, synaptogenesis, and plasticity and acts as a mediator of glucose utilization and energy metabolism [52]. Clinical and experimental studies have demonstrated that GDM results in reduced cerebral nerve growth factor expression, increased tumor necrosis factor alpha concentration, impaired cell proliferation, and enhanced apoptosis in the hippocampus of offspring. These changes lead to impaired nervous system development [53–55].

Maternal GDM leads to systemic inflammation, releasing substantial amounts of pro-inflammatory cytokines that activate fetal immune cells upon entering the fetal bloodstream. These molecules and cytokines, including interleukin-6, can penetrate the blood–brain barrier and contribute to neuroinflammation [56]. This, combined with the toxic effects of hyperglycemia on the fetal brain, can result in severe neurological sequelae and mental illness [57]. Under conditions of increased levels of pro-inflammatory cytokines in the fetal brain, decreased density of serotonin axons was observed. This negatively affects neuronal migration and cortical neurogenesis, promotes neuronal apoptosis, and leads to hyperactivity and anxiety in the offspring of experimental animals [58]. Microglia cells produce cytokines and free radicals that can suppress oligodendrocyte maturation and myelination, inducing damage of neuronal structures [59]. Adipocytokines, including pro-inflammatory ones such as leptin, may mediate or worsen intrauterine neuroinflammation caused by maternal metabolic disturbances in obesity and GDM [60]. This can affect the development of the dopaminergic system in the fetal brain, which is involved in the onset of schizophrenia, autism, hyperactivity syndrome, and eating disorders [61, 62].

Accumulating evidence reveals that GDM can lead to impaired serum iron levels in offspring, and this effect is strongly correlated with maternal glucose levels [63]. The first trimester of pregnancy is a critical period of high iron requirement to adequately support the developing fetal brain. Studies have shown that iron deficiency alters neuronal differentiation in the hippocampus and affects the architecture of dendritic cells in the brain and levels of neurotransmitters and neuromodulators such as dopamine, norepinephrine, and serotonin [64]. Research has demonstrated that iron deficiency during fetal development can negatively impact neurological function. Additionally, iron deficiency has been associated with dysregulation of gene expression critical for brain function and synaptic plasticity [65].

Docosahexaenoic acid (DHA), an omega-3 fatty acid, is necessary for nervous tissue, retina, mitochondrial membrane, and fetal cerebral cortex development. Animal studies have demonstrated that omega-3 fatty acid deficiency leads to reduced DHA levels in the cerebral cortex, resulting in learning disabilities [66]. Moreover, GDM impairs lipid metabolism and docosahexaenoic acid transport to the fetus [67]. A meta-analysis of 24 studies confirmed that cord blood in GDM pregnancies contains low levels of polyunsaturated fatty acids, which can lead to severe neurocognitive effects in the offspring [68]. Therefore, pregnant women with GDM should consume adequate amounts of omega-3 fatty acids [69].

CONSEQUENCES OF PROGRAMMING NEUROPSYCHIATRIC PATHOLOGY IN OFFSPRING DURING PREGNANCY COMPLICATED BY DIABETES MELLITUS

Epidemiological studies have shown that children aged 4.5–14.5 years, whose mothers had GDM, experience fine and large motor skill developmental delay. This is particularly evident when the mother has higher glycosylated hemoglobin levels or severe acetonuria [44]. Between ages 16 and 60 months, children born to mothers with GDM exhibited lower motor function scores [70–72]. Impaired development of the serotoninergic and dopaminergic systems of the fetal brain in cases of maternal obesity and GDM may contribute to the development of schizophrenia, autism, hyperactivity syndrome, and eating disorders [57].

Attention deficit hyperactivity disorder (ADHD) is a common developmental disorder of the nervous system. Children with ADHD may experience learning difficulties, speech impairments, communication difficulties, and an increased risk of substance abuse [73]. Research has shown that the severity of hyperglycemia during pregnancy is an independent risk factor for ADHD [74]. GDM increased the risk of future ADHD 2.6-fold compared with controls [75]. A study reported a sixfold increase in the probability of ADHD and autism in children aged below 11 years born to mothers with GDM and high body mass index during pregnancy [22]. A correlation between GDM and increased incidence of autism in offspring was found [18]. Further, a retrospective cohort study showed that GDM diagnosed before week 26 of gestation significantly increases the risk of autism [17].

Several studies have indicated that maternal diabetes may increase the risk of offspring developing schizophrenia [19]. Children exposed to maternal hyperglycemia have been observed to develop psychiatric disorders at a younger age [6, 20]. Increased risk of schizophrenia has been associated with oxidative stress, altered lipid metabolism, high inflammatory cytokine levels, and impaired neurotransmitter metabolism [20]. However, further research is required to determine the role of these factors in maternal GDM and their potential effect on the development of psychiatric disorders in offspring.

CONCLUSIONS

GDM incidence has been increasing. Therefore, further research on the pathophysiological mechanisms of the harmful effects of GDM on the development of the child's nervous system is warranted [76]. These findings indicate that preventing neuropsychiatric diseases in offspring of women with obesity and/or diabetes should begin during family planning and focus on normalizing the body's metabolism and antioxidant status. Prophylaxis should be combined with continuous glycemic control, identification and treatment of concomitant pathology, and individualized selection of diet and exercise regimen. In some cases, early screening for GDM should be considered. Obesity and GDM do not exhibit the circadian rhythm of maternal melatonin, which plays a crucial role in the development of the fetal brain and its protection from adverse environmental influences [77]. Determining the state of a woman's circadian system can help assess the risk of pregnancy complications and offspring disease programming. Further, it can also serve as a basis for using melatonin in clinical practice to reprogram brain development disorders during the perinatal period [78].

ADDITIONAL INFORMATION

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