УДК 618.3-056.25:613.25:616.379-008.64]-06:616-053.2-009
https://doi.org/10.17816/JOWD69333-38

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

© I.I. Evsyukova

The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia

For citation: Evsyukova II. The impact of maternal obesity and diabetes on fetal brain development (mechanisms and prevention). *Journal of Obstetrics and Women's Diseases.* 2020;69(3):33-38. https://doi.org/10.17816/JOWD69333-38

Received: April 14, 2020 Revised: May 21, 2020 Accepted: June 8, 2020

▪ The review presents the results of clinical and experimental studies that indicate a high frequency of neuropsychiatric diseases and mechanisms of adverse effects during intrauterine development, determining long-term effects in offspring of obese and / or diabetic mothers. Approaches to prevention in the planning stage and during pregnancy are also discussed in the review.

▪ **Keywords:** obesity; diabetes; child; brain; development; mechanisms.

ВЛИЯНИЕ ОЖИРЕНИЯ И САХАРНОГО ДИАБЕТА МАТЕРИ НА РАЗВИТИЕ МОЗГА РЕБЕНКА (МЕХАНИЗМЫ И ПРОФИЛАКТИКА)

© И.И. Евсюкова

Федеральное государственное бюджетное научное учреждение «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта», Санкт-Петербург

Для цитирования: Евсюкова И.И. Влияние ожирения и сахарного диабета матери на развитие мозга ребенка (механизмы и профилактика) // Журнал акушерства и женских болезней. – 2020. – Т. 69. – № 3. – С. 33–38. https://doi.org/10.17816/JOWD69333-38

Поступила: 14.04.2020 Одобрена: 21.05.2020 Принята: 08.06.2020

▪ В обзоре представлены результаты клинических и экспериментальных исследований, свидетельствующие о высокой частоте нервно-психических заболеваний и механизмах неблагоприятных воздействий в период внутриутробного развития, определяющих долгосрочные последствия у потомства матерей, страдающих ожирением и/или сахарным диабетом. Рассмотрены подходы к профилактике на этапе планирования и в процессе беременности.

▪ **Ключевые слова:** ожирение; сахарный диабет; ребенок; мозг; развитие; механизмы.

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 serotonergic 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

1. Damm P, Houshmand-Oeregaard A, Kelstrup L, et al. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia*. 2016;59(7):1396-1399. https://doi.org/10.1007/s00125-016-3985-5.
2. Connolly N, Anixt J, Manning P, et al. Maternal metabolic risk factors for autism spectrum disorder-an analysis of electronic medical records and linked birth data. *Autism Res*. 2016;9(8):829-837. https://doi.org/10.1002/aur.1586.
3. Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. *Prenat. Diagn*. 2017;37(1):95-110. https://doi.org/10.1002/pd.4932.
4. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care*. 2007;30 Suppl 2:S141-S146. https://doi.org/10.2337/dc07-s206.
5. Gabbay-Benziv R, Baschat AA. Gestational diabetes as one of the "great obstetrical syndromes" – the maternal, placental, and fetal dialog. *Best Pract Res Clin Obstet Gynaecol*. 2015;29(2):150-155. https://doi.org/10.1016/j.bpobgyn.2014.04.025.
6. Devlieger R, Benhalima K, Damm P, et al. Maternal obesity in Europe: where do we stand and how to move forward? A scientific paper commissioned by the European board and college of obstetrics and gynecology (EBCOG). *Eur J Obstet Gynecol Reprod Biol.* 2016;201:203-208. https://doi.org/10.1016/j.ejogrb.2016.04.005.
7. Olfson M, Blanco C, Wang S, et al. National trends in the mental health care of children, adolescents, and adults by office-based physicians. *JAMA Psychiatry*. 2014;71(1):81-90. https://doi.org/10.1001/jamapsychiatry.2013.3074.
8. Morris G, Fernandes BS, Puri BK, et al. Leaky brain in neurological and psychiatric disorders: drivers and consequences. *Aust N Z J Psyhiatry*. 2018;52(10):924-948. https://doi.org/10.1177/0004867418796955.
9. Huang L, Yu X, Keim S, et al. Maternal obesity pre-pregnancy and child neurodevelopment in the collaborative perinatal project. *Int J Epidemiol*. 2014;43(3):783-792. https://doi.org/10.1093/ije/dyu030.
10. Tanda R, Salsberry PJ, Reagan PB, Fang MZ. The impact of pre-pregnancy obesity on children's cognitive test scores. *Matern Child Health J.* 2013;17(2):222-229. https://doi.org/10.1007/s10995-012-0964-4.
11. Rodriguez A. Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. *J Child Psychol Psychiatry*. 2010;51(2):134-143. https://doi.org/10.1111/j.1469-7610.2009.02133.x.
12. Buss C, Entringer S, Davis EP, et al. Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. *PLoS One*. 2012;7(6):e37758. https://doi.org/10.1371/journal.pone.0037758.
13. Basatemur E, Gardiner J, Williams C, et al. Maternal pre-pregnancy BMI and child cognition: a longitudinal cohort study. *Pediatrics*. 2013;131(1):56-63. https://doi.org/10.1542/peds.2012-0788.
14. Bliddal M, Olsen J, Stovring H, et al. Maternal pre-pregnancy BMI and intelligence quotient (IQ) in 5-year-old children: a cohort based study. *PLoS One*. 2014;9(4):e94498. https://doi.org/10.1371/journal.pone.0094498.
15. Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics*. 2012;129(5):e1121-1128. https://doi.org/10.1542/peds.2011-2583.
16. Bilder DA, Bakian AV, Viskochil J, et al. Maternal prenatal weight gain and autism spectrum disorders. *Pediatrics*. 2013;132(5):e1276-1283. https://doi.org/10.1542/peds.2013-1188.
17. Gardner RM, Lee BK, Magnusson C, et al. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study. *Int J Epidemiol*. 2015;44(3):870-883. https://doi.org/10.1093/ije/dyv081.
18. Antoniou EE, Fowler T, Reed K, et al. Maternal pre-pregnancy weight and externalizing behavior problems in preschool children: a UK-based twin study. *BMJ Open*. 2014;4(4):e005974. https://doi.org/10.1136/bmjope-2014-005974.
19. Lieshout RJ. Role of maternal adiposity prior to and during pregnancy in cognitive and psychiatric problemsin offspring. *Nutr Rev*. 2020;71 Suppl 1:95-101. https://doi.org/10.1111/nure.12059.
20. Schaefer CA, Brown AS, Wyatt RJ, et al. Maternal pre-pregnant body mass and risk of schizophrenia in adult offspring. *Schizophr Bull*. 2000;26(2):275-286. https://doi.org/10.1093/oxfordjournals.schbul.a033452.
21. Kawai M, Minabe Y, Takagai S, et al. Poor maternal care and high maternal body mass index in pregnancy as a risk factor for schizophrenia in offspring. *Acta Psychiatr Scand*. 2004;110(4):257-263. https://doi.org/10.1111/j.1600-0447.2004.0380.x.
22. Marmorstein NR, Iacono WG. Associations between depression and obesity in parents and their late-adolescent offspring: a community-based study. *Psychosom Med*. 2016;78(7):861-866. https://doi.org/10.1097/PSY.0000000000000334.
23. Харитонова Л.А., Папышева О.В., Катайш Г.А., и др. Состояние здоровья детей от матерей с сахарным диабетом // Российский вестник перинатологии и педиатрии. – 2018. – Т. 63. – № 3. – С. 26–31. [Kharitonova LA, Papyshe-

va OV, Kataysh GA, et al. The state of health of children born to mothers with diabetes mellitus. *Rossiyskiy vestnik perinatologii i pediatrii*. 2018;63(3):26-31. (In Russ.)]. https://doi.org/10.21508/1027-4065-2018-63-3-26-31.
24. Cordero MA, Garcia LB, Blanque RR, et al. [Maternal diabetes mellitus and its impact on child neurodevelopment: systemic review. (In Spanish)]. *Nutr Hosp*. 2015;32(6):2484-2495. https://doi.org/10.3305/nh.2015.32.6.10069.
25. Towpik I, Wender-Ozegowska E. [Is diabetes mellitus worth treating? (In Polish)]. *Ginekol Pol*. 2014;85(3):220-225. https://doi.org/10.17772/gp/1717.
26. Krzeczkowski JE, Boylan K, Arbuckle TE, et al. Neurodevelopment in 3-4 year old children exposed to maternal hyperglycemia or adiposity *in utero*. *Early Hum Dev*. 2018;125:8-16. https://doi.org/10.1016/j.earlhumdev.2018.08.005.
27. Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *J Psychiatry Neurosci*. 2008;33(5):395-404.
28. Dionne G, Boivin M, Srguin JR, et al. Gestational diabetes hinders language development in offspring. *Pediatrics*. 2008;122(5):e1073-1079. https://doi.org/10.1542/peds.007-3028.
29. Perna R, Loughan AR, Le J, Tyson K. Gestational diabetes: long-term central nervous system developmental and cognitive sequelae. *Appl Neuropsychol Child*. 2015;4(3):217-220. https://doi.org/19.1080/21622965.2013.874951.
30. Евсюкова И.И. Молекулярные механизмы функционирования системы «мать – плацента – плод» при ожирении и гестационном сахарном диабете // Молекулярная медицина. – 2020. – Т. 18. – № 1. – С. 11–15. [Evsyukova II. Molecular mechanisms of the functioning system mother-placenta-fetus in women with obesity and gestational diabetes mellitus. *Molekulyarnaya meditsina.* 2020;18(1):11-15. (In Russ.)]. https://doi.org/10.29296/24999490-2020-01-02.
31. Silha JV, Krsek M, Skrha JV, et al. Plasma resistin, adiponectin and leptin level in lean and obese subjects: correlations with insulin resistance. *Eur J Endocrinol*. 2003;149(4):331-335. https://doi.org/10.1530/eje.0.1490331.
32. Sobrevia L, Salsoso R, Fuenzalida B, et al. Insulin is a key modulator of fetoplacental endothelium metabolic disturbances in gestational diabetes mellitus. *Front Physiol*. 2016;7:119. https://doi.org/10.3389/fphys.2016.00119.
33. Montelongo A, Lasuncion MA, Pallardo E, Herrera E. Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women. *Diabetes*. 1992;41(12):1651-1659. https://doi.org/10.2337/diab.41.12.1651.
34. Sharafati-Chaleshtori R, Shirzad H, Rafiean-Kopaei M, Soltani A. Melatonin and human mitochondrial diseases. *J Res Med Sci*. 2017;22(2):1-11. https://doi.org/10.4103/1735-1995.199092.
35. Lenna S, Han R, Trojanowska M. Endoplasmic reticulum stress and endothelial dysfunction. *IUBMB Life.* 2014;66(8):530-537. https://doi.org/10.1002/jub.1292.
36. Liong S, Lappas M. Endoplasmic reticulum stress is increased in adipose tissue of women with gestational diabetes. *PLoS One*. 2015;10(4):e0122633. https://doi.org/10.1371/journal.pone.0122633.
37. Bronson SL, Bale TL. The placenta as a mediator of stress effects on neurodevelopmental reprogramming. *Neuropsychopharmacology.* 2016;41(1):207-218. https://doi.org/10.1038/npp.2015.231.
38. Edlow AG, Hui L, Wick HC, et al. Assessing the fetal effects of maternal obesity via transcriptomic analysis of cord blood: a prospective case-control study. *BJOG.* 2016;123(2):180-189. https://doi.org/10.1111/1471-0528.13795.
39. Allard C, Desgagne V, Patenaude J, et al. Mendelian randomization supports causality between maternal hyperglycemia and epigenetic regulation of leptin gene in newborns. *Epigenetics*. 2015;10(4):342-351. https://doi.org/10.1080/15592294.2015.1029700.
40. Tozuka Y, Wada E, Wada K. Diet-induced obesity in female mice leads to peroxidized lipid accumulations and impairment of hippocampal neurogenesis during the early life of their offspring. *FASEB J.* 2009;23(6):1920-1934. https://doi.org/10.1096/fj.08-124784.
41. Hami J, Shojae F, Vafaee-Nezhad S, et al. Some of the experimental and clinical aspects of the effects of the maternal diabetes on developing hippocampus. *World J Diabetes.* 2015;6(3):412-422. https://doi.org/10.4239/wjd.v6.i3.412.
42. Khaksar Z, Jelodar GA, Hematian H. Morphometric study of cerebrum in fetuses of diabetic mothers. *Iranian J Veterinary Res Shiraz University*. 2011;12(36):199-204.
43. White CL, Pistell PJ, Purpera MN, et al. Effects of high fat diet on Morris maze performance, oxidative stress, and inflammation in rats: contributions of maternal diet. *Neurobiol Dis*. 2009;35(1):3-13. https://doi.org/10.1016/j.nbd.2009.04.002.
44. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumu- lation and inflammation in the placenta. *Placenta*. 2008;29(3):274-281. https://doi.org/10.1016/j.placenta.2007.12.010.
45. Aye IL, Lager S, Ramirez VI, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. *Biol Reprod*. 2014;90(6):129. https://doi.org/10.1095/biolreprod.113.116186.
46. Van der Burg JW, Sen S, Chomitz VR, et al. The role of systemic inflammation linking maternal BMI to neurodevelopment in children. *Pediatr Res*. 2016;79(1-1):3-12. https://doi.org/10.1038/pr.2015.179.
47. Ogata J, Yamanishi H, Ishibashi-Ueda H. Review: role of cerebral vessels in ischaemic injury of the brain. *Neuropathol Appl Neurobiol*. 2011;37(1):40-55. https://doi.org/10.1111/j.1365-2990.2010.01141.x.
48. Feldhaus B, Dietzel ID, Heumann R, Berger R. Effects of interferon-gamma and tumor necrosis factor-alpha on survival and differentiation of oligodendrocyte progenitors. *J Soc Gynecol Investig*. 2004;11(2):89-96. https://doi.org/10.1016/j.jsgi.2003.08.004.
49. Goines PE, Croen LA, Braunschweig D, et al. Increased midgestational IFN-gamma, IL-4 and IL-5 in women bearing a child with autism: a case-control study. *Mol Autism*. 2011;2:13. https://doi.org/10.1186/2040-2392-2-13.
50. Bilbo SD, Tsang V. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. *FASEB J*. 2010;24(6):2104-2115. https://doi.org/10.1096.fj.09-144014.
51. Sullivan EL, Nousen EK, Chamlou KA. Maternal high fat diet consumption during the perinatal period programs off-

spring behavior. *Physiol Behav*. 2014;123:236-242. https://doi.org/10.1016/j.physbeh.2012.07.014.
52. Murabayashi N, Sugiyama T, Zhang L, et al. Maternal high-fat diets cause insulin resistance through inflammatory changes in fetal adipose tissue. *Eur J Obstet Gynecol Reprod Biol*. 2013;169(1):39-44. https://doi.org/10.1016/j.ejogrb.2013.02.003.
53. Cordner ZA, Tamashiro KL. Effects of high-fat diet exposure on learning and memory. *Physiol Behav*. 2015;152(pt B):363-371. https://doi.org/10.1016/j.physbeh.2015.06.008.
54. Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. *Mol Cell Endocrinol*. 2001;177(1-2):125-134. https://doi.org/10.1016/s0303-7207(01)00455-5.
55. Sullivan EL, Grayson B, Takahashi D, et al. Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring. *J Neurosci*. 2010;30(10):3826-3830. https://doi.org/10.1523/JNEUROSCI.5560-09.2010.
56. Hauguel-de Mouzon S, Lepercq J, Catalano P. The known and unknown of leptin in pregnancy. *Am J Obstet Gynecol*. 2006;194(6):1537-1545. https://doi.org/10.1016/j.ajog.2005.06.064.
57. Dodds L, Fell DB, Shea S, et al. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord*. 2011;41(7):891-902. https://doi.org/10.1007/s10803-010-1114-8.
58. Alonso-Alconada D, Alvarez A, Lacalle J, Hilario E. Histological study of the protective effect of melatonin on neural cells after neonatal hypoxia-ischemia. *Histol Histopathol.* 2012;27(6):771-783. https://doi.org/10.14670/HH-27.771.
59. Money KM, Barke TL, Serezani A, et al. Gestational diabetes exacerbates maternal immune activation effects in the developing brain. *Molecular Psychiatry*. 2018;23(9):1920-1928. https://doi.org/10.1038/mp.2017.191.
60. Vucetic Z, Kimmel J, Totoki K, et al. Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. *Endocrinology*. 2010;151(10):4756-4764. https://doi.org/10.1210/en.2010-0505.
61. Naef L, Moquin L, Dal Bo G, et al. Maternal high-fat intake alters presynaptic regulation of dopamine in the nucleus accumbens and increases motivation for fat rewards in the offspring. *Neuroscience*. 2011;176:225-236. https://doi.org/10.1016/j.neuroscience.2010.12.037.
62. Naef L, Gratton A, Walker CD. Exposure to high fat during early development impairs adaptations in dopamine and neuroendocrine responses to repeated stress. *Stress.* 2013;16(5):540-548. https://doi.org/10.3109/10253890.2013.805321.
63. Sullivan EL, Riper KM, Lockard R, Valleau JC. Maternal high-fat diet programming of the neuroendocrine system and behavior. *Horm Behav*. 2015;76:153-161. https://doi.org/10.1016/j.yhbeh.2015.04.008.
64. Lu B, Nagappan G, Guan X, et al. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nat Rev Neurosci*. 2013;14(6):401-416. https://doi.org/10.1038/nrn3505.
65. Molteni R, Barnard RJ, Ying Z, et al. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience.* 2002;112(4):803-814. https://doi.org/10.1016/s0306-4522(02)00123-9.
66. Page KC, Jones EK, Anday EK. Maternal and postweaning high-fat diets disturb hippocampal gene expression, learning, and memory function. *Am J Physiol Regul Integr Comp Physiol.* 2014;306(8):R527-537. https://doi.org/10.1152/ajpregu,00319.2013.
67. Kang SS, Kurti A, Fair DA, Fryer JD. Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. *J Neuroinflammation.* 2014;11:156. https://doi.org/10.1186/s12974-014-0156-9.
68. Carloni S, Favrais G, Saliba E, et al. Melatonin modulates neonatal brain inflammation through endoplasmic reticulum stress, autophagy, and mir-34a/silent information regulator 1 pathway. *J Pineal Res*. 2016;61(3):370-380. https://doi.org/10.1111/jpi.12354.
69. Bouslama M, Renaud J, Oliver P, et al. Melatonin prevents learning disorders in brain-lesioned newborn mice. *Neuroscience*. 2007;150(3):712-719. https://doi.org/10.1016/j.neuroscience.2007.09.030.
70. Sagrillo-Fagundes L, Salustiano EMA, Yen PW. Melatonin in pregnancy: effects on brain development and CNS programming disorders. *Curr Pharm Des*. 2016;22(8):978-986. https://doi.org/10.2174/1381612822666151214104624.
71. Liu S, Guo Y, Yuan Q. Melatonin prevents neural tube defects in the offspring of diabetic pregnancy. *J Pineal Res*. 2015;59(4):508-517. https://doi.org/10.1111/jpi.12282.
72. Tain YL, Huang LT, Hsu CN. Developmental programming of adult disease: reprogramming by melatonin? *Int J Mol Sci*. 2017;18(2):426. https://doi.org/10/3390/ijms18020426.
73. Арутюнян А.В., Евсюкова И.И., Полякова В.О. Роль мелатонина в морфофункциональном развитии мозга в раннем онтогенезе // Нейрохимия. – 2019. – Т. 36. – № 3. – С. 208–217. [Arutyunyan AV, Evsyukova II, Polyakova VO. The role of melatonin in morphofunctional developmentof the brain in early ontogeny. *Neirohimiia*. 2019;36(3):208-217. (In Russ.)]. https://doi.org/10.1134/S1027813319030038.
74. Боровик Н.В., Главнова О.Б., Тиселько А.В., Суслова С.В. Планирование беременности у женщин с сахарным диабетом 2-го типа // Журнал акушерства и женских болезней. – 2017. – Т. 66. – № 4. – С. 25–31. [Borovik NV, Glavnova OB, Tisel'ko AV, Suslova SV. Pregnancy planning in women with diabetes mellitus type 2. *Journal of obstetrics and women's diseases.* 2017;66(4):25-31. (In Russ.)]. https://doi.org/10.17816/JOWD66425-31.
75. Kim SY, Deputy NP, Robbins CL. Diabetes during pregnancy: surveillance, preconception, care, and postpartum care. *J Womens Health (Larchmt).* 2018;27(5):536-541. https://doi.org/10.1089/jwh.2018.7052.
76. Bolton JL, Bilbo SD. Development programming of brain ad behavior by perinatal diet: focus on inflammatory mechanisms. *Dialogues Clin Neurosci*. 2014;16(3):307-320.

Information about the authors *(Информация об авторах)*

Inna I. Evsyukova — MD, PhD, DSci (Medicine), Professor, leading researcher. The Department of Physiology and Pathology of the Newborn, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. https://orcid.org/0000-0003-4456-2198. RSCI Author ID: 520074. **E-mail:** eevs@yandex.ru.

Инна Ивановна Евсюкова — д-р мед. наук, профессор, ведущий научный сотрудник отделения физиологии и патологии новорожденных. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. https://orcid.org/0000-0003-4456-2198. РИНЦ Author ID: 520074. **E-mail:** eevs@yandex.ru.