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

母亲肥胖和糖尿病对儿童大脑发育的影响（机制和预防）

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

▪ 该综述展示了临床和实验研究的结果，表明神经精神疾病的高发病率以及宫内发育期间的不良反应机制，其不良反应决定了肥胖和/或糖尿病母亲的子女的长期后果。考虑在计划阶段和怀孕期间采取预防措施。

▪ **关键词：** 肥胖；糖尿病；儿童；大脑；发展；机制

▪ 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.

育龄患者肥胖症和糖尿病发病率的增加是世界上的一个严重问题，因为母亲的这种病理不仅决定了围产期的高发病率和死亡率，而且也决定了后代在随后几年的生活中神经精神疾病的发展[1-3]。妊娠期糖尿病的不良影响的研究引起了研究者的特别关注，使超重或肥胖妇女怀孕复杂化[4,5]，在美国育龄人群中，这一数字已经上升到70%，在欧洲，达到20- 27%[6]。与此同时，世界上儿童和青少年的神经系统疾病呈上升趋势[3,7]，找出其发生机制并制定预防措施是当务之急[8,9]。

大量流行病学研究的结果表明，肥胖妇女的后代认知发育受损的风险增加3.6倍[10]，患注意缺陷多动障碍的风险为2.8倍[11,12]，智商指标明显降低[9,13,14]。建立了自闭症发病频率与母亲体重指数值的关系[15-17]，以及母亲肥胖与子女攻击性行为、焦虑、抑郁、精神分裂症的发展之间的关系[18-22]。

在研究糖尿病对后代中枢神经系统发育的影响时，也得到了类似的结果。

其中描述了认知功能、语言和精神运动发育的迟缓，并引起了人们对注意力缺陷多动障碍、精神分裂症的关注[23-26]，尤其是在妊娠合并糖尿病的情况下[27,28]。需要强调的是，在后代血糖控制不足的情况下，语言和智力发育障碍更为明显[29]。因此，如果孕妇同时患有肥胖症和糖尿病，环境对遗传信息和大脑发育的不利影响会显著增加，这可能会产生长期的后果。

据了解，在肥胖和妊娠糖尿病中，母体-胎盘-胎儿统一功能系统存在一套激素和代谢紊乱[30]。孕妇因胰岛素抵抗而出现高瘦素血症、高胰岛素血症和高血糖[31,32]。改变血清脂质谱：甘油三酯、胆固醇、低密度和极低密度脂蛋白含量升高，高密度脂蛋白降低[33]。高血糖、高脂血症、高胰岛素血症和胰岛素抵抗有助于激活线粒体链中氧的自

由基合成，增加一氧化氮的产生，使电子运输系统和线粒体通透性恶化，这导致了线粒体功能障碍的发展，而线粒体功能障碍是机体几乎所有功能系统（神经、免疫、内分泌等）病理过程启动的主要因素[34]。

由于蛋白质的氧化修饰，细胞膜、受体、酶和细胞内结构，特别是内质网的功能被破坏，内皮功能紊乱形成[35]。内质网的氧化应激导致炎症反应的激活，诱导脂肪组织中分泌白细胞介素（IL-1α、IL-1β、IL-6）[36]。在孕妇体内的全部病理过程对胎盘的形态功能形成产生负面影响。其营养、代谢、内分泌和运输功能的破坏是规划子代围产期和长期病理的基础[37]。

在个体发育的早期，儿童的大脑在结构和功能组织上都经历了重大的变化，包括在产前期间的神经细胞生长、细胞增殖和迁移的过程，而在新生后突触形成中，大多数神经元的树突树结构的大小和复杂性都有所增加。神经过程和末梢的髓鞘形成也在出生时开始。在大脑发育的各个阶段，环境和遗传器官都相互作用。通过选择性地开启或关闭DNA片段，脑细胞中的基因表达可以在一定范围内改变。在来自肥胖和糖尿病母亲的新生儿中，发现了与大脑结构发展、炎症和免疫信号、碳水化合物和脂质稳态以及氧化应激相关的基因表达的变化[38,39]。不良环境因素影响下的表观遗传变化决定了围产期脑损伤的后果，这是动物神经生物学领域的研究热点。

实验研究表明，肥胖的母亲的后代和糖尿病患者增加了脂质过氧化反应在海马体中，受损的神经元增殖，神经网络的形成[40]，抑制胰岛素受体的活性和胰岛素样生长因子[41]，降低大脑皮层的体积[42]。大脑中的氧化应激持续几个月，影响细胞核中染色质的重排，是认知发育障碍、兴奋性增强、惊厥综合征和抑郁的基础[43]。

肥胖和妊娠期糖尿病时，母体、胎盘和胎儿血液中促炎细胞因子含量增加[44,45]，这破坏了大脑结构的微循环和氧化作用，激活了小胶质细胞细胞因子和自由基的产生，抑制了少突胶质细胞的成熟和髓鞘化过程，导致过氧化反应的激活和神经元结构的损伤[46-48]。随后，儿童出现发育迟缓，并自闭症障碍[49]。大量实验研究结果证实，肥胖女性的后代存在神经和全身炎症、注意缺陷、多动症和认知能力受损[50,51]。

众所周知，胎儿脂肪组织和骨骼肌的炎症变化导致胰岛素抵抗和胰腺产生过量胰岛素[52]。胰岛素受体在皮质和海马中显著表达，突触胰岛素信号在学习和记忆过程中发挥关键作用[53,54]。在孕妇肥胖和高胰岛素血症实验中，观察到胎儿海马区胰岛素受体和葡萄糖转运体基因表达抑制，对中枢神经系统功能发育产生不良影响[55]。

肥胖和妊娠糖尿病孕妇的高瘦素血症和瘦素抵抗也是胎儿脑发育敏感期的重要不利因素，因为观察到瘦素受体基因在皮质、丘脑和下丘脑表达的抑制破坏了神经元分化、突触可塑性，并延缓了儿童的精神运动发育[56,57]。

在胎儿大脑中促炎细胞因子水平升高的情况下，血清素轴突密度降低，对神经元迁移和皮层神经发生产生负面影响，促进神经元凋亡，最终导致实验动物后代的过度活跃和焦虑[55,58]。

在孕妇肥胖和妊娠糖尿病中，不仅血清素能的发育受到干扰，而且胎儿大脑中参与调节包括食物在内的各种行为的多巴胺能系统也受到干扰[59-62]。众所周知，在人类中，多巴胺信号的破坏在精神分裂症、自闭症、多动症和饮食紊乱的发生过程中被检测到[63]。值得注意的是，由于大脑皮层和海马中的脑源性神经营养因子（BDNF）基因表达受到抑制，后代恢复和发展受损功能的能力降低[64,65]。实验研究结果表明，这不仅会导致生命最初几周的空间记忆缺失和学习障碍，成年动物也会出现空间记忆缺失和学习障碍[66]。

在过去的十年中获得的数据对孕产妇的影响肥胖和糖尿病的发展孩子的大脑和机制确定不良后果的发展吸引了研究者的注意方法预防和早期诊断中枢神经系统病理变化。研究发现，在妊娠和哺乳期排除高脂肪饮食和体育活动有助于海马神经元的正常发育，提高突触可塑性和学习能力[67]。研究表明，在妊娠期给予褪黑素可防止诱发炎症的妊娠大鼠胎儿脑部炎症过程的发生[68]，褪黑素及其代谢物可激活修复过程和轴突生

长，从而防止神经系统疾病的后续发展[69]。氧化应激下的褪黑素降低了缺氧引起的损伤，提高了少突胶质细胞的成熟，抑制了小胶质细胞的激活，有助于新生动物的髓鞘化正常化[70]。此外，在小鼠糖尿病妊娠高血糖状态下，可刺激干细胞增殖，抑制细胞凋亡，防止脑和脊髓畸形[71]，其使得作者在临床实践中推荐使用褪黑素，以在围产期重新编程儿童的大脑发育障碍[72]。一个严重的原因是，在肥胖和糖尿病的昼夜节律中，母体褪黑素的缺失，而褪黑素在胎儿大脑的发育和保护其免受不利环境影响中发挥关键作用[73]。

因此，预防肥胖和/或糖尿病妇女的后代的神经精神疾病应在计划生育阶段进行，并旨在使睡眠、新陈代谢和身体的抗氧化状态正常化，并结合血糖的持续监测、共病的检测和治疗，以及饮食和运动活动的个体选择[74]。在达到必要的健康指标之前，建议采用特定的避孕方法[75]。严格控制血糖状态，孕期使用叶酸、抗氧化剂、维生素、多不饱和脂肪酸，预防分娩时胎儿缺氧、新生儿低血糖和母乳喂养都为患病母亲的孩子提供正常大脑发育的条件[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 prepregnancy 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 prepregnant 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, Papysheva 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 offspring 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 author*

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.