УДК 618.29-008.9-001.8
DOI: https://doi.org/10.17816/JOWD71300

# Биохимические факторы гипоксии и их роль в оценке функционального состояния плода

О.В. Рождественская[1], А.А. Кокая[2, 3], В.Ф. Беженарь[1]

[1] Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова, Санкт-Петербург, Россия;
[2] Родильный дом № 16, Санкт-Петербург, Россия;
[3] Государственный научно-исследовательский институт прикладных проблем, Санкт-Петербург, Россия

Неизменная частота случаев гипоксии плода во время беременности и родов остается ведущей нерешенной проблемой современного практического акушерства. Путем своевременного отслеживания нарушений функционального состояния плода в ряде случаев удается рано диагностировать патологический процесс. Однако существующие методы не позволяют выявлять компенсаторно-приспособительные возможности плода, не ведут к углубленному пониманию патофизиологических основ данного состояния и внедрению терапии. Целью обзора стали обобщение современных знаний о диагностике функционального состояния плода, анализ возможных способов оценки адаптационно-приспособительных механизмов плода в ответ на воздействие стресс-факторов при беременности и в родах. В статье показано развитие биохимических методов диагностики функционального состояния плода и представлены предполагаемые биохимические маркеры для оценки компенсаторных возможностей плода во время беременности и родов.

**Ключевые слова:** гипоксия плода; дистресс плода; нейротрофический фактор мозга; глиальный нейротрофический фактор.

**Как цитировать:**
Рождественская О.В., Кокая А.А., Беженарь В.Ф. Биохимические факторы гипоксии и их роль в оценке функционального состояния плода // Журнал акушерства и женских болезней. 2021. Т. 70. № 6. С. 117–126. DOI: https://doi.org/10.17816/JOWD71300

**Рукопись получена:** 04.06.2021 **Рукопись одобрена:** 22.10.2021 **Опубликована:** 29.12.2021

DOI: https://doi.org/10.17816/JOWD71300

# Biochemical factors of hypoxia and their role in assessing the functional state of the fetus

Olga V. Rozhdestvenskaya[1], Anna A. Kokaya[2, 3], Vitaly F. Bezhenar[1]

[1] Academician I.P. Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia;
[2] Maternity Hospital No. 16, Saint Petersburg, Russia;
[3] State Research Institute of Applied Problems, Saint Petersburg, Russia

The constant frequent incidents of fetal hypoxia during pregnancy and childbirth remain the leading unsolved problem in modern practical obstetrics. In some cases, the onset of a pathological process can be diagnosed earlier due to the on-time monitoring of functional disorders of the fetus. However, the existing diagnostic methods do not show the compensatory and adaptive capabilities of the fetus; do not lead to an in-depth understanding of the pathophysiology of this condition and do not contribute to the implementation of evidence-based therapy. This review summarizes current knowledge about the diagnosis of functional disorders of the fetus and discusses possible ways of assessing adaptive mechanisms in response to stress during pregnancy and childbirth. The article shows the development of biochemical methods for diagnosing functional disorders of the fetus. The putative biochemical markers for assessing the compensatory capabilities of the fetus during pregnancy and childbirth are presented.

**Keywords:** fetal hypoxia; fetal distress; brain-derived neurotrophic factor; glial cell-derived neurotrophic factor.

**To cite this article:**
Rozhdestvenskaya OV, Kokaya AA, Bezhenar VF. Biochemical factors of hypoxia and their role in assessing the functional state of the fetus. *Journal of Obstetrics and Women's Diseases.* 2021;70(6):117–126. DOI: https://doi.org/10.17816/JOWD71300

**Received:** 04.06.2021 **Accepted:** 22.10.2021 **Published:** 29.12.2021

DOI: https://doi.org/10.17816/JOWD71300

# 缺氧的生化因素及其在评估胎儿功能状态中的作用

Olga V. Rozhdestvenskaya[1], Anna A. Kokaya[2, 3], Vitaly F. Bezhenar[1]

[1] Academician I.P. Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia;
[2] Maternity Hospital No. 16, Saint Petersburg, Russia;
[3] State Research Institute of Applied Problems, Saint Petersburg, Russia

妊娠和分娩期间胎儿缺氧的持续频率仍然是现代实用产科尚未解决的主要问题。通过及时监测胎儿功能状态的异常情况，在某些情况下，可以早期诊断病理过程。然而，现有的方法不允许识别胎儿的代偿性适应能力，也不能深入理解这种疾病的病理生理基础和引入治疗。该综述的目的是总结关于胎儿功能状态诊断的现有知识，分析评估胎儿在妊娠和分娩期间对应激因素的适应机制的可能方法。本文展示了诊断胎儿功能状态的生化方法的发展，并提出了评估胎儿在妊娠和分娩期间代偿能力的生化标记物。

**关键词：** 胎儿缺氧；胎儿窘迫；脑源性神经营养因子；胶质神经营养因子。

**引用本文：**
Rozhdestvenskaya OV, Kokaya AA, Bezhenar VF. 缺氧的生化因素及其在评估胎儿功能状态中的作用. *Journal of Obstetrics and Women's Diseases.* 2021;70(6):117–126. DOI: https://doi.org/10.17816/JOWD71300

**收稿日期：** 2021年6月4日 **审稿日期：** 2021年10月22日 **出版时间：** 2021年12月29日

尽管已有诊断分娩期间胎儿功能状态的方法，但现代产科学的一个全球性问题是，一方面，功能状态受损的新生儿不断出现，另一方面，分娩期间越来越多的手术干预，有时是不合理的[1]。

分娩是一个生理过程，然而，母亲和胎儿都在代偿性适应能力的边缘经历压力，分娩的有利结果在很大程度上取决于在胎儿和母亲中成功实施代偿性适应机制[2]。

在医学发展的现阶段，任何一种诊断方法都不可能客观地评估胎儿的功能状态。为了确定胎儿功能状态受损的诊断，使用了多种方法的组合，而胎儿代偿性适应性反应的发病机制研究甚少，主要在实验模型中描述。

在临床实践中，用于诊断胎儿功能状态的方法包括听诊胎儿心音、目视评估羊水性质、心电图和胎儿心电描记术。它们被很好地研究并成功地应用于临床实践。然而，应该注意的是，关于其使用的数据存在争议和矛盾[3]。提供合格医疗服务的现代原则意味着对病理过程采取更客观（谨慎）的方法，形成更清晰的算法以降低围产期并发症的水平。其中一种可能的方法是扩大对胎儿代偿性适应性反应发病机制的认识，从而确定具有诊断和预后价值的新标志物。

这种方法最早的例子是1962年引入扎林试验。然而，这种方法有明显的缺点—侵入性，无法确定酸中毒的性质。新生儿并发症，如神经发育受损和终末器官损伤，与代谢性酸中毒有关，而不是与呼吸性酸中毒有关[4,5]，导致了乳酸的研究。许多作者发现，第二产程的持续时间、新生儿脐带血中的乳酸浓度与围产期结局之间存在正相关[6]。其他研究人员得出结论，测定乳酸水平比测定胎儿头部血液中的pH值更合适[7]。然而，一些研究表明，尽管这两种方法具有较高的敏感性和特异性，但由于不合理的手术干预增加，不建议在临床实践中结合使用[8]。还应注意的是，在扎林试验或乳酸测量期间，只有少数作品描述并关联了分娩阶段和胎儿相对于小骨盆平面的位置[8-10]。

普遍接受的乳酸水平正常上限为4.8毫摩尔/升，这得到了使用LactateProTM分析仪的研究支持，该分析仪最初是为测试运动员而开发的。同时，使用其他便携式设备获得的指标可能会有所不同，说明书中的参考值是在未考虑乳酸分析仪类型的情况下标明的[7,11]。

大多数胎儿乳酸是在分娩的第二阶段形成的[7]。在N. Wiberg和合著者2016年发表，使用LactateProTM提出了第二产程期间胎头血液中生理乳酸水平的新范围[1.1和5.2毫摩尔/升(±2SD)] [10]。此外，作者注意到胎头血液中的乳酸水平对产次、局部麻醉方法和宫缩剂（催产素）的依赖性。2018年N. Wiberg和合著者评估了在第二产程中测量的胎头血液中乳酸浓度对四岁儿童结果的依赖性，并得出结论认为认知功能障碍的数量有所增加，这些儿童出生时乳酸水平升高的精细运动障碍[12]。

POCT（Point-of-care testing - lactate test strip method）已变得很有吸引力，但请注意，各种手册中给出的参考值因使用的分析仪而异。O.V. Remneva和合著者显示了确定羊水中乳酸水平和乳酸-肌酐比值以准确确定胎儿缺氧程度存在的可行性[13]。在T.N. Pogorelova和合著者研究分析了羊水的蛋白质组学成分，从而确定锌-$\alpha_2$-糖蛋白可推荐为胎儿生长迟缓的信息标志物[14]。

M. Loukovaara和合著者(2009)发现通过羊水取样获得的促红细胞生成素和S100B也可以作为胎儿缺氧的标志物[15]。在随后M. Summanen和合著者（2017）的研究中得出结论，新生儿血清中的S100B和促红细胞生成素不是出生窒息的可靠生物标志物。作者研究了和肽素在新生儿脐带血血清中的作用，指出其作为急性出生窒息和新生儿窘迫的生物标志物的潜力。发现该参数与脐动脉的过量碱和pH值相关。此外，阴道分娩儿童的脐带血清和肽素水平显着升高，并随着分娩时间的延长而升高[16]。

许多作者指出，在缺氧的影响下，会发生缺血和心肌坏死，进而靶器官改变的标志物可以成为缺氧的生化因素[17、18]。一种这样的标志物是肌钙蛋白。V. Stefanovic和合著者发现羊水中肌钙蛋白水平升高是胎儿呼吸窘迫综合征发展的独立预测因子[19]。后来发现窒息组患儿出生后4小时静脉血心肌肌钙蛋白T平均水平明显升高，且该方法本身具有较高的敏感性（83.9%）和特异性（96.6%）。此外，标志物水平与缺氧缺血性脑病程度的增加呈正相关[20]。然而，其他研究人员指出，在不干扰其功能的情况下，患有先天性胎儿心脏畸形的早产新生儿脐带动脉血浆中肌钙蛋白水平升高，这表明需要研究阈值及其作用蛋白质作为胎儿缺氧的标志物更详细[21]。

在2019年Bin Wan和合著者证明了血清蛋白S-100β、C反应蛋白和胱抑素C以及肌钙蛋白I(cTnI)、脐血肌酸激酶同工型MB和CK-MB水平与新生儿缺氧缺血性脑病的发展之间的关系[22]。I. Turrini和合著者(2018)作为一个临床例子，我们将举一个孕妇静脉血中cTnI水平升高的案例排除了导致该指标值增加的外生殖器疾病（心包炎、心肌炎、肺栓塞、肾脏疾病等），得出的结论是cTnI水平的增加可能是宫内引起的[23]。

S.M. Fleming和合著者发现cTnI浓度的增加是由于高血压引起的肌原纤维损伤[24]。然而，其他作者并未观察到先兆子痫/子痫患者静脉血浆中cTnI含量的增加[25]。所述临床病例的作者认为，肌钙蛋白水平的升高与严重的胎儿缺氧有关。研究人员在他们的报告中提到，传统观点认为cTnI不会穿过胎盘。然而，在这种情况下，作者认为胎盘的深度损伤可能与胎儿cTnI进入母亲血液有关。关于该分子的宫内起源的一个积极论点是，在胎儿死亡期间，cTnI水平降低，在妊娠终止后恢复正常。

尽管有上述研究的优点，但这些方法的主要缺点之一是其创伤（如果在胎儿分娩期间采血）或其仅对胎儿的回顾性评估（在胎儿出生后脐带血取样的情况下）具有重要意义。

在2013年Whitehead 和合著者他们在发表的论文中表明，存在缺氧诱导的miRNA，当胎儿出现急性缺氧时，分娩期间母体血液中的miRNA水平增加。同时，还证明了与出生时的胎儿酸血症水平以及多普勒检测期间胎儿血管的血流动力学紊乱相关[22，26]。除了与该方法的敏感性和特异性相关的优势外，前瞻性诊断的可能性和相对较低的侵袭性也发挥了重要作用[27]。在2015年A.M. Looney和合著者据报道，围产期窒息儿童脐血中microRNA（hsa-miR-374a）表达显著降低，并发展为新生儿缺氧缺血性脑病[28]。其他作者在一项针对患有缺氧缺血性脑病的新生儿的临床研究中研究了miRNA-21和HIF-1α的表达。与对照组相比，患有缺氧缺血性脑病的儿童的血清中它们的水平更高[29]。在一篇关于miRNA在新生儿缺氧缺血性脑病发展中的作用的临床综述中，V. Ponnusamy（2019）试图结合在细胞水平上发生的所有已知变化，包括在新生儿发育中的大脑缺氧缺血性脑病中观察到的生理和病理生理过程。作者认为，对这一问题的进一步研究可能为改善新生儿创伤性脑损伤的诊断和寻找有效的神经保护剂铺平道路[30]。

2010年发生M.S. Tissot van Patot的科学研究工作。作者不仅谈到了胎儿窘迫的诊断，还谈到了代偿能力的评估。比较生活在海平面和海拔3100米的产妇胎盘的变化，可以得出结论，后者的代偿性适应机制被激活。与生活在海平面上的女性相比，胎盘中多不饱和脂肪酸、磷酸肌酸、牛磺酸和肌醇的浓度增加，单不饱和脂肪酸的浓度和三磷酸腺苷/二磷酸腺苷的比例降低[31]。

在目标器官受损的情况下，我们不能不提到中枢神经系统的组织，它对缺氧的影响极为敏感。人类胎儿的代偿性适应机制实际上没有被研究，对它们的研究主要是实验性的。尽管引进了新技术，改善了围产期高危新生儿的预后，但发达国家围产期神经并发症的发生率目前并没有下降，它们在围产期脑损伤的结构中占很大一部分，并显著影响了儿童早期发病率，残疾和死亡率[30，32]。

缺血期间脑细胞受损的主要因素之一是缺氧。随着氧气浓度的降低，线粒体膜上的氧化磷酸化受到影响，呼吸链的成分解耦，能量不足，出现酸中毒，谷氨酸释放和$Ca^{2+}$积累受到干扰，导致自由基过程的激活，是一种神经元死亡的主要原因[32-35]。在成功的复苏措施后，新生儿大脑的氧合和灌注恢复，但在心血管稳定工作的背景下，在不改变细胞内pH值的情况下发生所谓的继发性或延迟性中枢神经系统损害和呼吸系统，这与复氧有关[13，32，36]。

增加神经系统代偿适应能力的一种有前途的方法是激活内源性系统，这些系统有助于神经细胞在压力因素的作用下存活并维持其功能活动。非常感兴趣的是神经营养因子的使用，例如胶质神经营养因子（GDNF）、脑源性神经营养因子（BDNF）等。I.V. Ostrova和M.Sh. Avrushchenko在实验*in vivo*中显示了在小脑浦肯野细胞的神经元群中合成BDNF的能力。作者认为，这种特性是在复苏后期间增加神经元对死亡的抵抗力的最重要因素之一。可以推测，该因素可能在缺氧损伤期间胎儿的代偿适应机制中发挥作用[37]。在2016年E.V. Mitroshina和合著者发表了一项实验结果，以研究GDNF在全脑缺血条件下对动物对缺血性脑损伤抵抗力的影响，这是一种双侧颈动脉闭塞模型。作者得出结论，GDNF有助于动物在脑缺血模拟和缺血后神经状态正常化中的存活[33]。

在A.Yu. Morozov和合著者实验工作中（2018年）发现，产前缺氧后，个体发育早期大鼠大脑结构（树皮、海马和小脑）中的BDNF、生长因子NGF以及S-100蛋白水平显著降低[39]。随后，这些作者在出生后5天、10天和30天，研究了产前缺氧对大鼠海马和血清中BDNF和神经特异性烯醇化酶（NSE）含量的影响。此时，低氧组大鼠下壶腹的BDNF和NSE水平降低。同时，动物血液中这些因子的水平也增加了。作者得出结论，产前缺氧可能会干扰这些蛋白质的功能，影响突触可塑性过程的形成，这是由于突触发育的滞后和神经元完整性的紊乱，以及在早期个体发育和动物后期生计方面的发育失败[40]。在2020年N.A. Shchelchkova和合著者已发表的研究表明，怀孕雌性小鼠在妊娠I期和II期的慢性低压缺氧导致血浆中神经营养因子BDNF和GDNF水平显著降低[41]。GDNF维持呼吸链的效率，即线粒体的功能状态，有助于细胞适应缺血的影响。GDNF保护作用的机制之一是减少

缺血期间形成的自由基数量[42-44]。几项研究发现，间充质干细胞通过复杂的机制发挥神经保护作用，如分泌神经营养因子、血管生成、抑制凋亡和调节免疫系统[45-48]。

作为说明，我们展示了N.M. Lee和合著者[49]的一项实验研究。作者认为，干细胞释放到培养基中的神经营养因子可以赋予海马脑片缺氧损伤器官型培养的再生能力。发现在所有研究区域中，在条件培养基中生长后的海马体损伤比在Gautailer培养基[由25%汉克平衡盐溶液（HBSS，GibcoBRL / Life Technologies，美国），25%热灭活马血清(Hyclone, Logan, UT, USA)、50% Eagle 培养基 (BME, GibcoBRL / Life Technologies, USA)、6.5 mg/ml 葡萄糖和200 mM Glutamax I (GibcoBRL / Life Technologies, USA)]。同时，干细胞可以表达各种神经营养因子和生长因子。该研究的作者指出，NGF、GDNF和血管生长因子VEGF在缺氧损伤条件下充当神经保护剂[49]。

其他研究已经证实了关于间充质干细胞神经保护作用机制的数据——神经营养素的分泌，包括大脑和胶质神经营养因子[50，51]，这是另一种降低缺氧缺血性损伤致病效应的方法，S. Sheng和合著者在2018年描述了这一点[52]。*In vitro*研究的结果表明，长期缺氧可下调BDNF-TrkB信号传导，导致大脑皮层TNFα水平升高，从而诱发神经炎症和神经毒性，而δ阿片受体的激活可调节BDNF-TrkB信号传导，降低大脑皮层TNFα水平。Δ-阿片受体激活后，星形胶质细胞BDNF、NGF和GDNF的表达增加，从而导致细胞生长增加，改善其功能和表型发育，最终在保护大脑免受缺氧/缺血性脑病[52]中发挥决定性作用。

在*vitro*研究中，在缺血性损伤条件下将神经营养因子引入培养基，可促进神经网络功能活动的保存和恢复[53,54]。最近，一项实验研究显示，在急性低压缺氧的影响下，经鼻给予GDNF具有抗缺氧作用[55]。GDNF具有明显的神经保护特性。其预防性使用可在缺氧损伤后保留原代海马培养物的细胞活力、自发生物电活动、神经网络的形态和功能结构。研究还表明，GDNF参与维持含有GluR2亚单位的AMPA受体水平，这可能是GDNF神经保护作用的关键机制[56]。T. Ikeda和合著者发表了模拟7天大鼠缺血/缺氧脑损伤的实验结果。当在卒中后30分钟内脑内注射来源于胶质细胞系的神经营养因子（GDNF；2或4μg）时，损伤程度显著减轻。作者指出，与成人大脑相比，发育中大脑中GDNF及其mRNA的高表达可能是导致胎儿和新生儿对缺血相对抵抗的因素之一[38]。

实验研究已成为临床实践中研究神经营养因子作用的基础。2006年G.S. Golosnaya和S.A. Kotiy研究发现，新生儿血清中BDNF水平在出生后第一天的追踪值，以及VEGF水平在出生后第一周的下降，对预后不利。这些神经营养素的含量增加1.5-3倍，表明神经系统具有良好的适应能力。该研究指出，在先兆子痫患者中，发现其与新生儿出生后第一天的低水平VEGF直接相关，这表明该组患者围产期缺氧性脑损伤的风险较高[58]。N.A. Shchelchkova和合著者（2016年）发现，在生理分娩和缺氧分娩期间，新生儿静脉脐血血浆中的GDNF和NSE含量没有显著差异。作者将其归因于分娩期间代偿机制的激活。然而，在复杂分娩的新生儿组中，BDNF水平显著降低。据研究人员称，这表明大脑对缺氧损伤的保护程度较低，这可能导致新生儿脑组织的退化过程[57]。根据A.Yu. Morozov和合著者中在胎盘功能不全的慢性缺氧条件下，胎儿身体所有功能系统发育的遗传程序被破坏，这使出生后适应变得复杂，并对不良后果的风险进行编程，包括脑内稳态的深度紊乱。作者强调，为了获得成功的围产期预后，不仅要确定损伤的存在和程度，还要确定代偿机制的可能性。2019年他们发表了一项研究结果，结果显示，患有II-III度宫内发育迟缓的足月新生儿脐血血清中NSE水平升高，而BDNF含量较低。获得的数据表明，脑损伤加上缺乏足够的代偿能力。在这些情况下，随着妊娠期的延长，神经元结构的损伤程度增加[59]。2020年在临床观察过程中，N.A. Shchelchkova和合著者在新生儿出生结局良好的组中，发现脐血血清中神经营养因子BDNF、GDNF的表达增加，这与之前的结果和文献数据一致。作者认为，这可以部分解释新生儿的代偿能力，即使在分娩期间存在和实施压力因素的情况下。同时，在一组婴儿中，记录到脐血血清中的神经营养因子BDNF、GDNF水平较低，这些婴儿有发生缺氧损伤不良后果的高风险[41]。

上述研究开辟了在神经病学和其他一些专业，例如新生儿缺氧缺血性脑损伤的新生儿学中，寻找影响缺氧缺血性病因学脑功能障碍的全新、病因学证实的方法的可能性，使用神经营养素的合成类似物[60]。

因此，对文献的回顾表明，今天有许多方法可以评估分娩期间胎儿的功能状态。

关于常规诊断方法的敏感性和特异性的数据仍然相互矛盾，胎儿缺氧的验证问题尚未解决。胎儿的代偿性适应机制是在分娩时实现的，但研

究很少。近年来，作为靶器官改变标志物的mRNA蛋白的表达受到了高度重视。神经营养因子在代偿性适应能力调节机制中具有重要的实验和临床意义，神经营养因子是由基因决定的。寻找侵入性最小、更可靠、更具成本效益的方法来评估分娩中胎儿的状况，以改善围产期结局仍然是一个紧迫的问题，需要进一步研究。

## 附加信息

**资金来源。**该研究在未经赞助和财务支持的情况下进行。

**利益冲突。**作者声明，没有明显的和潜在的利益冲突相关的发表这篇文章。

所有作者都对文章的研究和准备做出了重大贡献，在发表前阅读并批准了最终版本。

## REFERENCES

**1.** Perepelica SA, Golubev AM, Moroz VV, et al. Causes of acute intranatal and postnatal hypoxia in neonatal infants. *Obshchaya reanimatologiya.* 2012;VIII(6):17–22. (In Russ.)
**2.** Gunin AG, Milovanov MM, Denisova TG. Methods of fetal assessment in labors. *Zdravoohranenie Chuvashii*. 2014;3(3):9–48. (In Russ.)
**3.** Kuznetsov PA, Kozlov PV. Fetal hypoxia and neonatal asphyxia. *Lechebnoe delo*. 2017;(4):9–15. (In Russ.)
**4.** Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: Systematic review and meta-analysis. *BMJ.* 2010;340(7756):1121. DOI: 10.1136/bmj.c1471
**5.** Goodwin TM, Belai I, Hernandez P, et al. Asphyxial complications in the term newborn with severe umbilical acidemia. *Am J Obstet Gynecol*. 1992;167(6):1506–1512. DOI: 10.1016/0002-9378(92)91728-s
**6.** Rubak SL. Lactate measurement in umbilical cord blood in neonates. *Ugeskr Laeger*. 2010;172(1):364–368.
**7.** East CE, Leader LR, Sheehan P, et al. Intrapartum fetal scalp lactate sampling for fetal assessment in the presence of a non-reassuring fetal heart rate trace. *Cochrane Database Syst Rev*. 2015;(5):CD006174. DOI: 10.1002/14651858.CD006174.pub3
**8.** Wiberg-Itzel E. Determination of pH or lactate in fetal scalp blood in management of intrapartum fetal distress: randomised controlled multicenter trial. *Br Med J*. 2008;336:1284–1287. DOI: 10.1136/bmj.39553.406991.25
**9.** Nordström L, Achanna S, Naka K, Arulkumaran S. Fetal and maternal lactate increase during active second stage of labour. *BJOG.* 2001;108(3):263–268. DOI: 10.1136/10.1111/j.1471-0528.2001.00034.x
**10.** Wiberg N, Källén K. Fetal scalp blood lactate during second stage of labor: determination of reference values and impact of obstetrical interventions. *J Matern Fetal Neonatal Med*. 2017;30(5):612–617. DOI: 10.1080/14767058.2016.1181167
**11.** Orsonneau J-L, Fraissinet F, Sébille-Rivain V, et al. Suitability of POC lactate methods for fetal and perinatal lactate testing: considerations for accuracy, specificity and decision making criteria. *Clin Chem Lab Med.* 2013;51(2):397–404. DOI: 10.1515/cclm-2012-0201
**12.** Wiberg N, Klausen TW, Tyrberg T, et al. Infant outcome at four years of age after intrapartum sampling of scalp blood lactate for fetal assessment. A cohort study. *PLoS One.* 2018;13(3):e0193887. DOI: 10.1371/journal.pone.0193887
**13.** Remneva OV, Fadeeva NI, Fil'chakova ON, et al. Intranatal fetal hypoxia: diagnostic possibilities, reserves reducing the incidence of cerebral disorders in full-term newborns. *Rossijskij vestnik pediatrii*. 2015;5(5):61–66. (In Russ.)
**14.** Pogorelova TM, Gun'ko VO, Drukker NA, Linde VA. Proteins-markers of placental insufficiency. *Biomedicinskaya himiya*. 2010;56(5):616–620. (In Russ.)
**15.** Loukovaara M, Teramo K, Alfthan H, et al. Amniotic fluid S100B protein and erythropoietin in pregnancies at risk for fetal hypoxia. *Eur J Obstet Gynecol Reprod Biol*. 2009;142(2):115–118. DOI: 10.1016/j.ejogrb.2008.10.008
**16.** Summanen M, Seikku L, Rahkonen P, et al. Comparison of umbilical serum copeptin relative to erythropoietin and S100B as asphyxia biomarkers at birth. *Neonatology*. 2017;112(1):60–66. DOI: 10.1159/000456063
**17.** Irmak K, Tüten N, Karaoglu G, et al. Evaluation of cord blood creatine kinase (CK), cardiac troponin T (cTnT), N-terminal-pro-B-type natriuretic peptide (NT-proBNP), and s100B levels in nonreassuring foetal heart rate. *J Matern Fetal Neonatal Med*. 2021;34(8):1249–1254. DOI: 10.1080/14767058.2019.1632285
**18.** Trevisanuto D, Picco G, Golin R, et al. Cardiac troponin I in asphyxiated neonates. *Biol Neonate.* 2006;89(3):190–193. DOI: 10.1159/000089795
**19.** Stefanović V, Loukovaara M. Amniotic fluid cardiac troponin T in pathological pregnancies with evidence of chronic fetal hypoxia. *Croat Med J*. 2005;46(5):801–807.
**20.** Joseph S, Kumar S, Ahamed MZ, Lakshmi S. Cardiac troponin-T as a marker of myocardial dysfunction in term neonates with perinatal asphyxia. *Indian J Pediatr*. 2018;85(10):877–84. DOI: 10.1007/s12098-018-2667-3
**21.** Asrani P, Aly AM, Jiwani AK, et al. High-sensitivity troponin T in preterm infants with a hemodynamically significant patent ductus arteriosus. *J Perinatol.* 2018;38(11):1483–1489. DOI: 10.1038/s41372-018-0192-x
**22.** Whitehead C, Teh WT, Walker SP, et al. Quantifying circulating hypoxia-induced RNA transcripts in maternal blood to determine *in utero* fetal hypoxic status. *BMC Med*. 2013;11(1):1–12. DOI: 10.1186/1741-7015-11-256
**23.** Turrini I, Sorbi F, Ghizzoni V, et al. Severe fetal distress and placental damage might be associated with high troponin i (cTnI) levels in mothers. *Am J Case Rep.* 2018;19:194–198. DOI: 10.12659/AJCR.906617
**24.** Fleming SM, O'Gorman T, Finn J, et al. Cardiac troponin I in pre-eclampsia and gestational hypertension. *BJOG.* 2000;107(11):1417–1420. DOI: 10.1111/j.1471-0528.2000.tb11658.x
**25.** Joyal D, Leya F, Koh M, et al. Troponin I levels in patients with preeclampsia. *Am J Med.* 2007;120(9):819.e13–14. DOI: 10.1016/j.amjmed.2006.05.068
**26.** Whitehead CL, Teh WT, Walker SP, et al. Circulating MicroRNAs in maternal blood as potential biomarkers for fetal hypoxia *in-utero*. *PLoS One*. 2013;8(11):e78487. DOI: 10.1371/journal.pone.0078487
**27.** Human reproductive and prenatal genetics. Ed. by P.C.K. Leung, J. Qiao. London: Academic Press; 2019.
**28.** Looney AM, Walsh BH, Moloney G, et al. Downregulation of umbilical cord blood levels of mir-374a in neonatal hypoxic ischemic encephalopathy. *J Pediatr*. 2015;167(2):269–273. DOI: 10.1016/j.jpeds.2015.04.060
**29.** Shi J-P, Li Y-W, Sang G-M, et al. Expression and significance of serum miRNA-21 expression in neonates with HIE. *Pr Prev Med.* 2018;25:655–658. DOI: 10.3969/j.issn.1006-3110.2018.06.005
**30.** Ponnusamy V, Yip PK. The role of microRNAs in newborn brain development and hypoxic ischaemic encephalopathy. *Neuropharmacology.* 2019;149:55–65. DOI: 10.1016/j.neuropharm.2018.11.041
**31.** Tissot van Patot MC, Murray AJ, Beckey V, et al. Human placental metabolic adaptation to chronic hypoxia, high altitude: hypoxic preconditioning. *Am J Physiol Regul Integr Comp Physiol*. 2010;298(1):R166–172. DOI: 10.1152/ajpregu.00383.2009
**32.** Nuñez A, Benavente I, Blanco D, et al. Oxidative stress in perinatal asphyxia and hypoxic-ischaemic encephalopathy. *An Pediatr (Barc)*. 2018;88(4):228.e1–228.e9. DOI: 10.1016/j.anpedi.2017.05.005

**33.** Mitroshina EV, Abogessimengane BZH, Urazov MD, et al. Adaptive role of glial cell line-derived neurotrophic factorin cerebral ischemia. *Sovremennye Tekhnologii V Medicine*. 2017;9(1):68–76. (In Russ.)
**34.** Turovsky EA, Zinchenko VP, Gaidin SG, Turovskaya MV. Calcium-binding proteins protect gabaergic neurons of the hippocampus from hypoxia and ischemia *in vitro*. *Biol Membr.* 2017;34(5):68–80. DOI: 10.1134/S1990747818010105
**35.** Coimbra-Costa D, Alva N, Duran M, et al. Oxidative stress and apoptosis after acute respiratory hypoxia and reoxygenation in rat brain. *Redox Biol.* 2017;12:216–25. DOI: 10.1016/j.redox.2017.02.014
**36.** Grow J, Barks JD. Pathogenesis of hypoxic-ischemic cerebral injury in the term infant: current concepts. *Clin Perinatol*. 2002;29(4):585–602. DOI: 10.1016/s0095-5108(02)00059-3
**37.** Ostrova IV, Avrushchenko MS. Expression of brain-derived neurotrophic factor (BDNF) increases the resistance of neurons to death in the postresuscitation period. *General Reanimatology*. 2015;11(3):45–53. (In Russ.). DOI: 10.15360/1813-9779-2015-3-45-53
**38.** Ikeda T, Xia XY, Xia YX, et al. Glial cell line-derived neurotrophic factor protects against ischemia/hypoxia-induced brain injury in neonatal rat. *Acta Neuropathol*. 2000;100(2):161–7. DOI: 10.1007/s004019900162
**39.** Morozova AYu, Arutyunyan AV, Milyutina YuP, et al. The dynamics of the contents of neurotrophic factors in early ontogenyin the brain structures of rats subjected to prenatal hypoxia. *Neurochemistry.* 2018;35(3):256–263. (In Russ.). DOI: 10.1134/S1027813318030081
**40.** Morozova AYu, Arutyunyan AV, Milyutina Yu P, et al. Influence of prenatal hypoxia on the content of neuron specific enolasein the structures of the brain and blood serum of rats in early ontogeny. *Neurochemistry.* 2020;37(3):233–239. (In Russ.). DOI: 10.31857/S1027813320030085
**41.** Shchelchkova NA, Kokaya AA, Bezhenar' VF, et al. The role of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor in chronic fetal oxygen deprivation. *Sovremennye Tekhnologii V Medicine.* 2020;12(1):25–33. (In Russ.). DOI: 10.17691/stm2020.12.1.03+
**42.** Cheng H, Fu Y-S, Guo J-W. Ability of GDNF to diminish free radical production leads to protection against kainate-induced excitotoxicity in hippocampus. *Hippocampus.* 2004;14(1):77–86. DOI: 10.1002/hipo.10145
**43.** Shang J, Deguchi K, Yamashita T, et al. Antiapoptotic and antiautophagic effects of glial cell line-derived neurotrophic factor and hepatocyte growth factor after transient middle cerebral artery occlusion in rats. *J Neurosci Res.* 2010;88(10):2197–2206. DOI: 10.1002/jnr.22373
**44.** Szydlowska K, Tymianski M. Calcium, ischemia and excitotoxicity. *Cell Calcium.* 2010;47(2):122–129. DOI: 10.1016/j.ceca.2010.01.003
**45.** Ahn SY, Chang YS, Sung DK, et al. Pivotal role of brain-derived neurotrophic factor secreted by mesenchymal stem cells in severe intraventricular hemorrhage in newborn rats. *Cell Transplant.* 2017;26(1):145–156. DOI: 10.3727/096368916X692861
**46.** Feng N, Hao G, Yang F, et al. Transplantation of mesenchymal stem cells promotes the functional recovery of the central nervous system following cerebral ischemia by inhibiting myelin-associated inhibitor expression and neural apoptosis. *Exp Ther Med.* 2016;11(5):1595–600. DOI: 10.3892/etm.2016.3089
**47.** Mitkari B, Nitzsche F, Kerkelä E, et al. Human bone marrow mesenchymal stem/stromal cells produce efficient localization in the brain and enhanced angiogenesis after intra-arterial delivery in rats with cerebral ischemia, but this is not translated to behavioral recovery. *Behav Brain Res*. 2014;259:50–59. DOI: 10.1016/j.bbr.2013.10.030
**48.** Zhang R, Liu Y, Yan K, et al. Anti-inflammatory and immunomodulatory mechanisms of mesenchymal stem cell transplantation in experimental traumatic brain injury. *J Neuroinflammation.* 2013;10:106. DOI: 10.1186/1742-2094-10-106
**49.** Lee NM, Chae SA, Lee HJ. Effects of neural stem cell media on hypoxic injury in rat hippocampal slice cultures. *Brain Res.* 2017;1677:20–25. DOI: 10.1016/j.brainres.2017.09.018
**50.** Liu X, Wang X, Li A, Jiao X. Effect of mesenchymal stem cell transplantation on brain-derived neurotrophic factor expression in rats with Tourette syndrome. *Exp Ther Med.* 2016;11(4):1211–1216. DOI: 10.3892/etm.2016.3059
**51.** Zheng Z, Zhang L, Qu Y, et al. Mesenchymal stem cells protect against hypoxia-ischemia brain damage by enhancing autophagy through brain derived neurotrophic factor/mammalin target of rapamycin signaling pathway. *Stem Cells.* 2018;36(7):1109–1121. DOI: 10.1002/stem.2808
**52.** Sheng S, Huang J, Ren Y, et al. Neuroprotection against hypoxic/ischemic injury: δ-opioid receptors and BDNF-TrkB pathway. *Cell Physiol Biochem*. 2018;47(1):302–315. DOI: 10.1159/000489808
**53.** Vedunova MV, Sakharnova TA, Mitroshina EV, et al. Antihypoxic and neuroprotective properties of BDNF and GDNF *in vitro* and *in vivo* under hypoxic conditions. *Sovremennye Tehnologii v Medicine*. 2014;6(4):38–47. (In Russ.)
**54.** Duarte EP, Curcio M, Canzoniero LM, Duarte CB. Neuroprotection by GDNF in the ischemic brain. *Growth Factors*. 2012;30(4):242–257. DOI: 10.3109/08977194.2012.691478
**55.** Shishkina TV. Antigipoksicheskoe i nejroprotektornoe dejstvie glial'nogo nejrotroficheskogo faktora pri modelirovanii faktorov ishemii [dissertation abstract]. Saint Petersburg; 2017 [cited 23 Aug 2021]. Available from: http://www.dslib.net/fiziologia/antigipoksicheskoe-i-nejroprotektornoe-dejstvie-glialnogo-nejrotroficheskogo.html. (In Russ.)
**56.** Shishkina TV, Mishchenko TA, Mitroshina EV, et al. Glial cell line-derived neurotrophic factor (GDNF) counteracts hypoxic damage to hippocampal neural network function *in vitro*. *Brain Res*. 2018;1678:310–321. DOI: 10.1016/j.brainres.2017.10.023
**57.** Shhelchkova NA, Kokaja AA, Vedunova MV. Rol' nejrotroficheskih faktorov pri gipoksii novorozhdennyh. In: VI Baltijskij kongress po detskoj nevrologii: sbornik tezisov. Ed. by V.I. Guzeva. Saint Petersburg; 2016. P. 409–410. (In Russ.)
**58.** Golosnaya GS, Kotij SA. Vaskuloendotelial'nyj faktor rosta (VEGF) i nejrotroficheskij faktor golovnogo mozga (BDNF) u novorozhdennyh s perinatal'nymi gipoksicheskimi porazheniyami CNS. *Questions of modern pediatrics*. 2006;5(1):149. (In Russ.)
**59.** Morozova AY, Milyutina YP, Kovalchuk-Kovalevskaya OV, et al. Neuron-specific enolase and brain-derived neurotrophic factor levels in umbilical cord blood in full-term newborns with intrauterine growth retardation. *Journal of obstetrics and women's diseases.* 2019;68(1):29–36. (In Russ.). DOI: 10.17816/JOWD68129-36
**60.** Vedunova MV, Mishchenko TA, Mitroshina EV, Mukhina IV. TrkB-mediated neuroprotective and antihypoxic properties of brain-derived neurotrophic factor. *Oxid Med Cell Longev*. 2015;2015:453901. DOI: 10.1155/2015/453901

## СПИСОК ЛИТЕРАТУРЫ

**1.** Перепелица С.А., Голубев А.М., Мороз В.В. и др. Причины острой интранатальной и постнатальной гипоксии у новорожденных // Общая реаниматология. 2012. Т. VIII. № 6. С. 17–22.
**2.** Гунин А.Г., Милованов М.М., Денисова Т.Г. Методы оценки состояния плода в родах // Здравоохранение Чувашии. 2014. Т. 3. № 3. С. 39–48.
**3.** Кузнецов П.А., Козлов П.В. Гипоксия плода и асфиксия новорожденного // Лечебное дело. 2017. № 4. С. 9–15.
**4.** Malin G.L., Morris R.K., Khan K.S. Strength of association between umbilical cord pH and perinatal and long term outcomes: Systematic review and meta-analysis // BMJ. 2010. Vol. 340 (7756). P. 1121. DOI: 10.1136/bmj.c1471

**5.** Goodwin T.M., Belai I., Hernandez P. et al. Asphyxial complications in the term newborn with severe umbilical acidemia // Am. J. Obstet. Gynecol. 1992. Vol. 167. No. 6. P. 1506–1512. DOI: 10.1016/0002-9378(92)91728-s
**6.** Rubak S.L. Lactate measurement in umbilical cord blood in neonates // Ugeskr Laeger. 2010. Vol. 172. No. 1. P. 364–368.
**7.** East C.E., Leader L.R., Sheehan P. et al. Intrapartum fetal scalp lactate sampling for fetal assessment in the presence of a non-reassuring fetal heart rate trace // Cochrane Database Syst. Rev. 2015. No. 5. P. CD006174. DOI: 10.1002/14651858.CD006174.pub3
**8.** Wiberg-Itzel E. Determination of pH or lactate in fetal scalp blood in management of intrapartum fetal distress: randomised controlled multicenter trial // Br. Med. J. 2008. Vol. 336. P. 1284–1287. DOI: 10.1136/bmj.39553.406991.25
**9.** Nordström L., Achanna S., Naka K., Arulkumaran S. Fetal and maternal lactate increase during active second stage of labour // BJOG. 2001. Vol. 108. No. 3. P. 263–268. DOI: 10.1136/10.1111/j.1471-0528.2001.00034.x
**10.** Wiberg N., Källén K. Fetal scalp blood lactate during second stage of labor: determination of reference values and impact of obstetrical interventions // J. Matern. Fetal. Neonatal. Med. 2017. Vol. 30. No. 5. P. 612–617. DOI: 10.1080/14767058.2016.1181167
**11.** Orsonneau J.-L., Fraissinet F., Sébille-Rivain V. et al. Suitability of POC lactate methods for fetal and perinatal lactate testing: considerations for accuracy, specificity and decision making criteria // Clin. Chem. Lab. Med. 2013. Vol. 51. No. 2. P. 397–404. DOI: 10.1515/cclm-2012-0201
**12.** Wiberg N., Klausen T.W., Tyrberg T. et al. Infant outcome at four years of age after intrapartum sampling of scalp blood lactate for fetal assessment. A cohort study // PLoS One. 2018. Vol. 13. No. 3. P. e0193887. DOI: 10.1371/journal.pone.0193887
**13.** Ремнева О.В., Фадеева Н.И., Фильчакова О.Н. и др. Интранатальная гипоксия плода: возможности диагностики, резервы снижения частоты церебральных расстройств у доношенных новорожденных // Российский вестник педиатрии. 2015. Т. 5. № 5. С. 61–66.
**14.** Погорелова Т.М., Гунько В.О., Друккер Н.А., Линде В.А. Белки-маркеры плацентарной недостаточности // Биомедицинская химия. 2010. Т. 56. № 5. С. 616–620.
**15.** Loukovaara M., Teramo K., Alfthan H. et al. Amniotic fluid S100B protein and erythropoietin in pregnancies at risk for fetal hypoxia // Eur. J. Obstet. Gynecol. Reprod. Biol. 2009. Vol. 142. No. 2. P. 115–118. DOI: 10.1016/j.ejogrb.2008.10.008
**16.** Summanen M., Seikku L., Rahkonen P. et al. Comparison of umbilical serum copeptin relative to erythropoietin and S100B as asphyxia biomarkers at birth // Neonatology. 2017. Vol. 112. No. 1. P. 60–66. DOI: 10.1159/000456063
**17.** Irmak K., Tüten N., Karaoglu G. et al. Evaluation of cord blood creatine kinase (CK), cardiac troponin T (cTnT), N-terminal-pro-B-type natriuretic peptide (NT-proBNP), and s100B levels in nonreassuring foetal heart rate // J. Matern. Fetal Neonatal. Med. 2021. Vol. 34. No. 8. P. 1249–1254. DOI: 10.1080/14767058.2019.1632285
**18.** Trevisanuto D., Picco G., Golin R. et al. Cardiac troponin I in asphyxiated neonates // Biol. Neonate. 2006. Vol. 89. No. 3. P. 190–193. DOI: 10.1159/000089795
**19.** Stefanović V., Loukovaara M. Amniotic fluid cardiac troponin T in pathological pregnancies with evidence of chronic fetal hypoxia // Croat. Med. J. 2005. Vol. 46. No. 5. P. 801–807.
**20.** Joseph S., Kumar S., Ahamed M.Z., Lakshmi S. Cardiac troponin-T as a marker of myocardial dysfunction in term neonates with perinatal asphyxia // Indian J. Pediatr. 2018. Vol. 85. No. 10. P. 877–884. DOI: 10.1007/s12098-018-2667-3
**21.** Asrani P., Aly A.M., Jiwani A.K. et al. High-sensitivity troponin T in preterm infants with a hemodynamically significant patent ductus arteriosus // J. Perinatol. 2018. Vol. 38. No. 11. P. 1483–1489. DOI: 10.1038/s41372-018-0192-x
**22.** Whitehead C., Teh W.T., Walker S.P. et al. Quantifying circulating hypoxia-induced RNA transcripts in maternal blood to determine *in utero* fetal hypoxic status // BMC Med. 2013. Vol. 11. No. 1. P. 1–12. DOI: 10.1186/1741-7015-11-25
**23.** Turrini I., Sorbi F., Ghizzoni V. et al. Severe fetal distress and placental damage might be associated with high troponin i (cTnI) levels in mothers // Am. J. Case Rep. 2018. Vol. 19. P. 194–198. DOI: 10.12659/AJCR.906617
**24.** Fleming S.M., O'Gorman T., Finn J. et al. Cardiac troponin I in pre-eclampsia and gestational hypertension // BJOG. 2000. Vol. 107. No. 11. P. 1417–1420. DOI: 10.1111/j.1471-0528.2000.tb11658.x
**25.** Joyal D., Leya F., Koh M. et al. Troponin I levels in patients with preeclampsia // Am. J. Med. 2007. Vol. 120. No. 9. P. 819. DOI: 10.1016/j.amjmed.2006.05.068
**26.** Whitehead C.L., Teh W.T., Walker S.P. et al. Circulating MicroRNAs in maternal blood as potential biomarkers for fetal hypoxia *in-utero* // PLoS One. 2013. Vol. 8. No. 11. P. e78487. DOI: 10.1371/journal.pone.0078487
**27.** Human reproductive and prenatal genetics. Ed. by P.C.K. Leung, J. Qiao. London: Academic Press; 2019.
**28.** Looney A.M., Walsh B.H., Moloney G. et al. Downregulation of umbilical cord blood levels of mir-374a in neonatal hypoxic ischemic encephalopathy // J. Pediatr. 2015. Vol. 167. No. 2. P. 269–273. DOI: 10.1016/j.jpeds.2015.04.060
**29.** Shi J.-P., Li Y.-W., Sang G.-M. et al. Expression and significance of serum miRNA-21 expression in neonates with HIE // Pr. Prev. Med. 2018. Vol. 25. P. 655–658. DOI: 10.3969/j.issn.1006-3110.2018.06.005
**30.** Ponnusamy V., Yip P.K. The role of microRNAs in newborn brain development and hypoxic ischaemic encephalopathy // Neuropharmacology. 2019. Vol. 149. P. 55–65. DOI: 10.1016/j.neuropharm.2018.11.041
**31.** Tissot van Patot M.C., Murray A.J., Beckey V. et al. Human placental metabolic adaptation to chronic hypoxia, high altitude: hypoxic preconditioning // Am. J. Physiol. Regul. Integr. Comp. Physiol. 2010. Vol. 298. No. 1. P. R166–172. DOI: 10.1152/ajpregu.00383.2009
**32.** Nuñez A., Benavente I., Blanco D. et al. Oxidative stress in perinatal asphyxia and hypoxic-ischaemic encephalopathy // An. Pediatr. (Barc). 2018. Vol. 88. No. 4. P. 228.e1–228.e9. DOI: 10.1016/j.anpedi.2017.05.005
**33.** Митрошина Е.В., Абогессименгане Б.Ж., Уразов М.Д. и др. Адаптационная роль глиального нейротрофического фактора при ишемии головного мозга // Современные технологии в медицине. 2017. Т. 9. № 1. С. 68–76.
**34.** Turovsky E.A., Zinchenko V.P., Gaidin S.G., Turovskaya M.V. Calcium-binding proteins protect gabaergic neurons of the hippocampus from hypoxia and ischemia *in vitro* // Biol. Membr. 2017. Vol. 34. No. 5. P. 68–80. DOI: 10.1134/S1990747818010105
**35.** Coimbra-Costa D., Alva N., Duran M. et al. Oxidative stress and apoptosis after acute respiratory hypoxia and reoxygenation in rat brain // Redox. Biol. 2017. Vol. 12. P. 216–225. DOI: 10.1016/j.redox.2017.02.014
**36.** Grow J., Barks J.D. Pathogenesis of hypoxic-ischemic cerebral injury in the term infant: current concepts // Clin. Perinatol. 2002. Vol. 29. No. 4. P. 585–602. DOI: 10.1016/s0095-5108(02)00059-3
**37.** Острова И.В., Аврущенко М.Ш. Экспрессия мозгового нейротрофического фактора (BDNF) повышает устойчивость нейронов к гибели в постреанимационном периоде // Общая реаниматология. 2015. Т. 11. № 3. С. 45–53. DOI: 10.15360/1813-9779-2015-3-45-53
**38.** Ikeda T., Xia X.Y., Xia Y.X. et al. Glial cell line-derived neurotrophic factor protects against ischemia/hypoxia-induced brain injury in neonatal rat // Acta Neuropathol. 2000. Vol. 100. No. 2. P. 161–167. DOI: 10.1007/s004019900162
**39.** Морозова А.Ю., Арутюнян А.В., Милютина Ю.П. и др. Динамика изменения содержания нейротрофических факторов в структурах головного мозга крыс в раннем онтогенезе после пренатальной гипоксии // Нейрохимия. 2018. Т. 35. № 3. С. 256–263. DOI: 10.1134/S1027813318030081

**40.** Морозова А.Ю., Арутюнян, А.В., Милютина, Ю.П. и др. Влияние пренатальной гипоксии на содержание нейронспецифической енолазы в структурах головного мозга и сыворотке крови крыс в раннем онтогенезе // Нейрохимия. 2020. Т. 37. № 3. С. 233–239. DOI: 10.31857/S1027813320030085
**41.** Щелчкова Н.А., Кокая А.А., Беженарь В.Ф. и др. Роль мозгового и глиального нейротрофических факторов при хронической внутриутробной кислородной депривации плода // Современные технологии в медицине. 2020. Т. 12. № 1. С. 25–33. DOI: 10.17691/stm2020.12.1.03
**42.** Cheng H., Fu Y.-S., Guo J.-W. Ability of GDNF to diminish free radical production leads to protection against kainate-induced excitotoxicity in hippocampus // Hippocampus. 2004. Vol. 14. No. 1. P. 77–86. DOI: 10.1002/hipo.10145
**43.** Shang J., Deguchi K., Yamashita T. et al. Antiapoptotic and anti-autophagic effects of glial cell line-derived neurotrophic factor and hepatocyte growth factor after transient middle cerebral artery occlusion in rats // J. Neurosci. Res. 2010. Vol. 88. No. 10. P. 2197–206. DOI: 10.1002/jnr.22373
**44.** Szydlowska K., Tymianski M. Calcium, ischemia and excitotoxicity // Cell Calcium. 2010. Vol. 47. No. 2. P. 122–129. DOI: 10.1016/j.ceca.2010.01.003
**45.** Ahn S.Y., Chang Y.S., Sung D.K. et al. Pivotal role of brain-derived neurotrophic factor secreted by mesenchymal stem cells in severe intraventricular hemorrhage in newborn rats // Cell. Transplant. 2017. Vol. 26. No. 1. P. 145–56. DOI: 10.3727/096368916X692861
**46.** Feng N., Hao G., Yang F. et al. Transplantation of mesenchymal stem cells promotes the functional recovery of the central nervous system following cerebral ischemia by inhibiting myelin-associated inhibitor expression and neural apoptosis // Exp. Ther. Med. 2016. Vol. 11. No. 5. P. 1595–1600. DOI: 10.3892/etm.2016.3089
**47.** Mitkari B., Nitzsche F., Kerkelä E. et al. Human bone marrow mesenchymal stem/stromal cells produce efficient localization in the brain and enhanced angiogenesis after intra-arterial delivery in rats with cerebral ischemia, but this is not translated to behavioral recovery // Behav. Brain Res. 2014. Vol. 259. P. 50–59. DOI: 10.1016/j.bbr.2013.10.030
**48.** Zhang R., Liu Y., Yan K. et al. Anti-inflammatory and immunomodulatory mechanisms of mesenchymal stem cell transplantation in experimental traumatic brain injury // J. Neuroinflammation. 2013. Vol. 10. P. 106. DOI: 10.1186/1742-2094-10-106
**49.** Lee N.M., Chae S.A., Lee H.J. Effects of neural stem cell media on hypoxic injury in rat hippocampal slice cultures // Brain Res. 2017. Vol. 1677. P. 20–25. DOI: 10.1016/j.brainres.2017.09.018
**50.** Liu X., Wang X., Li A., Jiao X. Effect of mesenchymal stem cell transplantation on brain-derived neurotrophic factor expression in rats with Tourette syndrome // Exp. Ther. Med. 2016. Vol. 11. No. 4. P. 1211–1216. DOI: 10.3892/etm.2016.3059
**51.** Zheng Z., Zhang L., Qu Y. et al. Mesenchymal stem cells protect against hypoxia-ischemia brain damage by enhancing autophagy through brain derived neurotrophic factor/mammalin target of rapamycin signaling pathway // Stem. Cells. 2018. Vol. 36. No. 7. P. 1109–1121. DOI: 10.1002/stem.2808
**52.** Sheng S., Huang J., Ren Y. et al. Neuroprotection against hypoxic/ischemic injury: δ-opioid receptors and BDNF-TrkB pathway // Cell. Physiol. Biochem. 2018. Vol. 47. No. 1. P. 302–315.
**53.** Ведунова М.В., Сахарнова Т.А., Митрошина Е.В. и др. Антигипоксические и нейропротективные свойства нейротрофических факторов BDNF и GDNF при гипоксии *in vitro* и *in vivo* // Современные технологии в медицине. 2014. Т. 6. № 4. С. 48–47.
**54.** Duarte E.P., Curcio M., Canzoniero L.M., Duarte C.B. Neuroprotection by GDNF in the ischemic brain // Growth Factors. 2012. Vol. 30. No. 4. P. 242–257. DOI: 10.3109/08977194.2012.691478
**55.** Шишкина Т.В. Антигипоксическое и нейропротекторное действие глиального нейротрофического фактора при моделировании факторов ишемии: автореф. ... дис. канд. биол. наук. Санкт-Петербург, 2017 [дата обращения: 22.08.2021]. Доступ по ссылке: http://www.dslib.net/fiziologia/antigipoksicheskoe-i-nejroprotektornoe-dejstvie-glialnogo-nejrotroficheskogo.html
**56.** Shishkina T.V., Mishchenko T.A., Mitroshina E.V. et al. Glial cell line-derived neurotrophic factor (GDNF) counteracts hypoxic damage to hippocampal neural network function *in vitro* // Brain Res. 2018. Vol. 1678. P. 310–321. DOI: 10.1016/j.brainres.2017.10.023
**57.** Щелчкова Н.А., Кокая А.А., Ведунова М.В. Роль нейротрофических факторов при гипоксии новорожденных // VI Балтийский конгресс по детской неврологии: сборник тезисов / под ред. В.И. Гузева. Санкт-Петербург, 2016. С. 409–410.
**58.** Голосная Г.С., Котий С.А. Васкулоэндотелиальный фактор роста (VEGF) и нейротрофический фактор головного мозга (BDNF) у новорожденных с перинатальными гипоксическими поражениями ЦНС // Вопросы современной педиатрии. 2006. Т. 5. № 1. С. 149.
**59.** Морозова А.Ю., Милютина Ю.П., Ковальчук-Ковалевская О.В. и др. Содержание нейронспецифической енолазы и мозгового нейротрофического фактора в пуповинной крови доношенных новорожденных с задержкой внутриутробного развития // Журнал акушерства и женских болезней. 2019. Т. 68. № 1. С. 29–36. DOI: 10.17816/JOWD68129-36
**60.** Vedunova M.V., Mishchenko T.A., Mitroshina E.V., Mukhina I.V. TrkB-mediated neuroprotective and antihypoxic properties of brain-derived neurotrophic factor // Oxid. Med. Cell Longev. 2015. Vol. 2015. P. 453901. DOI: 10.1155/2015/453901

## AUTHORS INFO

*** Olga V. Rozhdestvenskaya**, MD;
address: 6-8 building 4 L'va Tolstogo St., Saint Petersburg, 197022, Russia;
ORCID: https://orcid.org/0000-0003-2280-9196;
e-mail: olgamish@inbox.ru

**Anna A. Kokaya**, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-7324-5947;
e-mail: kann9998@yandex.ru

**Vitaly F. Bezhenar**, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-7807-4929;
Researcher ID: R-7055-2017; Scopus Author ID: 57191963583;
eLibrary SPIN: 8626-7555; e-mail: bez-vitaliy@yandex.ru

## ОБ АВТОРАХ

*** Ольга Викторовна Рождественская**;
адрес: Россия, 197022, Санкт-Петербург, ул. Льва Толстого, д. 6–8, корп. 4;
ORCID: https://orcid.org/0000-0003-2280-9196;
e-mail: olgamish@inbox.ru

**Анна Александровна Кокая**, канд. мед. наук;
ORCID: https://orcid.org/0000-0001-7324-5947;
e-mail: kann9998@yandex.ru

**Виталий Федорович Беженарь**, д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0002-7807-4929;
Researcher ID: R-7055-2017; Scopus Author ID: 57191963583;
eLibrary SPIN: 8626-7555; e-mail: bez-vitaliy@yandex.ru

* Corresponding author / Автор, ответственный за переписку