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宫内感染与早产儿脑损伤的研究进展

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摘　要

宫内感染是导致早产儿脑损伤的重要因素之一，近年来的研究揭示了其在导致早产儿脑损伤中的关键作用。宫内感染通过多种机制对早产儿的大脑发育造成影响，包括炎症反应、氧化应激和血脑屏障的破坏。现研究对宫内感染机制的深入理解，以及早期诊断和干预策略的探索显示通过抗感染、亚低温、促红细胞生成素、高压氧以及干细胞靶向治疗等可能有助于减少宫内感染对早产儿的负面影响。未来的研究需要进一步探索宫内感染与早产儿脑损伤之间的复杂关系，并研制更有效的干预措施，以改善早产儿的长期神经发育预后。

关键词

宫内感染，早产儿脑损伤，炎症，发病机制，干预措施

Research Progress on Intrauterine Infection and Brain Injury in Premature Infants

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Abstract

Intrauterine infection is one of the important factors leading to brain damage in premature infants, and recent studies have revealed its key role in causing brain damage in premature infants.

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Intrauterine infection affects the brain development of premature infants through various mechanisms, including inflammatory response, oxidative stress, and disruption of the blood-brain barrier. The in-depth understanding of the mechanism of intrauterine infection and the exploration of early diagnosis and intervention strategies have shown that anti-infection, hypothermia, erythropoietin, hyperbaric oxygen, and targeted stem cell therapy may help reduce the negative impact of intrauterine infection on premature infants. Future research needs to further explore the complex relationship between intrauterine infection and brain injury in premature infants, and develop more effective intervention measures to improve the long-term neurodevelopmental prognosis of premature infants.

Keywords

Intrauterine Infection, Premature Infant Brain Injury, Inflammation, Pathogenesis, Intervention Measures

1. 引言

早产是一个重大的全球健康挑战，其是指在妊娠 37 周之前发生的分娩，分娩的胎儿称之为早产儿。早产是导致新生儿以及 5 岁以下儿童死亡的主要风险之一，其中大多数早产儿死亡发生在新生儿期[1]。依据对 2020 年全球 194 个国家和地区的早产情况进行统计显示，全球每年约有 1500 万早产儿，全球早产率约为 10%，我国新生儿早产率约为 6.1%，每年大约有 7 万早产儿出生，其排名位居世界前 5 名[2]。与足月出生的新生儿相比，早产儿出现不良后果的风险要高得多。死亡和发病的风险根据早产程度而增加，极早产(妊娠 < 28 周)的婴儿风险最高，其次是极早产(28 周至 32 周)的婴儿，然后是中晚期早产(32 周至 37 周)的婴儿[3]-[5]。尽管目前早产病因仍不清楚，但现已提出多种因素可引发早产，例如基因遗传、免疫炎症、微生物、精神心理机制、环境、内分泌、机械刺激、血管功能失调等均存在联系。早产是一种多因素综合征，是体内多种生物学活动交互作用的结果[6]。

1955 年，Eastman 等人首次提出早产、炎症、脑损伤和脑瘫之间的关系。研究观察到，脑瘫与早产有关，而且产时母亲有发热后分娩的胎儿患有脑瘫的可能性是非发热对照组的七倍[7]。目前，临床和流行病学调查报告与动物实验相结合，依然表明母体与胎儿炎症、早产和后续脑损伤之间存在密切关系[8] [9]。有学者表明约 40%的早产归因于宫内上行感染[10]，其会引发胎膜早破和绒毛膜羊膜炎。在胎膜早破中，炎症反应有利于膜损伤，从而导致妊娠 37 周前羊水流失，导致将近 24%的早产。在绒毛膜羊膜炎中，炎症反应可能会影响脐带和绒毛膜血管，引起绳索炎和绒毛膜血管炎[11]。有研究提出接触过组织学或临床绒毛膜羊膜炎的早产儿患脑瘫或囊性脑室周围白质软化症(cPVL)的风险比未接触过的早产儿高 1.5~3 倍，且妊娠 22 至 25 周出生的婴儿中，高达 70%的婴儿患有组织学绒毛膜羊膜炎[12]。本文将系统综述目前有关宫内感染对早产儿神经发育和脑损伤影响的最新研究进展，探讨其潜在的病理生理机制和未来展望。

2. 宫内感染概述

宫内感染(Intrauterine infection, IAI)，指各种病原微生物进入宫腔，引起孕母宫腔内羊水、胎膜、胎盘等组织的感染性疾病[13]，中性粒细胞在胎盘组织内不同程度的浸润为其病理特点，绒毛膜羊膜炎

(Chorioamnionitis, CA)为其病理学诊断。根据母亲产前是否存在发热、心率增快、子宫压痛、白细胞升高等临床表现，将 CA 分为临床绒毛膜羊膜炎(Clinical chorioamnionitis, CCA)与组织学绒毛膜羊膜炎(Histological chorioamnionitis, HCA)，后者无典型临床表现，占宫内感染的 90%，故仅以临床表现判断孕妇是否存在 IAI 漏诊率高，胎盘病理检查见 HCA 为发生 IAI 提供了诊断的“金标准”[13] [14]。IAI 不仅对孕妇下生殖道有影响，微生物还可通过胎盘垂直传播，引起胎儿先天性感染[15]。IAI 可能会以不同的方式发生，例如血源性感染或进行羊膜穿刺术期间等。病原微生物在下生殖道定植会影响较多的未足月胎膜早孕[16]和 CA [17]，比如由支原体、解脲支原体、动支链菌、拟杆菌、B 族链球菌、大肠杆菌、粪肠球菌、白色念珠菌、肺炎克雷伯菌和阴道加德纳菌引发的上行感染[17]。

许多动物研究证实 IAI 与早产存在因果关系[18] [19]。动物模型还表明，维持完整的宿主炎症反应对于感染引起的早产至关重要，通过抑制对细菌炎症反应至关重要的分子途径(例如阻断 Toll 样受体 4 (TLR4)或其下游效应器)，接种的动物能够免受早产的影响[20]-[22]。综合所有证据表明，感染导致的早产很可能是由于炎症反应干扰了母体胎儿的耐受性，导致产程过早启动[23]。

当孕妇存在 IAI 时，病原微生物及其代谢产物、自身免疫产物等导致宫腔内炎细胞聚集，使胎儿暴露于炎症环境。其不仅与早产有关，还与胎儿炎症反应综合征(Fetal Inflammatory Response Syndrome, FIRS)、脑室周围白质软化(Periventricular leukomalacia, PVL)和支气管肺发育不良(Bronchopulmonary dysplasia, BPD)等多种并发症有关[24] [25]。实验室分析表明，在 CA 中，支原体和解脲支原体是胎盘膜和羊水中的主要定植菌[24]；同样有研究报告显示，在妊娠第 23 周至第 32 周期间进行的 351 次分娩中，有 23%的脐带血培养呈解脲支原体和人型支原体阳性；与指示性早产相比，自发性早产的发生率更高[25]。

3. 早产儿脑损伤的病因和发病机制

在大多数情况下，常见的损伤途径是由最初的缺氧引起的－缺血性或炎症性损伤，引发一系列事件，加剧围产期脑损伤[26]。

足月胎儿中存在的适应性生理机制，使其能够对氧合受损或全身性低血压时期作出反应。当含氧血液供应有限时，胎儿通过将更高浓度的氧与血红蛋白结合、优先将含氧血液分流至缺氧损伤风险最大的组织以及限制耗氧量来满足其代谢需求[27]。

与足月胎儿的适应机制不同，早产儿脑血管自动调节系统不成熟，表现为压力被动循环。当面临缺氧期或全身性低血压时，早产儿无法维持增加的脑灌注，更容易发生缺氧缺血和神经损伤。初始缺氧缺血性损伤是神经元损伤的主要机制，细胞无法满足其代谢需[26]。大脑中代谢需求最大的区域－感觉运动皮层、丘脑、小脑和脑干最容易受伤[28]。在初始损伤和脑组织再灌注后，细胞代谢功能有短暂的恢复，然而这一阶段过后是葡萄糖代谢的二次减少和高能磷酸盐的缺乏，从而导致兴奋性氨基酸、细胞凋亡、活性氧和炎症的二次损伤，随着时间的推移，炎症导致大部分脑损伤[29] [30]。

4. 宫内感染导致早产儿脑损伤的机制

在最初阶段，胎儿大脑容易受到炎症的影响，这些炎症会改变其自然发育并选择性地损害脑白质[31]，这是早产儿中观察到的最常见的脑损伤类型[32]。少突胶质细胞和少突胶质祖细胞是负责髓鞘形成的关键细胞，非常容易受到氧化应激和炎症的影响，但通常要到妊娠晚期才会发育成熟[26] [33]。正常情况下，皮质髓鞘形成仅在妊娠 34 周时开始，并持续到生命的最初几年[34]。当少突胶质细胞的成熟和髓鞘形成因炎症事件和(或)缺氧缺血而中断时，可能会发生涉及轴突和少突胶质细胞坏死的局部或弥漫性脑白质损伤(White Matter Injury)。由于免疫细胞上的 TLR4 受体激活，导致白质成熟不良，随后发生炎症反应，导致全身性炎症反应。低血糖、低灌注以及修饰后的巨噬细胞或小胶质细胞的进一步免疫活化[32] [35]。

这可以通过多种细胞和分子机制来实现，包括通过细胞因子和病原体相关分子模式(PAMPS)激活小胶质细胞和星形胶质细胞，从而导致：1) 谷氨酸增加，增强兴奋性毒性，使前少突胶质细胞容易受到损伤；2) 释放破坏性的活性氧和氮(分别为 ROS 和 RNS)；3) 抗氧化防御发展延迟；4) 活化的小胶质细胞释放 TNF-α，可进一步促进 WMI [36]。

尽管早产儿的一些神经系统并发症与发育不成熟有关，但有大量证据表明，围产期感染和炎症会损害发育中的大脑[37]-[39]。

胎盘炎症是后续脑损伤的重要预测因素，有对极低胎龄新生儿研究表明，即使从胎盘中分离出低毒力微生物，也可以预测随后的新生儿脑部病变和长期手足瘫痪[40]。宫内炎症如何导致胎儿脑损伤的确切机制尚不清楚，但一些动物实验研究表明，无论使用哪种病原体，炎症细胞因子都可能是早产和脑损伤之间的联系[41]-[43]。发育中大脑的正常细胞因子反应失调可能会扰乱神经发育过程，可能是通过母亲产生的细胞因子、胎盘细胞因子或胎儿产生的细胞因子经胎盘传递而发生的[44]。

炎症相关的脑损伤可能是由促炎细胞因子对少突胶质细胞和神经元的直接损伤以及促炎细胞因子激活小胶质细胞造成的间接损伤共同引起的(例如，IL-1b 已被证明可以在离体大鼠中激活海马小胶质细胞)[45]-[46]。激活的小胶质细胞通过进一步释放促炎细胞因子和兴奋性代谢物(例如具有细胞毒性的谷氨酸)或通过释放氧化自由基来造成损伤[47]-[49]。小胶质细胞激活已被发现与自闭症有关，并被认为会导致早产儿自闭症谱系障碍的高发病率[49]-[51]。

总体而言，早有证据表明母体炎症介质，包括趋化因子、细胞因子、前列腺素和活性氧，都可以穿过胎盘，与胎儿免疫系统相互作用并调节胎儿免疫系统，从而最终导致炎症介质跨过未成熟胎儿血脑屏障(BBB)造成局部伤害[52]-[54]。除了这些炎症介质引起的直接神经毒性外，有证据表明，围产期炎症诱导的炎症级联反应使已启动的新生儿大脑对产后损伤敏感，继发于缺氧或感染引起的损伤[55]。比如，绒毛膜羊膜炎会使新生儿容易受到一系列后果的影响，这些后果本身就是对新生儿造成损伤的危险因素，包括 PTB、早发性败血症、BPD、早产儿视网膜病变(ROP)和弥漫性 WMI [56] [57]。

对于胎儿来说，母体炎症级联反应也可引发胎儿炎症反应综合征(FIRS)，导致包括中枢神经系统损伤在内的多器官损害。FIRS 是母体炎症可能导致的严重后果之一，通常继发于绒毛膜羊膜炎，可在产前开始，但也可影响产后[58]。FIRS 对胎儿器官具有广泛的有害影响，可通过缺氧和缺血反复发作，直接损害脑血流，减少氧合，刺激局部和全身细胞因子释放破坏负责靶向血管舒张的一氧化氮合成酶(NOS)，并损害兴奋性氨基酸[58]-[60]。对于出生后不久继发于 FIRS 的新生儿，可能会出现多次损害导致胎儿发生脑损伤以及继发于持续炎症的胎龄依赖性脆弱性可显着改变临床表型。

5. 宫内感染及其所致脑损伤的早期干预措施

1) 抗生素的应用：宫内感染主要由细菌上行感染引发，因此，早期进行抗感染治疗能够有效降低新生儿脑损伤的发生率。在出现绒毛膜羊膜炎时，及时启动抗生素治疗对于预防母体和胎儿的并发症至关重要。有研究表明，及时应用广谱抗生素可以显著减少与绒毛膜羊膜炎相关的母婴并发症。妊娠中期或晚期预防性使用抗生素可有效降低妊娠期细菌性阴道病、分娩前胎膜破裂、产后子宫内膜炎和淋球菌感染的孕妇早产的风险[61]。

2) 亚低温治疗：亚低温对脑组织的保护机制有降低脑氧代谢率从而有助于神经功能的恢复、对兴奋性氨基酸、内源性毒性产物及自由基的释放有遏制作用、进一步延缓细胞因子(内皮素-1、白三烯)的产生、保护血脑屏障、减少脑血管源性脑水肿以及亚低温对 NO 合酶 CNOS 有抑制作用[62]。亚低温可以显著降低脑损伤的发病率，减少神经元的损伤，并保护因脑缺血而受损的神经。

3) 促红细胞生成素：静脉输注促红细胞生成素对脑神经祖细胞的增殖可起到促进作用，同时可以使

脑内胶质细胞的再生修复能力进行提升，加快患儿病情康复速度，另外还可以使患儿的脑神经功能得以改善，使其体格发育能力和智力发育能力恢复至正常[63]。

4) 干细胞靶向治疗：使用脐带血或脐带组织间充质干细胞和内皮祖细胞进行靶向细胞治疗可能是一种合适而有效的治疗方案。出生后不久在神经炎症的高峰期给予间充质干细胞，随后给予内皮祖细胞诱导血管重构，可能有助于大脑发育正常化和(或)修复绒毛膜羊膜炎造成的损伤。联合使用脐带血内皮祖细胞和脐带组织间充质干细胞作为新生儿脑损伤的治疗方法，从而可以减轻围产期脑损伤的负担[39]。

5) 高压氧：在高压氧环境下，血氧含量和血氧分压显著增加，脑血管和脑组织的含氧量也显著提升，同时无氧酵解和酸性物质生成减少，能量生成增加，从而减轻了组织酸中毒，此外高压氧还能够减轻脑水肿并降低颅内压[64]。高压氧治疗脑损伤的分子机制包括增加氧自由基清除能力、阻断细胞钙内流、降低细胞因子水平，以及阻断神经元凋亡等[65]。

6. 结论与展望

宫内感染与早产儿脑损伤的关系是一个复杂且多因素影响的研究领域，通过对现有文献的综述，我们发现宫内感染通过多种机制，如炎症反应、免疫激活和血脑屏障破坏等，显著增加早产儿脑损伤的风险。这些机制不仅涉及细胞水平的损伤，还包括分子和基因层面的改变，为脑损伤的发病机制提供了深刻的见解。尽管现有研究在揭示宫内感染导致早产儿脑损伤的机制方面取得了一定进展，但仍存在诸多不明确之处。未来的研究可以进一步研究感染引起的细胞和分子机制，特别是对不同病原体在脑损伤过程中的特异性作用，这有助于精准干预和治疗方案的开发；其次寻找能够早期预测宫内感染及其导致脑损伤的可靠生物标志物，并进行大规模验证，以便实现早期诊断和精准干预；最后基于患者个体的基因和环境因素，发展个体化的预防和治疗策略，以提高干预措施的效果和安全性。希望通过以上研究方向的拓展和深入，将有助于更好地理解宫内感染与早产儿脑损伤的复杂关系，进而推动预防、诊断和治疗水平的提升，最终改善早产儿的预后。

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