· 综 述 ·

孕期应激性生活事件与不良妊娠结局关系的研究进展

朱家姝[1, 2] 综述，关素珍[1, 2] 审校

1.宁夏医科大学公共卫生学院，宁夏 银川 750004；2.宁夏环境因素与慢性病控制重点实验室，宁夏 银川 750004

摘要：提高出生人口素质是世界各国重视的健康发展战略，早产、低出生体重和小于胎龄儿等不良妊娠结局是围产儿死亡和残疾的主要原因。本文收集2007—2023年国内外关于孕期应激性生活事件与不良妊娠结局关系的研究文献，对孕期应激性生活事件与早产、低出生体重、小于胎龄儿等不良妊娠结局的关系及其潜在生物学机制进行综述，发现孕期应激性生活事件与不良妊娠结局相关，但机制尚不明确，主要涉及神经内分泌调节、炎症反应和微生物群途径，提出应关注应激性生活事件与不良妊娠结局关系的关键窗口期研究，并深入开展相关研究阐明不良妊娠结局发生机制，为减少不良妊娠结局的发生提供依据。

关键词：孕期；应激性生活事件；不良妊娠结局

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Association between stressful life events during pregnancy and adverse pregnancy outcomes: a review

ZHU Jiashu[1, 2], GUAN Suzhen[1, 2]

1.School of Public Health, Ningxia Medical University, Yinchuan, Ningxia 750004, China; 2.Ningxia Key Laboratory of Environmental Factors and Chronic Disease Control, Yinchuan, Ningxia 750004, China

Abstract: Improving the quality of newborns is a health development strategy, which has attracted global attention. Adverse pregnancy outcomes, including preterm birth, low birth weight and small for gestational age, are major causes of perinatal mortality and disability. Based on review of international and national publications pertaining to associations between stressful life events during pregnancy and adverse pregnancy outcomes from 2007 to 2023, this review summarizes the correlation between stressful life events during pregnancy and adverse pregnancy outcomes, including preterm birth, low birth weight and small for gestational age, and describes the underlying biological mechanisms. Previous studies have demonstrated the associations between maternal stressful life events during pregnancy and adverse pregnancy outcomes, and the underlying mechanisms mainly include neuroendocrine regulation, inflammation and microbiota pathways; however, the exact mechanisms remain unclear until now. Further studies to identify the critical window period for the association between stressful life events and adverse pregnancy outcomes, and unravel the pathogenesis of adverse pregnancy outcomes are warranted, so as to provide insights into reduction of adverse pregnancy outcomes.

Keywords: pregnancy; stressful life events; adverse pregnancy outcome

应激性生活事件是指对个体有害或有潜在威胁，需要个体适应的生活事件[1]。孕妇因生活环境变化会经历多种应激性生活事件，包括工作、生活压力和家庭矛盾等[2]。这些应激性生活事件可导致孕妇焦虑、抑郁，增加产后抑郁发生率[3]，还可能改变宫内环境，影响子代生长发育，导致代谢性疾病、神经损伤等发育源性疾病[4-7]。通过检索PubMed、SCI-hub和中国知网等数据库，系统回顾2007—2023年国内外孕期应激性生活事件与不良妊娠结局研究进展，本文对孕期应激性生活事件与早产、低出生体重、小于胎龄儿的相关性及其潜在生物学机制进行综述，为减少不良妊娠结局的发生提供依据。

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作者简介：朱家姝，硕士研究生在读

通信作者：关素珍，E-mail：guansz_nx2017@sina.com

1　孕期应激性生活事件对不良妊娠结局的影响

1.1　孕期应激性生活事件与早产风险

早产是指妊娠达到28周但不足37周分娩，娩出的新生儿称为早产儿。世界卫生组织（WHO）发布的《早产儿全球报告》显示，全球每年约有1 500万早产儿，占全部新生儿的10%以上[8]。孕妇经历伴侣暴力、家庭不和等应激性生活事件后发生早产的风险显著升高[9-11]。针对应激暴露关键窗口期的研究显示孕前和孕期经历应激性生活事件均可增加早产风险，但研究结论尚不一致：有研究表明，孕早期经历应激性生活事件可能增加早产风险[12]；另一项研究结果显示，孕中期经历应激性生活事件的女性发生早产的可能性更大[13]。分析新生儿性别发现，孕期经历应激性生活事件与男婴早产风险增加有关，而在女婴中并未发现相关性[14]。

1.2　孕期应激性生活事件与低出生体重风险

出生体重反映新生儿的发育程度和营养状况。低出生体重是指新生儿出生体重<2 500 g，2015年全球低出生体重率为14.6%[15]。大部分研究结果支持孕期应激性生活事件是低出生体重的危险因素[16]，严重应激性生活事件可增加娩出极低体重出生儿的风险[17]。不同妊娠阶段应激性生活事件对新生儿出生体重的影响不同，研究发现孕早期应激性生活事件可使低出生体重风险增加2倍以上[12]；另一项研究提示孕中期应激性生活事件与低出生体重有关[13]。

1.3　孕期应激性生活事件与小于胎龄儿风险

小于胎龄儿是指出生体重低于性别和胎龄第10百分位的新生儿。据估计，全球小于胎龄儿发生率为2.3%~10%，我国小于胎龄儿发生率为6.61%[18]。研究表明，孕期应激性生活事件与小于胎龄儿风险增加有关[19-20]。此关联可能存在性别差异，DING等[21]研究显示男婴小于胎龄儿的风险是女婴的1.66倍。不同妊娠阶段应激性生活事件的影响不同，有研究显示孕妇孕晚期经历应激性生活事件娩出小于胎龄儿的风险更高[22]。

2　孕期应激性生活事件影响不良妊娠结局的机制

孕期应激性生活事件影响不良妊娠结局的生物学机制主要包括神经内分泌调节、炎症反应和微生物群改变。吸烟、药物滥用和营养不良等应激相关行为也与不良妊娠结局有关。急性和慢性应激都可能导致体内稳态超负荷或平衡介质长期失衡，从而导致神经内分泌和免疫系统反应中断[23]。

2.1　神经内分泌调节

下丘脑-垂体-肾上腺轴在应对应激条件中发挥重要作用[24]。下丘脑-垂体-肾上腺轴构成了调节孕期应激性生活事件与不良妊娠结局关系的主要神经内分泌机制[25]。交感-肾上腺髓质系统促进机体对应激的初始反应，调节儿茶酚胺（包括去甲肾上腺素、肾上腺素和少量多巴胺）的释放，并最终触发“战斗或逃跑”反应。这些过程可激活下丘脑-垂体-肾上腺轴，触发下丘脑分泌促肾上腺皮质激素释放激素和垂体前叶产生促肾上腺皮质激素[26]，刺激肾上腺皮质束状带向血液释放糖皮质激素。皮质醇是主要的人类糖皮质激素[27]，被认为是目前研究昼夜节律最广泛使用的生物相位标志物[19]，昼夜皮质醇谱的失调可能介导孕期应激性生活事件对不良妊娠结局的影响[28]。胎盘11β-羟基类固醇脱氢酶2型能将生物活性皮质醇转化为非活性皮质醇，被视为母体糖皮质激素的生理屏障[29]。孕期应激性生活事件可能下调11β-羟基类固醇脱氢酶2型基因的表达，损害胎盘糖皮质激素屏障[30]。由11β-羟基类固醇脱氢酶2型mRNA的表达和活性下调而导致的母体糖皮质激素过度暴露可预测早产和低出生体重风险[31]。

2.2　炎症反应

正常情况下，母体免疫系统可为胎儿维持无病原体、无炎症的宫内环境[32]。然而，应激性生活事件可导致母体免疫失调[33-34]。有研究显示，孕期应激性生活事件可能介导炎症反应进而影响妊娠结局。例如孕期应激应激性生活事件与促炎基因表达上调、核因子-κB信号通路和蛋白转录因子AP-1活性增加有关[35]；白介素-6、肿瘤坏死因子-α与自发性早产密切相关[36]；胎盘热休克70kDa蛋白5（HSPA5）可能促进炎症反应并改变胎盘的抗炎状态，导致早产[37]。

2.3　微生物群改变

孕期应激性生活事件、母体微生物群改变和不良妊娠结局的相关研究尚处于起步阶段，但在肠道微生物组的表征及其与中枢神经系统关系方面取得了实质性进展[38]。孕期心理应激已被证明会改变肠道微生物群的组成[39]。母体肠道微生物群促进胎儿下丘脑皮质轴突生成，可能是通过微生物调节的代谢物向发育中的大脑神经元发出信号[40]。赵枫等[41]研究发现雌性大鼠孕期慢性应激不仅会导致肠道微生物群紊乱，还会改变宫内环境，影响后代肠道微生物群的多样性[42]。也有研究表明，心理压力与阴道微生物群组成相关[43]。有学者通过建立产前应激小鼠模型并

移植母体阴道微生物群发现，母体产前应激暴露可影响阴道微生物群，进而对雄性仔鼠肠道和下丘脑产生持久影响[44]。

3 小 结

孕期应激性生活事件可能增加早产、低出生体重和小于胎龄儿等不良妊娠结局的发生风险。应激性生活事件与不良妊娠结局关系的关键窗口期，以及该关联是否存在性别差异尚未得到广泛研究。孕期应激性生活事件导致不良妊娠结局的生物学机制尚不明确，目前认为其潜在机制涉及神经内分泌、炎症反应和微生物群。建议深入开展相关研究，揭示孕期应激性生活事件影响不良妊娠结局的潜在作用机制。

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