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运动重编程母体肥胖子代血管功能障碍的研究进展

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摘 要:肥胖已成为全球公共卫生挑战,其在育龄期女性中的发生率持续上升。母体肥胖不仅危害孕妇自身健康,还可通过发育源性机制对子代心血管系统产生深远影响,增加其成年后罹患心血管疾病的风险。血管功能障碍是母体肥胖对子代心血管系统产生不良影响的关键环节,表现为内皮功能受损、血管结构重塑及血管反应性异常。作为一种安全有效的非药物干预手段,母体规律运动可对子代血管系统实现重编程,通过优化宫内环境、改善胎盘结构与功能及调节表观遗传修饰,缓解母体肥胖的不良代际效应。本综述旨在总结母体肥胖对子代血管的不良编程效应,探讨运动的重编程效果及潜在的分子机制,为探索通过有效运动干预阻断肥胖代际传递提供理论参考。

关键词:肥胖;血管功能障碍;运动干预;发育源性健康与疾病学说
中图分类号:G804.2;Q987;R589.2 **文献标识码**:A

Exercise reprogramming of offspring vascular dysfunction induced by maternal obesity

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Abstract: Obesity has become a major global public health challenge, with a rapidly increasing incidence among women of reproductive age. Growing evidence indicates that maternal obesity not only impairs maternal metabolic health but also predisposes offspring to long-term cardiovascular diseases through developmental programming mechanisms. According to the developmental origins of health and disease (DOHaD) hypothesis, exposure to an obesogenic intrauterine environment confers persistent cardiovascular vulnerability across the lifespan. Vascular dysfunction is a key early manifestation linking maternal obesity to offspring cardiovascular risk. Offspring exposed to maternal obesity commonly exhibit vascular structural remodeling, including increased arterial stiffness and altered vascular wall composition, together with abnormal vascular reactivity and blood pressure regulation. Endothelial dysfunction is also frequently observed, characterized by impaired endothelium-dependent vasodilation, reduced nitric oxide bioavailability, and increased oxidative stress. These vascular abnormalities may arise early in life and persist into adulthood, contributing to the development of hypertension and cardiometabolic disorders. Exercise has emerged as a safe and effective non-pharmacological strategy to counteract obesity-induced adverse vascular programming. Evidence from both human and animal studies suggests that maternal exercise before and during pregnancy improves offspring vascular structure and function, while postnatal exercise may further ameliorate vascular dysfunction during childhood and adolescence. The magnitude of these benefits appears to depend on the timing and characteristics of the exercise intervention, with the prenatal period representing a particularly sensitive window. Mechanistically, exercise-induced vascular reprogramming involves multiple interrelated pathways. Maternal exercise improves the intrauterine environment by attenuating inflammation and oxidative stress, thereby preserving endothelial nitric oxide signaling and redox balance in offspring. In

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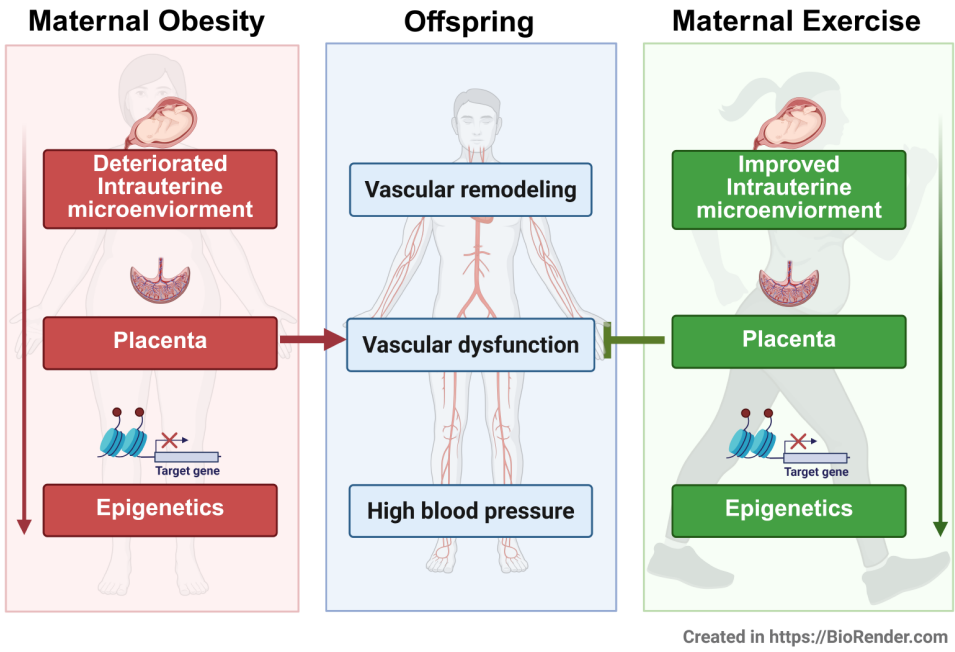
parallel, exercise promotes beneficial placental adaptations, including enhanced placental vascularization, improved mitochondrial function, and optimized nutrient and oxygen transport, supporting normal fetal vascular development. In addition, accumulating evidence highlights epigenetic regulation as a central mechanism underlying long-term vascular reprogramming. Exercise modulates DNA methylation, histone modifications, and non-coding RNA expression in offspring vascular tissues, leading to persistent alterations in genes involved in vascular tone regulation, oxidative stress responses, and endothelial function. Further studies are needed to elucidate the optimal exercise strategies and the mechanisms underlying long-term vascular reprogramming, thereby facilitating the prevention of cardiovascular disease across generations.



Key words: obesity; vascular dysfunction; exercise intervention; developmental origins of health and disease (DOHaD)

肥胖已成为全球范围内的重大公共卫生问题，尤其在育龄女性中，其发生率正迅速增长。全球数据显示，在2010–2019年间，约1/6的妊娠受到母体肥胖的影响，母体合并超重与肥胖的比例接近50%，预计到2030年全球母体肥胖患病率将上升至23.3%[1]。中国同样面临相似挑战，成年女性超重与肥胖率持续上升，给国家公共卫生系统带来沉重负担[2]。母体肥胖不仅显著增加妊娠期并发症(如妊娠期糖尿病、子痫前期、剖宫产风险等)的发生风险[1]，还与不良围产结局，如巨大儿、先天畸形等呈正相关[3]。更重要的是，根据“发育源性健康与疾病”(developmental origins of health and disease，DOHaD)理论，生命早期，尤其是宫内阶段的环境暴露，如母体营养状况和代谢状态可通过发育编程机制影响胎儿组织和器官的结构与功能，进而决定其成年期慢性疾病的易感性[4,5]。在此背景下，母体肥胖所营造的不良宫内环境不仅是妊娠期的短期风险事件，更是一种具有持久发育效应的环境暴露因素。

大量流行病学和临床研究证据表明，母体肥胖显著增加子代在成年期发生心血管疾病(cardiovascular disease，CVD)的风险[6]。值得关注的是，这种跨代风险往往在生命早期即可表现为血管结构与功能的异常表型，如内皮功能障碍、动脉僵硬度增加等，它们可能构成连接母体肥胖与子代远期CVD易感性的重要中介[7]。因此，理解母体肥胖导致子代血管功能障碍的发育编程过程，对于阻断跨代CVD风险具有重要意义。在应对这种不良编程效应的策略中，运动作为一种简单、有效的生活方式干预，受到广泛关注。母体运动不仅改善子代代谢健康[8,9]，还可通过优化宫内环境、改善胎盘结构与功能及调节表观遗传状态，减轻母体肥胖对子代血管的不良编程效应。基于此，

本综述旨在总结母体肥胖对子代血管的不良编程效应,并重点论述运动作为一种重编程干预手段在改善这一不良结局中的潜在价值。

1 母体肥胖对子代血管的不良编程效应

母体肥胖可对子代血管系统的发育和功能造成持久性不良影响,这些影响构成了子代未来罹患CVD的基础。相关证据主要来源于流行病学调查、人体观察性研究以及动物模型实验。这些研究表明,母体孕前或孕期肥胖与子代在整个生命周期内心血管健康状况不佳存在关联。这不仅表现为子代成年期CVD发病率、住院率和死亡率的增加[6],还体现在其生命早期即可检测到的血管结构改变、血管反应性与张力调控异常以及血管内皮功能障碍。图1总结了母体肥胖对子代血管的不良编程效应。

1.1 血管结构改变

母体肥胖可引起子代血管结构的早期重塑。动物研究显示,在妊娠和哺乳期接受高脂饮食(high-fat diet,HFD)的母鼠,其子代在6月龄时出现主动脉结构改变,表现为内皮细胞体积减少、平滑肌细胞数量下降及主动脉僵硬度增加[10]。在母体HFD喂养的非人灵长类子代中也观察到腹主动脉的结构变化,与正常饮食组相比,这些子代的腹主动脉内膜中层增厚、血管形态异常[11]。人体研究也提供了有力证据。母体孕前体重指数(body mass index,BMI)较高,其子代学龄期(4~6岁)视网膜小动脉扭曲度随之增加[12],而该指标与高血压、冠心病和卒中风险呈正相关。另有研究报道,肥胖母体的子代颈动脉内中膜厚度(carotid intima-media thickness,CIMT)增加[13],提示其存在早期动脉粥样硬化趋势。此外,儿童和青少年肥胖本身与动脉僵硬度增加,如脉搏波速度(pulse wave velocity,PWV,评估动脉僵硬度的常用指标)升高、β-僵硬指数增加呈正相关[14],提示母体肥胖可能通过诱导子代肥胖,

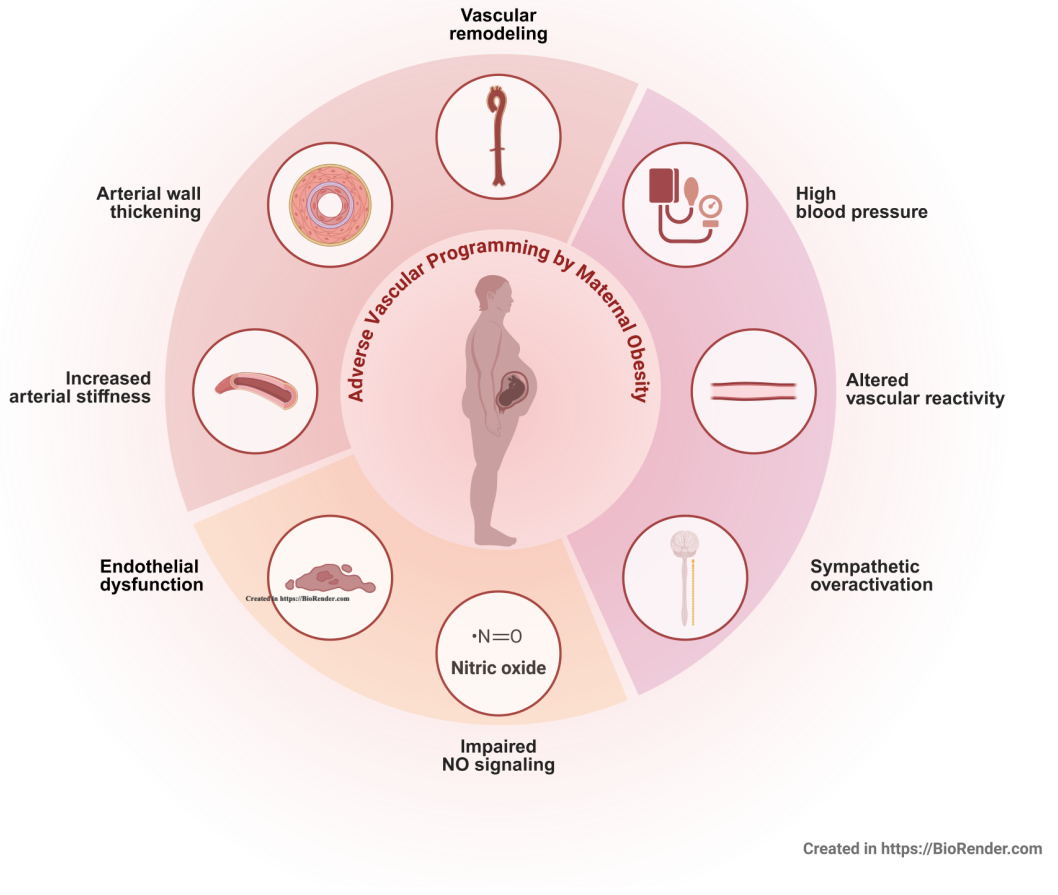


图1 母体肥胖对子代血管的不良编程效应

Figure 1 Developmental programming effects of maternal obesity on offspring vascular function

进而影响其动脉僵硬度。

1.2 血管反应性与张力调控异常

除血管结构改变外,母体肥胖还与子代的血管张力调控紊乱相关,表现为血压调控异常、交感神经活动增强及对血管活性物质反应的改变。已有流行病学证据支持,母亲孕期肥胖可增加子代高血压风险,其子代从儿童早期到成年期普遍出现血压升高的趋势[12,15-18]。有趣的是,这种关联并非完全依赖于子代的体重状态——在控制子代体重的情况下,母体肥胖仍与子代高血压显著相关[12,15,19],提示母体肥胖可能通过胎儿期发育编程直接影响子代血压调控系统。与此同时,也有研究指出,母体肥胖导致子代血压升高可能部分通过促进子代脂肪积累而实现[20]。因此,母体肥胖对子代血压的影响是多因素介导的,既包括直接的发育编程效应,也包括通过促进子代脂肪积累而产生的间接作用。动物实验结果进一步支持上述结论。在HFD诱导的母体肥胖大鼠模型中,其子代尚未出现自身肥胖时,已在幼年阶段观察到高血压的发生[21]。还有研究表明,母体肥胖和子代出生后高脂饮食在升高子代血压方面具有协同作用[22]。这些证据共同强调母体肥胖对子代高血压风险的双重机制,即通过宫内不良环境进行早期"编程",以及与出生后生活方式共同作用,促发血压异常。母体肥胖还可导致子代对血管活性物质的反应性异常。例如,母体HFD可导致子代对去甲肾上腺素(norepinephrine,NE)收缩反应增强[23],而对苯肾上腺素(phenylephrine,PE)收缩反应减弱[24],提示血管α/β肾上腺素能信号通路发生改变。研究还观察到,肥胖母鼠的子代表现出交感神经兴奋性增高/过度驱动(sympathetic hyper-reactivity/overdrive)的迹象,如应激状态下血压升高更明显、肾脏儿茶酚胺水平增加、α/β受体阻滞剂降压效果更强[21]。值得注意的是,即使在无并发症的妊娠中,肥胖孕妇(尤其在孕晚期)的静息肌肉交感神经活动也显著高于正常体重孕妇[25],这可能通过影响胎盘功能对胎儿血管发育产生影响。

1.3 血管内皮功能障碍

血管内皮功能障碍是动脉粥样硬化等CVD发生的始动环节,而母体肥胖可显著损害子代的内皮依赖性血管舒张功能。在非人灵长类动物中,母体高脂饮食显著减弱其13月龄子代腹主动脉对乙酰胆碱(acetylcholine,ACh)的舒张反应,提示其内皮功能受损[11]。在啮齿类动物中,同样可观察到母体高脂饮食损害其子代主动脉[26]、股动脉[23,27,28]及肠系膜动脉[29-31]等多个血管床的内皮舒张功能。例如,母体高脂饮食可显著降低其雄性子代股动脉的ACh依赖性舒张反应和一氧化氮(nitric oxide,NO)生成量,即便子代断奶后接受正常饮食,该障碍依然存在,表明母体营养状态具有长期的发育编程效应[28]。Taylor等[30]进一步研究了母体高脂饮食对子代小动脉舒张功能的影响,发现即使在NO合成途径未明显受损的情况下,肠系膜动脉中内皮源性超级化因子(endothelium-derived hyperpolarizing factor,EDHF)介导的舒张反应也显著下降。这提示母体肥胖可能同时损伤NO依赖与非依赖的血管舒张机制,从而造成血管舒张功能的全面障碍。值得注意的是,这种血管障碍具有明显的性别依赖性,提示性激素可能参与母体饮食诱导的血管发育重编程机制[31]。

2 运动干预的重编程效应

鉴于母体肥胖对子代血管健康具有不良的编程效应,探索有效的重编程干预措施具有重要意义。运动作为一种安全、可行的非药物干预,已在不同生命窗口期展现出修正这种不良编程轨迹的潜力。表1总结了运动干预对血管的重编程效应。

2.1 孕前运动

孕前阶段是影响女性生殖健康和未来妊娠结局的关键时期,进行运动干预有望通过改善母体代谢健康状况,为受孕及胚胎早期发育营造更优化的生理环境,从而从源头上预防或降低不良发育编程的风险。尽管目前针对孕前运动干预对子代远期血管健康影响的实验较为缺乏,但已有系统评价显示,涵盖孕前饮食与体力活动的干预展现出子代心脏重塑改善的迹象[7],提示该领域具有潜在研究价值。同时,孕前建立的健康运动习惯易于在孕期延续,增强干预的持续性与效果。因此,明确孕前运动如何为子代设置更健康的初始编程,是该领域亟需填补的重要空白。

2.2 孕期运动

孕期是子代器官系统发育和功能编程的关键窗口期,在此阶段进行运动干预可为子代心血管健康提供早期保护。人体实验观察到,母体进行孕期运动干预后,其子代在出生后12周时CIMT显著降低,提示母体运动可对子代血管结构产生有益影响[32]。

表1 运动对血管功能的重编程效果

Table 1 Reprogramming effects of exercise on vascular function

研究对象	运动方案参数	干预时期	子代性别	主要心血管结局	参考文献
人类	功率自行车(60%~70% HR_{max})	孕期运动	未区分	子代出生后12周CIMT降低	[32]
猪	跑台运动(60%~85% HR_{max},5次/周)	孕期运动	雌性	子代出生后48小时内胸主动脉内皮舒张功能改善	[33]
肥胖小鼠	自愿转轮运动	孕期运动	雄性	主动脉ACh依赖性舒张恢复;NO信号改善	[29]
肥胖小鼠	跑台运动:GD1.5~7.5,40% VO_{2max};GD8.5~14.5,65% VO_{2max};GD15.5~16.5,50% VO_{2max}	孕期运动	未区分	胎盘微血管密度恢复	[34]
肥胖小鼠	跑台运动(12.5 m/min,20 min,5d/w)	孕期运动	雄性	预防心肌肥厚和功能障碍,但未观察到对高血压的预防作用	[35]
高血压大鼠	游泳训练(GD1~20,20~60 min)	孕期运动	未区分	内皮依赖性血管舒张功能障碍减轻	[36]
肥胖青少年	6个月综合训练	子代运动	未区分	PWV、CIMT及舒张压降低	[37]
肥胖青少年	65%~85% HR_{max}功率自行车+55%~75%1RM抗阻训练(3次/周,共8周)	子代运动	男、女	血管内皮功能提升(FMD由5.3%升至8.8%),动脉僵硬度降低	[38]

HR_{max},最大心率;VO_{2max},最大摄氧量;GD,妊娠天数;CIMT,颈动脉内中膜厚度;ACh,乙酰胆碱;NO,一氧化氮;PWV,脉搏波速度;FMD,血流介导的血管舒张反应。

HR_{max}, maximal heart rate; VO_{2max}, maximal oxygen uptake; GD, gestational day; CIMT, carotid intima-media thickness; ACh, acetylcholine; NO, nitric oxide; PWV, pulse wave velocity; FMD, flow-mediated dilation.

动物实验亦支持上述观点:孕期母猪每周5天接受60%~85%最大心率(HR_{max})强度的跑台运动,其子代出生后48小时内体外检测的胸主动脉内皮功能得到改善,表明母体运动有助于改善子代血管内皮的早期发育[33]。上述研究提示,母体孕期运动对子代血管结构和功能具有直接保护作用。在母体肥胖这一不良代谢背景下,孕期运动的重编程效应尤为关键。在HFD诱导的肥胖小鼠模型中,母亲孕期及哺乳期进行自愿转轮运动,能够有效逆转成年雄性子代胸主动脉的内皮功能障碍,表现为对ACh诱导的血管舒张反应得到改善[29]。值得注意的是,这种保护作用可能依赖于子代出生后的饮食环境,只有当子代也暴露于高脂饮食时,母体运动的益处才显现出来[29]。这提示母体运动可能并非完全消除编程效应,而是增强了子代对不良环境,如高脂饮食的抵抗力或适应能力。这一发现对于理解运动干预的作用机制和指导后续生活方式具有重要意义,即母亲孕期运动虽有益,但子代维持健康的出生后生活方式仍然至关重要。从机制上看,这种重编程效应可能部分通过优化胎盘功能实现,例如,肥胖母鼠孕期游泳运动可激活胎盘腺苷酸活化蛋白激酶(AMP-activated protein kinase,AMPK)信号通路,恢复受损的胎盘微血管密度,进而重编程胎盘的营养运输功能,防止胎儿过度生长[34]。然而,虽然肥胖母体跑台运动预防了其子代的心肌肥厚和功能障碍,但并未能阻止子代高血压的发生[35]。这表明,导致心脏功能障碍和高血压的编程机制可能存在差异,运动干预对不同心血管表型的重编程敏感性亦不相同。

2.3 子代运动

除了母体干预,子代出生后自身的运动行为是否能够抵消母体肥胖所导致的不良编程效应,值得关注。一项荟萃分析表明,规律运动对儿童和青少年肥胖及其相关心血管风险因素具有改善作用,其中,有氧运动可改善83%的心血管风险指标,而有氧运动联合抗阻训练可改善62.5%的心血管风险指标,包括胰岛素敏感性、血脂、体脂等[39]。另一项研究指出,超重或肥胖的青少年进行6个月综合训练可有效降低PWV、CIMT及舒张压,并在停训3个月后依然维持[37]。此外,8周功率自行车联合抗阻训练可显著提升肥胖青少年的血管内皮功能,使其血流介导的血管扩张反应(flow-mediated dilation,FMD)由5.3%提升至8.8%,并降低其动脉僵硬度[38]。这些研究共同表明,运动干预在重编程肥胖儿童或青少年的心血管健康方面具有积极作用。然而,目前在该领域仍存在关键知识空白:子代自身的运动能否逆转或减轻由孕期肥胖母体引发的不良编程效果。现有研究多集中于普通肥胖儿童,尚未特异性评估运动对"出生于母体肥胖"这一群体的重编程效果。未区分其母体孕期体重状况,难以评估运动是否能够弥补宫内不良环境所带来的长远影响。母体肥胖可

能通过表观遗传修饰等机制对子代血管发育产生持久性影响，而出生后运动是否具备“重新编程”这些影响及其作用机制，仍有待深入探讨。因此，未来研究亟需聚焦于母体肥胖暴露背景下的子代群体，系统评估其出生后运动干预的有效性及潜在生物学机制，为开发针对性干预策略提供理论依据。

综上，无论是在孕前、孕期，还是自出生后，运动干预均展现出对抗母体肥胖所致不良血管编程的巨大潜力。现有证据多集中于有氧运动，但运动重编程的最佳干预时机、运动方式仍不明确。

3 运动重编程母体肥胖子代血管功能障碍的潜在机制

母体肥胖通过改变宫内微环境影响胎盘结构与功能，并结合表观遗传修饰，将不良代谢和炎症信号长期记忆并传递至子代，形成持久的不良血管编程，干扰子代血管的发育与功能。运动干预可通过优化宫内环境、改善胎盘结构与功能及修复异常的表观遗传修饰，实现对子代血管系统的重编程，部分逆转母体肥胖带来的不良影响。深入阐明这些调控机制，将有助于明确运动干预的关键作用靶点，并为母体肥胖背景下运动干预方案的优化提供理论依据。

3.1 改善宫内环境

母体肥胖通过改变胎盘功能及全身代谢，构建了一个以“氧化应激-炎症”为核心特征的异常宫内微环境。这两种病理过程相互促进，形成恶性循环，直接影响子代心血管发育[40,41]。一方面，母体循环中的高水平炎症介质及胎盘局部免疫激活[40]可在胎儿组织中诱导促炎反应，进一步激活NLR家族含pyrin结构域3蛋白(NLR family pyrin domain containing 3，NLRP3)炎症小体等信号通路，增强活性氧(reactive oxygen species，ROS)的生成[41]。另一方面，长期的高氧化应激环境将削弱子代的抗氧化防御能力。例如，在肥胖母鼠模型中，其子代心脏中超氧化物歧化酶1(superoxide dismutase 1，SOD1)和谷胱甘肽过氧化物酶4(glutathione peroxidase 4，GPX4)的表达显著下调[42]。ROS生成增强与清除能力减弱协同作用，使氧化应激在子代体内持续存在并进一步激活促炎通路，最终损伤子代血管内皮功能。宫内高氧化应激环境还会显著干扰胎儿NO信号通路，过量ROS会与NO迅速反应生成过氧亚硝酸盐，不仅直接消耗NO，还会诱导内皮功能障碍[43-45]。同时，宫内环境改变会干扰子代一碳代谢，降低辅因子四氢生物蝶呤(tetrahydrobiopterin，BH_4)的合成与再生效率[46]，导致内皮型一氧化氮合酶(endothelial nitric oxide synthase，eNOS)解偶联[29]。此时，eNOS不仅无法生成NO，反而转变为ROS的来源，进一步加剧宫内氧化应激[29]。宫内“氧化应激-炎症”状态还会影响胎儿中枢神经系统，诱导交感神经过度激活(sympathetic hyper-reactivity)[21,47]。这种编程效应通过加剧子代下丘脑-室旁核(PVN)等关键核团的神经炎症与氧化损伤，并改变其对瘦素、胰岛素和血管紧张素II(angiotensin II，Ang II)的敏感性[48,49]，上调中枢交感神经活性，最终导致子代交感神经张力升高[23]、动脉压力反射功能减弱[48]及心率变异性(heart rate variability，HRV)降低[50]。

孕期运动是打破上述恶性循环的有效干预手段，为子代提供稳定的发育微环境。运动可上调子代血管组织中沉默信息调节因子1(sirtuin 1，SIRT1)的表达，SIRT1通过H3K9ac去乙酰化作用调控NADPH氧化酶4(NADPH oxidase 4，NOX4)基因表达，从源头减少ROS生成[36]。鉴于氧化应激源头的有效遏制，子代不再需要维持较高的抗氧化水平，其SOD1表达水平随之降低[29]，这标志着机体氧化还原稳态的重塑。运动还可通过调节子代一碳代谢通路，上调子代肝脏及血管组织中关键酶蛋氨酸腺苷转移酶1A(methionine adenosyltransferase 1A，MAT1A)的表达，降低血清同型半胱氨酸水平，从源头保障BH_4供应，从而维持eNOS的功能性耦联状态[29]，恢复NO的稳定性与生物利用度。综上，孕期规律运动，特别是孕前即开始的持续性适度运动，是重塑子代发育轨迹、预防其远期心血管疾病风险的重要策略[51]。

3.2 改善胎盘结构与功能

胎盘是母体与胎儿进行物质交换和信息传递的关键界面，其功能状态与屏障完整性决定了宫内环境稳态和子代发育轨迹。母体肥胖通常伴随慢性低度炎症状态，其循环中促炎细胞因子，如肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)、白细胞介素-6(interleukin-6，IL-6)水平升高，而抗炎脂肪因子(脂联素)水平下降[40,52]。这些炎症介质不仅构成不良宫内环境的基础，还可直接作用于胎盘，通过穿越胎盘屏障或激活胎盘局部免疫反应，将母体炎症信号传递给胎儿，进而在胎儿组织中诱导促炎反应[40]。胎盘不仅是炎症信号的传递者，在母体肥胖这一不

良代谢背景下,胎盘自身也成为氧化应激的重要来源。母体肥胖可损害胎盘线粒体功能,降低胎盘和胎儿组织中电子传递链(electron transport chain,ETC)活性,从而增加ROS的生成。一项研究指出,肥胖母猪的胎盘线粒体中复合物I和复合物III的活性显著下降[53]。这提示电子传递效率降低导致电子异常泄露并与氧分子结合生成O^{2-}的风险增加,ROS水平显著升高[53,54]。因此,胎盘功能障碍是导致宫内高氧化应激状态的重要起点。

母鼠在妊娠期接受低强度的有氧运动干预,可激活胎盘AMPK信号通路,上调血管生成因子的表达,从而提高胎盘血管网络的密度和营养物质的转运能力[34]。此外,运动还能上调胎盘抗氧化酶SOD3的表达,从而减轻母体肥胖引起的胎盘氧化应激和炎症[55]。ROS水平下降有助于维持胎盘血管内皮细胞功能,减少对子代血管发育的不利影响。母体运动还可通过增强胎盘线粒体功能和能量代谢,为胎盘血管发育提供充足的能量支持。孕期运动能增加胎盘PR域含量蛋白16(PR domain containing 16,PRDM16)表达,促进线粒体生成和氧化代谢活性,从而改善胎盘整体功能和血管网络成熟度[56]。目前,关于肥胖母体运动如何通过重塑胎盘结构与功能而改善子代血管健康的研究仍十分有限。未来亟需深入探讨肥胖母体运动所介导的胎盘分泌因子变化及胎盘功能调节在促进子代血管健康中的具体作用机制,以更全面地揭示胎盘与子代心血管健康之间的内在联系。

3.3 调控表观遗传修饰

表观遗传修饰被认为是连接母体不良环境暴露与子代长期健康结局的核心机制,包括DNA甲基化、组蛋白修饰及非编码RNA等途径。这些修饰在不改变DNA序列的情况下调控基因表达,使宫内环境的"记忆"得以稳定传递,从而诱导子代出现持久的病理生理改变。在此背景下,母体肥胖所导致的氧化应激、炎症和代谢紊乱可通过介导异常的表观遗传"编程",对子代血管结构与功能产生深远影响。在DNA甲基化层面,动物研究表明,母体HFD可通过改变子代动脉中多不饱和脂肪酸合成相关基因的表观遗传修饰而引发血管功能障碍。具体而言,母体高脂饮食导致子代主动脉中*Fads*基因启动子区域发生高甲基化,进而抑制其转录表达,干扰血管张力调节相关的脂质代谢过程[57]。在人脐静脉内皮细胞(human umbilical vein endothelial cells,HUVECs)中,母体肥胖也常伴随子代内皮细胞中脂质代谢和线粒体功能相关通路的大量转录变化[58],提示母体代谢异常可在胎儿早期即引发生物学编程。此外,母体肥胖还可通过调控非编码RNA,特别是miRNA,进一步影响子代血管结构与功能。母体肥胖可诱导子代心脏、胎盘及内皮细胞中miRNA表达谱的广泛重塑,形成特征性的不良表观遗传图谱。例如,在HUVECs中,母体BMI与多种关键内皮miRNA,如miR-126-3p和miR-148a-3p的表达水平显著相关,而这些miRNA的失调被认为可促进血管内皮功能障碍及动脉粥样硬化的发生[59]。

值得注意的是,运动干预作为一种有效的表观遗传调节手段,显示出"重新编程"母体不良代谢记忆的潜力[60]。母体运动能在一定程度上逆转HFD或肥胖诱导的多种子代表观遗传异常。这些纠正作用体现在多个层面。例如,母体高脂饮食会诱导子代过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator-activated receptor gamma coactivator 1-alpha,PGC-1α)启动子高甲基化,而母体运动可抑制这一改变,从而恢复线粒体与能量代谢基因的表达并改善代谢表型[61];母体运动还能通过调节组蛋白甲基化及诱导抗氧化因子来修复异常的组蛋白标记,从而恢复靶基因表达[55]。同时,母体运动还被证明能纠正母体肥胖或代谢异常所致的子代miRNA谱失衡,并随之恢复这些miRNA的靶基因的表达,这可能是运动预防子代心血管功能障碍的重要机制之一[62]。总体而言,动物证据一致支持母体运动通过表观遗传修饰部分逆转母体不良环境对胎儿的表观遗传编程并改善后代代谢、心血管结局;但在人群层面的直接分子证据仍有限,需要更多纵向干预及分子机制研究加以验证。

4 总结与展望

综合现有研究证据,母体肥胖是导致子代血管功能障碍并增加其远期心血管疾病风险的关键因素。这一由母体环境引发的不良编程效应涉及子代血管内皮功能受损、血管结构重塑,以及血管反应性和血压调节异常。母体规律运动能够对子代血管系统进行重编程:通过改善胎盘结构与功能、优化宫内微环境及调节关键表观遗传修饰,逆转或缓解母体肥胖所带来的不良编程效应,促进子代血管系统的

健康发育。尽管现有研究取得了积极进展,但在将运动干预转化为精准、有效的临床策略方面,仍存在若干问题,亟待未来研究予以解答。

(1)目前仍缺乏直接证据来证明出生后运动能有效逆转或缓解母体孕期肥胖所导致的特定血管功能障碍。现有针对肥胖儿童的运动干预大多未区分其母体孕期体重状况,这在一定程度上限制了对运动能否抵消宫内不良环境长期影响的判断。因此,未来研究亟需聚焦于有母体肥胖暴露背景的子代群体,以阐明出生后运动的干预效果及其潜在的表观遗传学重编程机制。

(2)尽管孕期运动的益处已初步显现,但目前关于最佳运动时机、强度和类型的证据仍需完善。尤其是孕前阶段,运动干预对子代血管健康的长期效应研究相对较少,提示该领域存在重要研究空间。

(3)现有研究主要聚焦于有氧运动,而关于抗阻训练、间歇训练等其他运动模式对子代血管发育及功能编程影响的证据仍相对有限。这一研究局限在一定程度上阻碍了针对不同母体特征和子代风险状态制定更为精准、个体化的运动处方。未来需要拓展多种运动模式的比较研究,以明确其对母体肥胖相关发育编程的差异化调节作用。

(4)母体肥胖病因的异质性与精准干预策略亟待关注。既往研究多将母体肥胖视为单一表型,忽略了单纯性肥胖(以饮食诱导为主)与病理性肥胖,如多囊卵巢综合征(polycystic ovary syndrome, PCOS)在宫内致病机制上的显著差异。特别是PCOS合并肥胖的孕产妇,其特有的高雄激素环境及胰岛素抵抗可能扰乱宫内代谢,并通过影响卵母细胞质量及早期胚胎发育潜能,对子代心血管及代谢健康产生特异性影响。未来研究应重视肥胖亚型分层,深入解析运动干预对不同病因(如代谢性 vs 内分泌性)肥胖母体及其子代的差异化调节效应,从而为临床制定基于病因学的精准运动干预策略提供理论依据。

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