[37] JOHANSSON A, EKELÖF J, GISKE C G, et al. The detection and verification of carbapenemases using ertapenem and matrix assisted laser desorption ionization-time of flight[J]. BMC Microbiol, 2014, 14: 89-93.
[38] LASSERRE C, DE SAINT MARTIN L, CUZOU G, et al. Efficient detection of carbapenemase activity in Enterobacteriaceae by matrix-assisted laser desorption ionization-time of flight mass spectrometry in less than 30 minutes[J]. J Clin Microbiol, 2015, 53(7): 2163-2171.
[39] CALDERARO A, BUTTRINI M, PIERGIANNI M, et al. Evaluation of a modified meropenem hydrolysis assay on a large cohort of KPC and VIM carbapenemase-producing Enterobacteriaceae[J]. PLoS One, 2017, 12(4): e0174908.
[40] 冯丽娜, 李从荣. MALDI-TOF MS 检测产碳青霉烯酶肠杆菌科细菌的应用[J]. 中华微生物学和免疫学杂志, 2018, 38(3): 218-225.
[41] PARDO C A, TAN R N, HENNEQUIN C, et al. Rapid detection of AAC(6′)-Ⅰb-cr production using a MALDI-TOF MS strategy[J]. Eur J Clin Microbiol Infect Dis, 2016, 35(12): 2047-2051.
[42] OVIAÑO M, RODRÍGUEZ-MARTÍNEZ J M, PASCUAL Á, et al. Rapid detection of the plasmid-mediated quinolone resistance determinant AAC(6)-Ⅰb-cr in Enterobacteriaceae by MALDI-TOF MS analysis[J]. J Antimicrob Chemother, 2017, 72(4): 1074-1080.
[43] JUSTESEN U S, ACAR Z, SYDENHAM T V, et al. Antimicrobial susceptibility testing of Bacteroides fragilis using the MALDI Biotyper antibiotic susceptibility test rapid assay (MBT-ASTRA)[J]. Anaerobe, 2018, 54: 236-239.
[44] SPARBIER K, LANGE C, JUNG J, et al. MALDI biotyper-based rapid resistance detection by stable-isotope labeling[J]. J Clin Microbiol, 2013, 51(11): 3741-3748.
[45] DEMIREV P A, HAGAN N S, ANTOINE M D, et al. Establishing drug resistance in microorganisms by mass spectrometry[J]. J Am Soc Mass Spectrom, 2013, 24(8): 1194-1201.
[46] JUNG J S, EBERL T, SPARBIER K, et al. Rapid detection of antibiotic resistance based on mass spectrometry and stable isotopes[J]. Eur J Clin Microbiol Infect Dis, 2014, 33(6): 949-955.
[47] LANGE C, SCHUBERT S, JUNG J, et al. Quantitative matrix-assisted laser desorption ionization-time of flight mass spectrometry for rapid resistance detection[J]. J Clin Microbiol, 2014, 52(12): 4155-4162.

（收稿日期：2021-03-19　修回日期：2022-03-03）

·综　　述·

肠道微生态平衡监测对妊娠高血压疾病的诊断价值*

罗云桃，黄维纲 综述，赵　冉△ 审校
上海市临床检验中心，上海 200126

摘　要：妊娠高血压疾病是孕产妇和婴儿病死率增高的主要原因。然而临床上对于该类疾病的病因和发病机制并不十分清楚，除了评估孕妇血压水平、蛋白尿、器官受累程度及胎儿情况之外，缺乏有效的实验室预防、监测及诊疗手段。而肠道菌群作为人体最大的微生态系统，相关研究成果已在各类疾病中显现出巨大的临床潜在价值。相比之下，肠道菌群与妊娠高血压疾病的研究相对滞后。由于孕妇体质、代谢等状况的特殊性，疾病与肠道菌群变换叠加的病理过程更为复杂。目前，相关研究虽有报道，但在两者相互关系、致病机制等方面分析并不完整、全面。本文对肠道微生态与妊娠高血压疾病的多项研究结果进行综述，并分析了妊娠高血压疾病的研究现状以及相关实验室监测指标的应用价值，探讨了肠道菌群作为妊娠高血压疾病新型标志物的可行性，为临床上对妊娠高血压疾病的诊断提供了新思路。

关键词：妊娠高血压；　肠道菌群；　临床检测；　生物标志物
DOI：10.3969/j.issn.1673-4130.2022.11.023　　**中图法分类号**：R446.5
文章编号：1673-4130(2022)11-1389-06　　**文献标志码**：A

Diagnostic value of intestinal microeclogic balance monitoring in pregnancy-induced-hypertension*

LUO Yuntao, *HUANG Weigang*, *ZHAO Ran*△
Shanghai Clinical Laboratory Center, *Shanghai*, 200126, *China*

Abstract: Pregnancy-induced-hypertension(PIH) is a leading cause of mortality rate increase in pregnant women and infants. However, the etiology and pathogenesis of PIH is still unclear in clinic. Beside of evaluating the blood pressure level, proteinuria, degree of organ involvement and fetal condition, there is a lack of the

* **基金项目**：上海临床检验中心自选课题(2020ZXKT-03、2021ZXKT-06)。
△ **通信作者**，E-mail：zhaoran@sccl.org.cn。
网络首发　https://kns.cnki.net/kcms/detail/50.1176.R.20220419.1526.005.html(2022-04-20)

effective means of laboratory prevention, monitoring and diagnosis and treatment. The intestinal microbiota serve as the largest micro-ecosystem in the human body, the related study results show the enormous clinical potential values in various diseases. However, the researches on the relationship between intestinal microbiota and PIH are relatively lagging behind. Due to the particularity of pregnant women status such as the body constitution, metabolism, which makes the pathological process of disease and intestinal microbiota change superposition more complex. At present, although the related studies have reported, but the analysis on their relationship and pathogenesis is not complete and comprehensive. This paper reviews the multiple studies results of intestinal microbiota and PIH, analyze the study status quo of PIH and application value of related laboratory monitoring indicators, investigate the feasibility of intestinal microbiota as the new type marker of PIH, and provide a new ideal for the diagnosis of PIH in clinic.

Key words: pregnancy-induced-hypertension ; intestinal microbiota; clinical detection; biomarker

妊娠高血压疾病诱发、导致的与孕产妇和婴儿相关的并发症已有报道。严重的妊娠期并发症更是引起孕产妇和婴儿死亡的直接诱因。由于孕妇特殊的生理体质、代谢状况，临床对妊娠高血压疾病的诊断和治疗干预手段十分有限。随着近代微生物分子技术的飞速发展，研究者对肠道菌群与各类相关疾病的关联、病理机制已有了长足的认识，而肠道菌群与妊娠高血压疾病的研究相对滞后。为弥补这方面的认识不足，本文尝试对肠道微生态与妊娠高血压疾病的多项研究结果进行综述，分析妊娠高血压疾病的研究现状以及相关实验室监测指标的应用价值，探讨肠道菌群作为妊娠高血压疾病新型标志物的可行性，旨在为临床上对妊娠高血压疾病的诊断提供新思路。

1 妊娠高血压疾病概述

妊娠高血压疾病指妊娠诱发高血压引起的相关疾病，具有人群特异性，多数是暂时性高血压，分娩后即恢复正常，也有约 1/4 患者病情进展，出现蛋白尿、水肿等症状，严重者发生抽搐、昏迷、伴多器官受累。妊娠高血压是孕产妇和婴儿发病率及死亡率增高的主要诱因之一[1]。妊娠高血压疾病一般在妊娠 20 周左右出现，临床上通常根据严重程度分为妊娠期高血压、子痫前期和子痫[2]。妊娠子痫由子痫前期症状和体征加剧发展而来。初诊拟为妊娠高血压的孕妇，临床上一般前期采取改善血压的保守治疗。不过，由于孕产妇个体差异大，无论先天遗传、个人体质、生活环境以及饮食习惯都会影响孕产妇对药物的耐受力和疾病预后。并且，持续药物治疗对孕妇、胎儿产生的影响也具有一定的不确定性。孕期大于 28 周的重度妊娠高血压患者，其临床处理尤为困难，药物保守治疗往往难以达到预期效果。最近研究指出，妊娠高血压是多因素多系统性疾病。孕期的炎性反应过度激活、母-胎免疫平衡失调、遗传基因易感性、个体饮食习惯等均与妊娠高血压密切相关[2-5]。然而，目前除了监控孕妇血压水平、蛋白尿程度、器官受累及胎儿情况之外，临床上对妊娠高血压疾病缺乏有效的早期诊断指标以及安全、有效的预防策略[6-7]。

2 肠道菌群与妊娠高血压疾病

肠道微生态由肠道菌群及肠道内环境组成，是人体最大的微生态系统。人体肠道中定植约 10^{14} 个微生物，超过 3 500 种细菌组成，肠道微生物细胞数量是人体细胞总数的 10 倍左右，肠道微生物基因总和约为人类基因量的 100 倍以上，被称为人体的第二基因组[8-9]。肠道菌群与人体基因组通过与外环境的交互作用，影响着宿主的营养、代谢、免疫、行为、应激等众多生理过程[9-11]。

2.1 肠道菌群失调与高血压密切相关 目前，已有不少研究报道了肠道菌群失调与高血压疾病的关系。在肠道菌群组成上，YANG 等[12]研究发现，高血压组的肠道菌群结构存在显著差异，与健康对照组相比，高血压患者的菌群丰度和多样性显著下降，有益菌明显降低，放线菌和双歧杆菌数量减少，厚壁菌门和拟杆菌门的比值显著升高，普氏菌和克雷伯菌过度生长等。并且，类似的菌群失衡在高血压前期患者就已显现[12-14]。ADNAN 等[14]通过膳食和益菌剂的治疗方式，证实纠正肠道菌群失调可有效地降低心血管疾病和相关并发症发生的风险，缓解高血压症状。

2.2 孕期肠道菌群变化与妊娠高血压疾病的相关性 正常妊娠状态下，孕妇体内的肠道菌群变化是由于其参与了母体营养、代谢、免疫等众多生理活动所致。先前认为，孕期肠道菌群结构易受母体饮食习惯的影响，但与孕妇孕周、体质量变化之间的关系并不确定。随后研究发现，妊娠引起的女性肠道菌群变化在孕初期即已发生，而在持续的妊娠期间，肠道菌群结构保持相对稳定[15-16]。不过这些文献都存在样本量和研究手段上的局限性，并且群体孕妇间肠道菌群结构差异较大[17]。最近更深入的研究更新了此前的看法，认为孕期母体内肠道菌群会有相应的周期性变化，比如厚壁菌/拟杆菌比值升高、各类菌属丰度等在孕中晚期有明显差异[18]。而在妊娠高血压疾病的病理状态下，正常孕期状态引起的肠道菌群变化叠加了高血压疾病引起的肠道菌群病态改变，使得两者关系更为复杂。现有的研究已逐渐揭示，在妊娠高血压疾病过程中，不管是整体菌群结构还是某些特定属种的肠道菌群失调，都能够在一定程度上反映孕妇在不同状态下的疾病状况，可作为相应的临床诊疗标志物[19-22]。主要相关研究结果如表 1 所列举。

表 1　妊娠期潜在肠道菌群标志物

研究群体	研究结果	研究结论	文献
肥胖孕妇	产丁酸菌丰度下降	丁酸菌有维持孕妇血压稳定的功能	[11]
孕周妇女	孕期厚壁门、放线菌增加，类杆菌、普氏菌显著减少	特定肠道菌群丰度可监测各孕期生理异常状态	[23]
子痫前期孕妇	蜡样芽孢杆菌、李斯特菌、沙门菌、大肠杆菌增高	感染性细菌与子痫相关	[24]
	产气荚膜梭菌、布氏菌增加，粪球菌减少	病原菌增多、益生菌减少、肠道菌群丰度减少与子痫相关	[25]
子痫前期孕妇/孕鼠	梭杆菌、维氏杆菌增多；粪杆菌、阿克曼菌消失	肠道菌群丰度变化与子痫相关	[26]
	厚壁菌、布氏杆菌、链球菌、双歧杆菌、柯林斯菌、志贺杆菌丰度降低，变形杆菌、肠杆菌、大肠埃希菌丰度增高		[27]
高脂饮食的母鼠及后代	厚壁菌、梭状芽孢杆菌、粪杆菌、假丝酵母、拟杆菌属丰度减低；类杆菌、变形杆菌、放线杆菌、肠杆菌、脆弱类杆菌丰度增高	脂多糖合成相关的微生物基因增高	[28-29]
	类硬壁菌、阿克曼菌、疣状芽孢菌增加，乳酸杆菌减少	肠道菌群变化影响母体及后代血压	[30]
	厚壁菌/拟杆菌比率增加	白藜芦醇药剂可纠正菌群失调、维持血压稳定	[31]
	益生菌、益生元增多可减轻程序性高血压症状	有益菌可调节高脂饮食引起的高血压	[23,32]
微量元素缺乏的孕鼠	锌缺乏致疣状芽孢杆菌降低，厚壁菌门增多	肠道菌群构成比及炎症标志物可作为肠脑轴反馈的监测指标	[33]
	铁缺乏导致拟杆菌科和毛螺菌科丰度改变	肠道菌群丰度改变导致功能失调，影响孕体及后代正常生理	[34]
子痫孕鼠	变形杆菌、幽门杆菌属增多，厚壁菌减少	肠道菌群丰度与子痫相关	[35]

3　肠道菌群监测在妊娠高血压疾病诊疗中的临床价值

妊娠高血压疾病多因孕妇体内各类生理功能异常、代谢失调导致[36]。目前，实验室常规化检测指标主要分两大类：一类以病症监测为主，如子痫相关并发症引起的血凝障碍、器官受累等检测（凝血因子、血小板、血栓弹力图及肝、肾功能血清酶类指标等）；另一类以预防监测为目的，如激素、炎症因子、血脂代谢等[6-7]。由于孕产妇个体差异以及疾病的特殊性，现有的检测手段并无良好的特异性使临床诊治获得有效受益[37]。孕产期肠道菌群的检测是否能为临床诊疗作指引，已逐渐成为近年来的研究热点。本文简略概述几点需商榷的问题。

3.1　肠道菌群与妊娠高血压疾病的因果关系　肠道菌群丰度、数量的变化与多种疾病存在相关性已有明确证据[38-40]。然而，肠道菌群与相关疾病的因果关系多不明。如肠道菌群与高血压疾病[12,41]：一方面，饮食、环境、情绪等都是引发高血压的诱因，而这些因素理论上也同时能导致宿主肠道菌群的改变[42]；另一方面，肠道菌群的代谢产物也能反过来影响宿主血压，以及营养、代谢、免疫等活动[13,43-45]。在众多错综复杂的疾病机制中，理清其中因果链对分析肠道菌群的相关检测在临床诊疗过程中的应用价值就显得极为重要。

对于妊娠高血压疾病来说，相关的肠道菌群研究近年来虽初露成果，但同样存在很多问题。许多报告仅证实健康孕体与子痫母体的肠道菌群存在差异性，而不能更多揭示具体的疾病机制[24,35]。简单关联性并不能提供充分的证据链指引临床疾病诊疗。明确菌群失调在妊娠高血压发生、发展中的作用及因果，将对优化妊娠高血压疾病的临床诊疗产生巨大帮助。

3.2　肠道菌群影响妊娠高血压疾病的潜在机制（可能机制）　随研究深入，目前已有研究揭示肠道菌群参与妊娠高血压疾病过程的明确致病机制。比如近几年研究中发现，孕期的生理代谢会导致不同微量元素（铁、锌、铜、硒等）的缺乏，从而影响肠道菌群的变化。而相应的肠道菌群改变又进一步导致孕期的菌群功能性失调，引发妊娠高血压、子痫等相关疾病的发生[33-34]。根据这些明确的致病机制链，临床上可将血清微量元素类指标作为前期诊断指标，而将特征性菌群的监测可作为疗效、预后的评估指标。GOMEZ-ARANGO 等[46]认为，肠道微生物群中的某些特定细菌及代谢产物都会影响孕妇血压水平，如产丁酸盐细菌（Odoribactereae、Clostridiaceae）丰度及丁酸产物与孕妇血压水平呈负相关，提示此类菌群以及产物或可作为反映妊娠高血压疾病风险的特征性筛查标志物。

不仅如此，益生菌对孕期肠道菌群的纠正也具有潜在应用价值。研究发现，益生菌可产短链脂肪酸如乙酸酯，发挥降压、降脂、消炎等作用[28,47-48]。经常食用含有益生菌的奶制品和益菌剂，可降低妊娠高血压疾病的发病风险[4,49-50]。总之，明确的疾病机制对于肠道菌群干预妊娠高血压疾病的诊疗已显示出巨大的临床应用价值。

3.3　孕期肠道菌群检测的临床应用及挑战　传统观

念上，临床与实验室对细菌的检测更关注于某些特定致病菌的有或无，然后进行针对性的药物治疗。然而，现代肠道菌群的检测在孕期疾病诊疗中的应用已完全革新了这样的观点。更确切地说是综合采用各种手段评估孕妇体内肠道菌群的丰度和数量比，从而了解菌群整体的功能性状态[51]。现代分子测序技术为之提供了有力手段。例如通过 16S rRNA 测序技术对妊娠高血压患者肠道菌群的宏基因组进行分析，可筛选出特异性的菌群变化[52-53]，作为提示疾病风险的新型标志物群。

不过，将现代肠道菌群检测技术应用于妊娠高血压相关疾病，存在一些挑战。根据现有结果显示，临床患者的体质差异明显，可能正常生理上菌群结构已经存在不同，并且患者菌群门类组成上多无明显差异，而仅在菌群间互相的丰度和均匀度上与正常孕妇相比有差异，而且其中涉及的菌落谱系很广，有葡萄球菌属、肠杆菌科、双歧杆菌属、拟杆菌属等不同种别[11,31,54]。这对于肠道菌群测序成为实验室常规化手段之前，需克服的技术难点有：(1)肠道菌群的检测数据库必须做到具有足够菌种的覆盖度和深度；(2)肠道菌群量化方法的灵敏度、计算方式需要高精度、少误差；(3)患者个体异质性引起的菌群差异需要慎重区别。一些学者已考虑到宿主生理、免疫反应性等异质性因素，将孕期生理本身的特殊性以及病理过程相关的炎症类指标[肿瘤坏死因子-α(TNF-α)、白细胞介素-6(IL-6)及超敏 C 反应蛋白(hs-CRP)]、脂质代谢类指标[高密度脂蛋白(HDL)、低密度脂蛋白(LDL)]等联合菌群丰度的变化，作为综合评估宿主对肠道菌群免疫耐受性的手段[55-57]。随着大数据时代到来，根据不同地域和人群分布，分析并制订相应的判断标准来鉴别不同习俗孕妇群体的肠道菌群差异成为可能。而对于每个孕妇本身的肠道菌群数量、丰度、功能变化，理想的方案可选用个体横向时间动态比较，即基于每个孕妇自身怀孕前以及怀孕各周期的肠道菌群及其功能的状态，并结合其他类特定实验室指标进行比较判断更为合理，比如结合血清酶类、激素、蛋白等查看特定细菌的种类、代谢物[6-7]。在应用于临床前，这些制订的细节都需要足够的数据论证和更多的后续临床证据作为参考，比如怎样的肠道菌群丰度变化可能影响宿主的生理状态、医学临界值如何具体设定、菌群疗效周期如何判断等。克服这些挑战，将使肠道菌群检测在未来妊娠高血压相关疾病诊疗中的作用越来越广泛，临床应用价值也会越来越合理[31-32]。

4 结　语

妊娠高血压疾病由于其特殊的病理特征，很多研究目前仅是初步阶段。高通量分子技术的临床应用在许多普通临床实验室并不能普及到临床，不仅是因为对临床检验实验室技术要求较高，还受限于政策法规的影响。因此，在孕产妇妊娠高血压疾病的诊疗过程中，运用宏基因测序等技术进行定期、专业地检测肠道菌群存在一定的困难。不过，随着相关应用技术进一步成熟，检测成本下降，这些新技术正在逐步被推广到临床应用。孕产妇的肠道菌群监测成为常规化临床诊疗策略也具有可实现性，既能帮助相关疾病的早期检测、辅助诊断、临床治疗、病情预测，也给医院、第三方检测机构、健康管理机构和连带产业带来巨大的推动作用。

总之，研究妊娠高血压相关疾病患者肠道菌群的结构变化，并结合相关常规化指标，将会全面有助于优化现有的孕产期临床医学策略，对孕产妇及婴幼儿的健康产生长远影响。

参考文献

[1] WERTASCHNIGG D, WANG R, REDDY M, et al. Treatment of severe hypertension during pregnancy: we still do not know what the best option is[J]. Hypertens Pregnancy, 2020, 39(1): 25-32.

[2] MALIK A, JEE B, GUPTA S K. Preeclampsia: Disease biology and burden, its management strategies with reference to India[J]. Pregnancy Hypertens, 2019, 15: 23-31.

[3] HAJIANFAR H, ESMAILLZADEH A, FEIZI A, et al. The Association between major dietary patterns and pregnancy-related complications[J]. Arch Iran Med, 2018, 21(10): 443-451.

[4] HALKJAER S I, NILAS L, CARLSEN E M, et al. Effects of probiotics(Vivomixx(R)) in obese pregnant women and their newborn: study protocol for a randomized controlled trial[J]. Trials, 2016, 17(1): 491.

[5] HU M, EVISTON D, HSU P, et al. Decreased maternal serum acetate and impaired fetal thymic and regulatory T cell development in preeclampsia[J]. Nature communications, 2019, 10(1): 3031.

[6] MOSIMANN B, AMYLIDI-MOHR S K, SURBEK D, et al. First trimester screening for preeclampsia-a systematic review[J]. Hypertens Pregnancy, 2020, 39(1): 1-11.

[7] NGUYEN T P, PATRICK C J, PARRY L J, et al. Using proteomics to advance the search for potential biomarkers for preeclampsia: a systematic review and meta-analysis [J]. PLoS One, 2019, 14(4): e0214671.

[8] GRIFFIN C. Probiotics in obstetrics and gynaecology[J]. Aust N Z J Obstet Gynaecol, 2015, 55(3): 201-209.

[9] NOCE A, MARRONE G, DI DANIELE F, et al. Impact of gut microbiota composition on onset and progression of chronic non-communicable diseases[J]. Nutrients, 2019, 11(5): 1073.

[10] JOSE P A, RAJ D. Gut microbiota in hypertension[J]. Curr Opin Nephrol Hypertens, 2015, 24(5): 403-409.

[11] GOMEZ-ARANGO L F, BARRETT H L, MCINTYRE H D, et al. Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy[J]. Hyperten-

sion, 2016, 68(4): 974-981.
[12] YANG T, SANTISTEBAN M M, RODRIGUEZ V, et al. Gut dysbiosis is linked to hypertension[J]. Hypertension, 2015, 65(6): 1331-1340.
[13] LI J, ZHAO F, WANG Y, et al. Gut microbiota dysbiosis contributes to the development of hypertension[J]. Microbiome, 2017, 5(1): 14.
[14] ADNAN S, NELSON J W, AJAMI N J, et al. Alterations in the gut microbiota can elicit hypertension in rats[J]. Physiol Genomics, 2017, 49(2): 96-104.
[15] 吕思婷，潘礼龙，孙嘉，等. 妊娠期肠道菌群变化及益生菌干预研究进展[J]. 实用医学杂志，2018，34(23)：3849-3853.
[16] JOST T, LACROIX C, BRAEGGER C, et al. Stability of the maternal gut microbiota during late pregnancy and early lactation[J]. Curr Microbiol, 2014, 68(4): 419-427.
[17] AVERSHINA E, STORRØ O, ØIEN T, et al. Major faecal microbiota shifts in composition and diversity with age in a geographically restricted cohort of mothers and their children[J]. FEMS Microbiol Ecol, 2014, 87(1): 280-290.
[18] FAAS M M, LIU Y, BORGHUIS T, et al. Microbiota induced changes in the immune response in pregnant mice [J]. Front Immunol, 2019, 10: 2976.
[19] SHEPHERD E, GOMERSALL J C, TIEU J, et al. Combined diet and exercise interventions for preventing gestational diabetes mellitus[J]. Cochrane Database Syst Rev, 2017, 11(11): CD010443.
[20] WEBSTER K, FISHBURN S, MARESH M, et al. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance[J]. BMJ, 2019, 366: 15119.
[21] SUN L, NIU Z. A mushroom diet reduced the risk of pregnancy-induced hypertension and macrosomia: a randomized clinical trial[J/OL]. Food Nutr Res, (2020-06-08)[2021-06-10]. https://pubmed.ncbi.nlm.nih.gov/32577117/.
[22] TAIN Y L, HSU C N. Hypertension programmed by perinatal high-fat diet: effect of maternal gut microbiota-targeted therapy[J]. Nutrients, 2019, 11(12): 2908.
[23] SHAY J W, HOMMA N, ZHOU R, et al. Abstracts from the 3rd International Genomic Medicine Conference (3rd IGMC 2015): Jeddah, Kingdom of Saudi Arabia. 30 November－3 December 2015[J]. BMC Genomics, 2016, 17 Suppl 6(Suppl 6): 487.
[24] AMARASEKARA R, JAYASEKARA R W, SENANAYAKE H, et al. Microbiome of the placenta in pre-eclampsia supports the role of bacteria in the multifactorial cause of pre-eclampsia[J]. J Obstet Gynaecol Res, 2015, 41(5): 662-669.
[25] LIU J, YANG H, YIN Z, et al. Remodeling of the gut microbiota and structural shifts in Preeclampsia patients in South China[J]. Eur J Clin Microbiol Infect Dis, 2017, 36(4): 713-719.
[26] CHEN X, LI P, LIU M, et al. Gut dysbiosis induces the development of pre-eclampsia through bacterial translocation[J]. Gut, 2020, 69(3): 513-522.
[27] CHANG Y L, CHEN Y Y, ZHOU Q, et al. Short-chain fatty acids accompanying changes in the gut microbiome contribute to the development of hypertension in patients with preeclampsia[J]. Clin Sci(Lond), 2020, 134(2): 289-302.
[28] HSU C N, CHANG-CHIEN G P, LIN S, et al. Targeting on gut microbial metabolite trimethylamine-n-oxide and short-chain fatty acid to prevent maternal high-fructose-diet-induced developmental programming of hypertension in adult male offspring[J]. Mol Nutr Food Res, 2019, 63(18): e1900073.
[29] WANG J, GU X, YANG J, et al. Gut microbiota dysbiosis and increased plasma LPS and TMAO levels in patients with preeclampsia[J]. Front Cell Infect Microbiol, 2019, 9: 409.
[30] HSU C N, HOU C Y, LEE C T, et al. The interplay between maternal and post-weaning high-fat diet and gut microbiota in the developmental programming of hypertension[J]. Nutrients, 2019, 11(9): 1982.
[31] CHEN H E, LIN Y J, LIN I C, et al. Resveratrol prevents combined prenatal N(G)-nitro-L-arginine-methyl ester (L-NAME) treatment plus postnatal high-fat diet induced programmed hypertension in adult rat offspring: interplay between nutrient-sensing signals, oxidative stress and gut microbiota[J]. J Nutr Biochem, 2019, 70: 28-37.
[32] HSU C N, LIN Y J, HOU C Y, et al. Maternal administration of probiotic or prebiotic prevents male adult rat offspring against developmental programming of hypertension induced by high fructose consumption in pregnancy and lactation[J]. Nutrients, 2018, 10(9): 1229.
[33] SAUER A K, GRABRUCKER A M. Zinc deficiency during pregnancy leads to altered microbiome and elevated inflammatory markers in mice[J]. Front Neurosci, 2019, 13: 1295.
[34] HSIEH H Y, CHEN Y C, HSU M H, et al. Maternal iron deficiency programs offspring cognition and its relationship with gastrointestinal microbiota and metabolites[J]. Int J Environ Res Public Health, 2020, 17(17): 6070.
[35] ISHIMWE J A, AKINLEYE A A, JOHNSON A C, et al. Gestational gut microbial remodeling is impaired in a rat model of preeclampsia superimposed on chronic hypertension[J]. Physiol Genomics, 2021, 53(3): 125-136.
[36] LAMICHHANE S, SEN P, ALVES M A, et al. Linking gut microbiome and lipid metabolism: moving beyond associations[J]. Metabolites, 2021, 11(1): 55-58.
[37] ALLOTEY J, SNELL K I, SMUK M, et al. Validation and development of models using clinical, biochemical and ultrasound markers for predicting pre-eclampsia: an individual participant data meta-analysis [J]. Health Technol Assess, 2020, 24(72): 1-252.
[38] WINTER G, HART R A, CHARLESWORTH R P, et al. Gut microbiome and depression: what we know and

what we need to know[J]. Rev Neurosci, 2018, 29(6): 629-643.
[39] CANI P D. Human gut microbiome: hopes, threats and promises[J]. Gut, 2018, 67(9): 1716-1725.
[40] LEY R E, TURNBAUGH P J, KLEIN S, et al. Microbial ecology: human gut microbes associated with obesity[J]. Nature, 2006, 444(7122): 1022-1033.
[41] KANBAY M, ONAL E M, AFSAR B, et al. The crosstalk of gut microbiota and chronic kidney disease: role of inflammation, proteinuria, hypertension, and diabetes mellitus[J]. Int Urol Nephrol, 2018, 50(8): 1453-1466.
[42] GENTILE C L, WEIR T L. The gut microbiota at the intersection of diet and human health[J]. Science (New York, NY), 2018, 362(6416): 776-780.
[43] FELIZARDO R J, WATANABE I K, DARDI P, et al. The interplay among gut microbiota, hypertension and kidney diseases: The role of short-chain fatty acids[J]. Pharmacol Res, 2019, 141: 366-377.
[44] SUN S, LULLA A, SIODA M, et al. Gut microbiota composition and blood pressure[J]. Hypertension, 2019, 73(5): 998-1006.
[45] MEIJERS B, JOURET F, EVENEPOEL P. Linking gut microbiota to cardiovascular disease and hypertension: Lessons from chronic kidney disease[J]. Pharmacol Res, 2018, 133: 101-107.
[46] GOMEZ-ARANGO L F, BARRETT H L, MCINTYRE H D, et al. Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy[J]. Hypertension, 2016, 68(4): 974-981.
[47] POLL B G, XU J, JUN S, et al. Acetate, a short-chain fatty acid, acutely lowers heart rate and cardiac contractility along with blood pressure[J]. J Pharmacol Exp Ther, 2021, 377(1): 39-50.
[48] KANG Y, CAI Y. Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies[J]. Clin Res Hepatol Gastroenterol, 2018, 42(2): 110-117.
[49] BRANTSAETER A L, MYHRE R, HAUGEN M, et al. Intake of probiotic food and risk of preeclampsia in primiparous women: the norwegian mother and child cohort study[J]. Am J Epidemio, 2011, 174(7): 807-815.
[50] ASEMI Z, JAZAYERI S, NAJAFI M, et al. Effect of daily consumption of probiotic yogurt on oxidative stress in pregnant women: a randomized controlled clinical trial[J]. Ann Nutr Metab, 2012, 60(1): 62-68.
[51] 吴邹钰, 马霄, 苏艳丽, 等. 肠道菌谱分析在粪便细菌学检验中的应用及其临床价值[J]. 检验医学与临床, 2019, 16(24): 3643-3645.
[52] CHEN X, LI P, LIU M, et al. Gut dysbiosis induces the development of pre-eclampsia through bacterial translocation[J]. Gut, 2020, 69(3): 513-522.
[53] LIU J, YANG H, YIN Z, et al. Remodeling of the gut microbiota and structural shifts in preeclampsia patients in South China[J]. Eur J Clin Microbiol Infect Dis, 2017, 36(4): 713-719.
[54] GOMEZ-ARANGO L F, BARRETT H L, MCINTYRE H D, et al. Connections between the gut microbiome and metabolic hormones in early pregnancy in overweight and obese women[J]. Diabetes, 2016, 65(8): 2214-2223.
[55] MOKKALA K, HOUTTU N, KOIVUNIEMI E, et al. GlycA, a novel marker for low grade inflammation, reflects gut microbiome diversity and is more accurate than high sensitive CRP in reflecting metabolomic profile[J]. Metabolomics, 2020, 16(7): 76-79.
[56] HOUTTU N, MOKKALA K, LAITINEN K. Overweight and obesity status in pregnant women are related to intestinal microbiota and serum metabolic and inflammatory profiles[J]. Clin Nutr, 2018, 37(6 Pt A): 1955-1966.
[57] TADDEI C R, CORTEZ R V, MATTAR R, et al. Microbiome in normal and pathological pregnancies: a literature overview[J]. Am J Reprod Immunol, 2018, 80(2): e12993.

(收稿日期: 2021-06-09 修回日期: 2022-03-01)

·综 述·

代谢组学在非创伤性股骨头坏死的研究进展

郇昌翔[1,2] 综述, 卢发强[1,2△] 审校
1. 大连大学中山临床学院, 辽宁 大连 116001; 2. 大连大学附属中山医院医学检验中心, 辽宁 大连 116001

摘 要: 非创伤性股骨头坏死因其早期临床诊断难度高、发病机制未被证实和致残率高等原因, 而成为国内外骨科领域热门研究专项。近些年来, 代谢组学成为新的研究领域, 其在非创伤性股骨头坏死早期生物标志物筛选、代谢通路、药理学机制及疗效研究中取得了一定的进展, 为临床早期诊断提供了理论可能。本文对代谢组学在非创伤性股骨头坏死研究方法, 以及中西医降血脂药物预防非创伤性股骨头坏死的机制和疗效进展进行综述, 为下一步研究提供依据。

关键词: 代谢组学; 非创伤性股骨头坏死; 生物标志物; 代谢通路; 预防
DOI: 10.3969/j.issn.1673-4130.2022.11.024 **中图法分类号**: R681.8

△ **通信作者**, E-mail: faqiang3@163.com。
网络首发 https://kns.cnki.net/kcms/detail/50.1176.R.20220424.1507.002.html(2022-04-25)