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妊娠期代谢疾病的流行情况及对子代发育影响的研究现状

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摘　要

妊娠期代谢性疾病(Gestational Metabolic Disorders, GMD)可通过影响胎盘结构与功能、改变子宫－胎盘血流及营养物质转运，干扰胎儿宫内环境稳态，不仅增加孕妇发生早产、新生儿窒息、胎儿宫内窘迫、剖宫产等不良妊娠结局的风险，还可能通过“代谢记忆”效应对子代健康产生持续影响，包括生长发育异常、代谢异常及神经系统发育障碍等。本研究系统梳理了近年来国内外关于GMD流行病学特征的研究进展，并总结了其对不良妊娠结局、子代体格发育及神经发育影响的研究现状，旨在为制定科学的孕期管理策略及优化子代早期健康干预措施提供循证支持。

关键词

妊娠代谢性疾病，不良妊娠结局，生长发育

The Epidemiology of Gestational Metabolic Disorders and Current Evidence on Their Impact on Offspring Development

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Abstract

Gestational metabolic disorders may disrupt the intrauterine homeostasis by affecting placental

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structure and function, altering uteroplacental blood flow, and impairing nutrient transport. These disruptions not only increase the risk of adverse pregnancy outcomes, including preterm birth, neonatal asphyxia, fetal distress, and caesarean delivery, but may also exert long-term effects on offspring health through the mechanism of "metabolic memory", leading to abnormal physical development, metabolic disorders, and neurodevelopmental impairments. This study systematically reviews recent domestic and international research progress on the epidemiological characteristics of GMD and summarizes the current state of research on its impact on adverse pregnancy outcomes, offspring physical development, and neurological development. The aim is to provide evidence-based support for the development of scientific prenatal management strategies and the optimization of early health intervention measures for offspring.

Keywords

Gestational Metabolic Disorders, Adverse Pregnancy Outcomes, Growth and Development

1. 前言

妊娠期代谢性疾病(Gestational Metabolic Disorders, GMD)是一组与妊娠期代谢异常密切相关的疾病，主要包括妊娠期糖尿病(Gestational Diabetes Mellitus, GDM)、妊娠期高血压疾病(Hypertensive Disorders of Pregnancy, HDP)、妊娠期过度增重(Excessive Gestational Weight Gain, EGWG)及妊娠期代谢综合征(Gestational Metabolic Syndrome, GMS) [1]。妊娠期间的母体健康状况，尤其是代谢状态，对胎儿的生长发育具有关键性作用[2]。生命早期 1000 天被认为是影响子代体格生长、神经发育和行为形成的"关键窗口期"。因此，关注并干预生命早期的发育状况，对降低远期健康风险，提升人群健康水平，具有重要的公共卫生意义。

2. 妊娠代谢性疾病的流行情况

2.1. 妊娠期糖尿病

2017 年，全球约有 2130 万名新生儿(16.2%)在宫内暴露于妊娠期高血糖环境，其中高达 86.4%的病例归因于 GDM [3]。根据国际糖尿病与妊娠研究组协会(The International Association of the Diabetes and Pregnancy Study Groups, IADPSG)制定的诊断标准，2021 年全球 GDM 的总体患病率约为 14.0%。值得注意的是，GDM 的流行水平存在显著的地区差异：北美和加勒比地区的患病率约为 7.1%，而中东和北非地区则高达 27.6% [4]。一项涵盖 170 多万名 40~54 岁女性的回顾性出生队列研究发现，1998 年至 2014 年间全球各地区的 GDM 发病率整体呈现持续上升趋势，亚洲及太平洋地区增幅最为显著，GDM 的发病率从 13.7%上升至 22.4% [5]。

我国近年来的流行病学研究也表明，GDM 的患病率持续上升。一项涵盖中国 17 个地区、70,936 名孕妇的 Meta 分析显示，2012~2020 年我国 GDM 的总体患病率为 13.4% [6]。各地区患病率差异明显：如赵豆豆等开展的一项前瞻性研究指出，2019 年中国西北地区 GDM 患病率高达 27.44% [7]；而部分偏远地区，如新疆，GDM 患病率仅为 5.12% [8]，这可能与当地 GDM 筛查率偏低、孕产妇健康管理水平有限有关。随着居民膳食结构的改变、高龄妊娠比例的上升及肥胖女性比例的增加，GDM 在我国的流行趋势预计仍将持续上升。

2.2. 妊娠期高血压疾病

妊娠期高血压疾病影响约 10%的妊娠，占全球孕产妇死亡人数的 14% [9] [10]。根据全球疾病负担(Global Burden of Disease, GBD)研究数据，在过去 30 年中，HDP 的病例数增加了约 10.9% (95%UI: 6.1%~15.3%)，该增长主要集中在社会人口指数(Socio-Demographic Index, SDI)较低的国家和地区。尽管如此，全球在 HDP 防治方面取得了一定进展，其相关死亡率已由 1990 年的每 10 万活产 39.8 例下降至 2019 年的 27.8 例。从区域分布来看，非洲的 HDP 患病率最高(355 例/10 万)，其次为东南亚与中东地区；而西太平洋地区患病率最低(16 例/10 万) [11]。在各类 HDP 中，子痫前期(Preeclampsia, PE)是发病率和死亡率最高的一类妊娠期高血压疾病，其发病率约为5%~7% [12]，是妊娠高血压疾病中导致孕产妇死亡的主要类型。

作为人口大国，中国的 HDP 流行现状具有明显地域性和人群特征。近年来，我国妊娠期高血压疾病的总体患病率为 9.4%~10.4% [13]，与全球平均水平基本相当。但在不同地区之间存在差异，调查显示，湖南省孕妇 HDP 患病率由 2012 年的 4.3%上升至 2019 年的 7.1%，呈现逐年上升趋势[14]。四川省近二十年的监测数据显示，2022 年 HDP 的发病率为 5.11% [15]。随着国家“全面二孩”及“三孩”政策的实施，高龄孕妇比例显著上升，生育模式发生转变[16]。一项系统评价指出，高龄、超重或肥胖的孕妇 HDP 及其亚型疾病患病率均呈持续上升趋势[17]，提示在现行人口政策背景下，需重视对高危孕妇的早期识别与孕期干预。

2.3. 妊娠期过度增重

在全球范围内，育龄期女性超重与肥胖的发生率在发达国家及部分发展中国家持续上升[18]，EGWG 成为全球公共卫生领域广泛关注的重要问题。根据一项涵盖 29 个国家、共 63 项研究的系统评价结果，全球孕妇超重和肥胖的患病率分别为 23.0%和 16.3%，约 30%~50%的孕妇存在 EGWG 的情况，其中高收入国家尤为显著，欧洲和美国地区孕妇体重超标率高达 51%，而亚洲地区最低，为 20.2% [19]。此外，一项覆盖 70 个低收入和中等收入国家、共 234 项调查的研究显示，EGWG 的发生率从马拉维的 2%至巴基斯坦的 58%不等[20]。

中国作为人口大国，其育龄女性超重/肥胖问题与 EGWG 的流行现状具有典型性。纵向研究显示，1993 年至 2015 年间，中国成年人超重率从 26.6%增至 41.3%，肥胖率由 4.2%上升至 15.7% [21]。2019 年，一项涉及 1580 万人的大型横断面调查结果显示，中国女性超重率为 27.4%，肥胖率为 9.6%，北方地区的超重与肥胖率普遍高于华南地区[22]，可能与地域间饮食结构、气候条件及生活方式等差异有关。在孕期增重方面，毕烨等研究表明，我国孕妇在孕中期增重过度的患病率为 58.2%，孕晚期为 55.8% [23]。不同地区间 EGWG 的发生率亦存在明显差异。上海一项纳入 26,422 名孕妇的研究显示，37.9%的孕妇存在 EGWG [24]；西宁市、北京市和重庆市孕妇 EGWG 发生率分别为 40.82%、24.1%和 23.18% [25]。这表明，随着我国育龄女性超重、肥胖率的不断上升，妊娠期过度增重问题日益突出，亟需加强孕期体重管理和营养干预。

2.4. 妊娠期代谢综合征

代谢综合征(Metabolic Syndrome, MetS)在全球范围内的患病率呈持续上升趋势，全球成年人的总体患病率估计在 12.5%至 31.4%之间[26]。尽管 MetS 的诊断在普通人群中已有较为统一的标准，但在妊娠期女性中，由于个体体质差异以及孕期诊断指标(如血糖、血脂等)发生的显著生理变化，目前尚无统一的 GMS 诊断标准。现有研究多依据世界卫生组织(World Health Organization, WHO)、国际糖尿病联盟(International Diabetes Federation, IDF)及美国国家胆固醇教育计划成人治疗组第三版(National Cholesterol Education Program Adult Treatment Panel III, NCEP-ATP III)所提出的标准，并结合孕期特点加以修订，以评估

妊娠期代谢异常的发生情况。一项纳入 20 项研究的系统评价显示，全球 GMS 的汇总患病率为 16.3%，具体数值因所采用的诊断标准而异：基于 WHO 标准为 18.2%，IDF 标准为 15.0%，NCEP-ATP III 标准为 17.2% [27]。根据 NCEP-ATP III 标准，2022 年埃塞俄比亚孕妇 MetS 的患病率为 13.2% [28]。2019 年巴西开展的一项前瞻性队列研究中显示，孕 16 周时 GMS 患病率为 3.0%，至分娩后升高至 9.7% [29]，提示妊娠期可能是代谢综合征发生与发展的高风险时期。

在我国，一项 Meta 分析结果显示，15 岁及以上人群中 MetS 总体患病率达 24.5%，女性患病率高达 27.0% [30]。国内区域性研究也证实 GMS 的流行趋势，牛建民等在我国南方地区开展的一项孕期队列研究中发现，孕 20 周前约 27.12%的孕妇存在两种及以上的代谢异常聚集，10.2%的孕妇同时存在三种及以上异常，且这种代谢异常的聚集状态显著增加了不良妊娠结局的风险[31]。另一项采用 WHO 修订标准开展的临床交叉研究亦指出，在发生 GDM 的孕妇中，GMS 的患病率达 22.6% [32]，提示 GMS 与妊娠期糖代谢异常之间存在密切关系。

3. 研究现状

3.1. 妊娠期代谢性疾病与不良妊娠结局关系的研究现状

大量研究支持 GDM 孕妇所生子代在出生时表现出更高肥胖度。多项系统评价表明，GDM 显著增加巨大儿、早产及代谢性疾病等风险，并与母体剖宫产、肩难产和产伤等的发生密切相关[33] [34]。然而，相关研究结果并不完全一致。一项涵盖 156 项研究、共涉及 750 万例妊娠的大规模荟萃分析发现，GDM 除了与肩难产、器械助产和产后出血风险升高相关外，还可能增加死产、新生儿死亡、5 分钟 Apgar 评分低、低出生体重以及小于胎龄儿等结局的风险[35]。上述不一致性可能与研究设计的异质性、结局评估方法及混杂因素控制策略等有关。

HDP 对子代出生结局的影响亦存在争议。一项来自美国的回顾性队列研究显示，慢性高血压或妊娠期高血压孕妇的子代出生体重与血压正常孕妇相近[36]。然而，一项系统评价则指出妊娠期高血压显著增加了低出生体重(OR = 5.02)风险[37]。研究差异可能源于妊娠期高血压的严重程度是否进展为子痫前期。已有研究表明，与正常孕妇相比，孕期患有子痫前期对子代的不良影响更为显著，主要表现为低出生体重(OR = 1.61)、早产(OR = 2.22)及新生儿呼吸窘迫综合征(OR = 2.39)等[36]。国内研究也支持上述发现，钟志鸿等的研究表明，妊娠期高血压和子痫前期组胎儿生长受限的发生率显著高于正常妊娠组[38]。

孕期体重管理是影响母婴结局的重要因素。EGWG 已被证实与多种不良妊娠结局相关。冯银宏的研究发现，EGWG 显著增加妊娠期高血压、GDM、胎膜早破、巨大儿和剖宫产的发生率[39]。一项小样本研究指出，早期 EGWG 与新生儿体脂增加有关[40]。此外，EGWG 还与胎粪吸入综合征、头盆不称、肩难产和新生儿窒息等分娩并发症相关[41]。

关于 GMS 对子代影响的研究仍相对有限，且结果存在较大不一致性。希腊一项纳入 625 人的队列研究发现，孕早期即被诊断为 MetS 的经产妇早产风险是非 MetS 孕妇的 2.93 倍[42]。但 Baliutaviciene 等人的研究未发现患有 MetS (葡萄糖耐量受损、肥胖及高血压)孕妇所生新生儿在胎龄或出生体重方面存在差异[43]。Grieger 等人的研究也未发现孕妇 MetS 与大于胎龄儿(Large for Gestational Age, LGA)、小于胎龄儿(Small for Gestational Age, SGA)或自发性早产之间存在关联[44]。上述差异可能与目前尚无统一的 GMS 诊断标准、研究评估方法不同以及种族差异等因素有关。

3.2. 妊娠期代谢性疾病与子代生长发育关系的研究现状

妊娠期代谢性疾病通过复杂的生理变化及表观遗传机制对子代的生长发育及长期健康产生深远影响。

其中，最直接且可量化的影响体现在子代体格发育方面，表现为体重异常、生长轨迹偏离及肥胖风险增加等。美国“成长今日研究(Growing Up Today Study, GUTS)”发现，GDM 母亲所生的男性子代在儿童晚期肥胖风险增加(RR = 1.59) [45]。丹麦一项纵向研究对 GDM 子代从出生至 10 岁的体重指数(BMI)轨迹进行追踪，发现“晚期加速”和“早期加速”BMI 轨迹的子代面临超重及肥胖的风险[46]。天津开展的一项包含 1681 对母婴的随访研究也证实，GDM 显著增加了子代不良生长模式的发生风险[47]。

HDP 同样可能对子代体格发育产生长期影响。马新凯的长期随访研究发现，妊娠期高血压与子痫前期对子代儿童期的身高、体重及 BMI 增长均存在一定影响[48]。一项挪威的队列研究表明，子痫前期对子代生长的影响具有性别差异，仅在男童中观察到明显的人体测量差异[49]。日本北海道的出生队列研究发现，暴露于 HDP 的男婴出生体重较低，但在儿童期出现生长追赶现象，至 7 岁时体重增加(β = 1.21) [50]。另一项研究进一步支持了该结论，认为子痫前期暴露与儿童期早期身高的加速增长密切相关[51]。

国内外研究普遍认为 EGWG 是子代肥胖风险的重要决定因素之一。一项纳入 16 万中国婴儿的大规模队列研究发现，EGWG 是婴儿出生后前 6 个月体重快速增长的危险因素[52]。舟山市一项人群队列研究进一步提示，孕期体重增长轨迹显著影响 0~36 个月子代体格发育，EGWG 合并 GDM 的母亲所生子代的体重明显增加(β = 0.093)、BMI 显著升高(β = 0.113)、超重/肥胖的风险更高(OR = 1.40) [53]。新西兰一项孕期运动干预随机对照试验的二次分析结果发现，EGWG 母亲的子代在 7 岁时出现更高的腹部肥胖率，且血脂状况较差[54]。

近年来，GMS 对子代生长发育的影响逐渐受到关注。马鞍山出生队列研究表明，GMS 暴露与子代 BMI z 评分升高和肥胖风险增加显著相关，且女孩从出生至 6 岁期间 BMI 轨迹升高更为明显[55]。GMS 常与 GDM 及 EGWG 共存。多项研究发现，母体孕前肥胖、妊娠期过度增重及 GDM 等代谢异常因素，均可显著增加儿童早期肥胖风险和高 BMI 轨迹上升的发生概率[56] [57]。

3.3. 妊娠期代谢性疾病对子代神经发育的研究现状

自 2000 年以来，国际学界逐渐关注妊娠期代谢性疾病对子代神经发育的潜在影响，该领域已成为母婴健康研究的重要热点之一。现有大量证据表明，GDM 增加了子代在感知觉、运动、语言和智力发育等方面表现出发育障碍的风险[58]，相关结局包括自闭症谱系障碍(Autism Spectrum Disorder, ASD)、注意缺陷多动障碍(Attention Deficit Hyperactivity Disorder, ADHD)、智力障碍、特定发育障碍、沟通障碍、运动障碍和学习障碍等[2]。Templ 等学者指出，宫内高血糖环境暴露可能损伤胎儿神经系统，进而影响出生后的认知和行为发育[59]。

HDP 被广泛认为是影响子代神经系统发育的重要因素。多项研究表明，子痫前期与胎儿脑损伤及不良神经发育结局密切相关，暴露子代在认知、情绪调节与社会行为等方面的发育风险高于未暴露组[60] [61]。HDP 也与子代患 ASD (HR = 1.22, 95% CI: 1.13~1.31)及 ADHD (HR = 1.10, 95% CI, 1.05~1.16)的风险适度升高相关[62]。

孕期体重增长异常是近年来关注的重要代谢因素。2020 年一项系统评价和荟萃分析指出，EGWG 与子代发生 ASD 风险相关[63]。另一项纳入 200 对母婴对的研究表明，EGWG 母亲所生婴儿在出生后 3 至 12 个月期间表现出较差的精神运动发育水平[64]。

GMS 涵盖了多种代谢异常因素，可其对子代神经系统发育的影响可能更为复杂且具有协同作用。英国一项基于儿童发展评估的研究发现，GMS 暴露与子代 5 岁时沟通能力、识字能力以及社交–情感功能的发育迟缓有关[65]。动物模型实验结果证实了这一观点，GMS 可导致后代神经行为及代谢功能的持久改变，呈现出性别二态性[66]。2023 年的一项纵向母子出生队列研究发现，GDM 和母亲孕前肥胖联合暴露与 2 岁儿童神经发育技能减弱相关(β = −1.12)，尽管在该儿童群体中仍处于平均正常范围内[67]，提示

其对早期神经发育具有潜在干扰作用。

综上所述，基于近年来大量国内外的流行病学与实验研究证据，妊娠代谢性疾病已被明确为影响子代健康的重要危险因素，其不良影响可贯穿妊娠期、围产期、儿童早期乃至远期生命阶段。并在子代体格发育及神经行为发育等方面产生持续且深远影响。

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