

妊娠相关脑卒中

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【摘要】 妊娠相关脑卒中临床虽不常见,但可显著影响女性健康及家庭生活。目前关于存在妊娠相关脑卒中病史的女性后继妊娠和健康状况的研究有限。本文系统综述妊娠相关脑卒中的流行病学、危险因素、病理生理学机制和治疗方案,以期为妊娠相关脑卒中预防与治疗的进一步研究提供方向。

【关键词】 卒中; 妊娠; 综述

Stroke during pregnancy and postpartum

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【Abstract】 Stroke during pregnancy and postpartum, though uncommon, can significantly affect the lives of women and their families. However, the current research on the subsequent pregnancy and health status of women, with a history of pregnancy-related stroke, is limited. To provide reference for the prevention and treatment of stroke during pregnancy and postpartum, this article reviews the epidemiology, risk factors, pathophysiological mechanism, and treatment of pregnancy-related stroke.

【Key words】 Stroke; Pregnancy; Review

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妊娠相关脑卒中系指妊娠期或产褥期女性发生的脑卒中。妊娠相关脑卒中发生率为 13.4/10 万,其中,出血性卒中占有妊娠相关脑卒中的 60%,缺血性卒中占 40%^[1]。妊娠相关脑卒中致死亡占妊娠期或产褥期女性死亡的 17%^[1-2]。女性妊娠期或产褥期发生脑卒中虽不常见,但显著影响女性健康及家庭生活。近年来,青年人群的心血管病危险因素如高血压、糖尿病和肥胖等越来越多^[3],妊娠相关脑卒中相关危险因素和发病率亦不断上升^[4]。随着我国生育政策的放开,许多有脑卒中病史的女性可能希望再次妊娠,然而目前关于有妊娠相关脑卒中病史女性后继妊娠和健康状况的数据有限^[5],无法给出准确的评估和建议。本文拟对妊娠相关

脑卒中流行病学、危险因素、病理生理学机制、临床表现和治疗进行综述,以期为疾病预防与治疗的进一步研究提供方向。

一、妊娠相关脑卒中的流行病学

妊娠期和产褥期可以增加缺血性和出血性卒中风险^[6]。英国一项 1997-2014 年的研究结果发现,15~49 岁女性每年妊娠相关脑卒中发病率为 10.7/10 万^[7]。美国和加拿大妊娠相关脑卒中发病率逐年升高,新近基于加拿大全国人口(除外魁北克省)的调查显示,2003-2016 年妊娠相关脑卒中发病率增长 60%^[1,8];既往 20 年美国妊娠期和产褥期女性发生缺血性和出血性卒中的风险增加 50%~80%^[6]。最近一项囊括日本、美国、印度等 11 个国家数据的 Meta 分析显示,1990-2017 年妊娠相关缺血性和出血性卒中发病率为 12.2/10 万,脑静脉窦血栓形成(CVST)发病率为 9.1/10 万^[9]。国内颜晓和邵蓓^[10]统计的妊娠相关脑卒中发病率为(28.9~58.7)/10 万;另一项研究纳入 2014 年 1 月至 2016 年 6 月山西省妊娠期和产褥期女性共 20 479 例,随访

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30 个月发现其脑卒中发病率为 127/10 万^[11]。尽管女性在妊娠过程中均可能发生脑卒中,但最危险的时期是妊娠晚期和产后 6 周内^[12]。上述研究结果提示,妊娠相关脑卒中发病率不断升高,可能与诊断技术和影像学技术的不断发展以及种族、样本量和地域等的不同有关。

二、妊娠相关脑卒中的危险因素

妊娠相关脑卒中的危险因素主要包括高龄、既往脑卒中病史、子痫前期/子痫、偏头痛、吸烟、恶性肿瘤、高脂血症、系统性红斑狼疮(SLE)、心脏病、高血栓形成倾向、类风湿关节炎(RA)、镰状细胞贫血和抑郁症等^[13-14]。妊娠特有的危险因素包括由内皮细胞功能障碍引起的妊娠期高血压和脑血流自动调节(CA)障碍、妊娠期糖尿病、产后大出血、剖宫产等^[13,15-16]。Kuklina 等^[8]发现,女性高血压和心脏病患病率显著升高可以导致妊娠相关脑卒中发病风险升高。上述已知的血管危险因素均可能在妊娠期和产褥期诱发脑卒中。Cheng 等^[17]基于中国台湾地区健康保险数据库的研究显示,高血压、糖尿病、凝血功能障碍、偏头痛、肥胖、脑血管畸形和妊娠次数 > 3 次均与脑卒中相关。潜在心肌病、风湿性心脏病或瓣膜性心脏病、心力衰竭亦增加妊娠相关脑卒中的风险^[7]。年龄稍高[30(25,35)岁]的妊娠期和产褥期女性常发生妊娠相关缺血性卒中^[14],但 Miller 等^[18]的研究与之相反,< 35 岁女性妊娠相关脑卒中发病率高于 35~55 岁女性(18%对 1.4%, $P < 0.001$),可能是由于年龄较大的女性存在更多的血管危险因素,妊娠概率较低,故妊娠相关脑卒中发病率降低而非妊娠相关脑卒中发病率相应升高。子痫前期/子痫是妊娠相关脑卒中的危险因素,罹患子痫前期/子痫的女性妊娠期和产后 1 年发生脑卒中的风险显著升高。Brown 等^[19]认为,子痫前期可以使妊娠期和产褥期女性缺血性卒中的风险增加 60%。Tang 等^[20]的研究显示,罹患子痫前期/子痫的女性分娩前 3 个月发生缺血性卒中的风险最高($RR = 40.86, 95\%CI: 12.14 \sim 137.47; P < 0.001$),产后 1 年更易发生出血性卒中($RR = 19.90, 95\%CI: 7.75 \sim 51.11; P < 0.001$),且产后 1 年内脑卒中的风险持续存在。高血压既是脑卒中的危险因素,又是子痫前期/子痫的主要诊断标准,故与妊娠相关脑卒中的病理生理学机制密切相关。颅内动脉瘤和颅内动静脉畸形(AVM)是妊娠期和产褥期女性发生出血性卒中的重要原因。2002-2014 年美国女性在妊娠期

发生动脉瘤性蛛网膜下腔出血的风险从 4.16% 增至 6.33% ($P < 0.001$)^[21]。Zhu 等^[22]发现,妊娠期和产褥期女性颅内血管畸形致脑出血的年发生率高于未妊娠女性(5.59%对 2.52%, $95\%CI: 1.52 \sim 6.70; P = 0.002$)。亦有研究显示,与年龄相近的非妊娠期女性相比,妊娠期女性脑血管危险因素更少,发生潜在脑血管病变例如颅内动脉瘤和动静脉畸形的概率更低^[23]。近期 Joseph 等^[24]的前瞻性研究显示,妊娠并不增加脑或者脊髓海绵状血管瘤破裂出血的风险。由此可见,妊娠相关出血性卒中可能是一个独特的病理生理学过程,尚待针对性研究进一步探索。

三、妊娠相关脑卒中的病理生理学机制

1. 血流动力学改变 妊娠期和产褥期女性血流动力学发生明显改变,与水钠潴留和肾素-血管紧张素系统(RAS)活性增强有关,加之心输出量、每搏输出量和心率增加,全身血容量随之增加^[25]。上述血流动力学改变可以使全身小动脉痉挛,造成管腔狭窄,周围血管阻力增大,血管内皮细胞损伤,导致高血压。血流动力学变化通常自妊娠初始持续至产后 6~12 周,故此时期脑卒中特别是出血性卒中的发病率升高。颅内小动脉痉挛可以引起脑组织缺血、缺氧,毛细血管内皮细胞损伤,轻症出现头痛、头晕、恶心呕吐、视物模糊,重症出现脑血流自动调节机制受损,诱发脑出血。

2. 凝血功能变化 女性在妊娠晚期和产褥期早期处于血液高凝状态。自妊娠中期,血管顺应性明显增强,可诱发静脉淤血,导致病理性血栓形成。此外,此期间凝血因子 I、VII、VIII、IX、X、XII 和 XIII,血管性血友病因子(vWF),纤维蛋白原和纤维蛋白生成增多;抗凝血因子蛋白 C 水平不变(但有 1/2 女性妊娠晚期可发生活化蛋白 C 抵抗^[26]);而蛋白 S 和抗凝血酶等抗凝血因子则生成减少^[27]。故凝血因子生成增多和抗凝血因子生成减少可能是妊娠晚期和产褥期早期血液高凝状态的重要原因。

3. 子痫前期/子痫 子痫前期/子痫与妊娠相关脑卒中密切相关,其作用机制相对复杂。子痫前期基本病理生理学变化是全身小动脉痉挛,血管内皮细胞功能障碍,全身各系统靶器官血流灌注减少,导致不同的临床征象包括心血管、血液、肾脏、肝脏、脑和子宫胎盘灌注等。重度子痫前期患者血压 $\geq 160/110$ mm Hg。当血压缓慢升高时患者多无明显症状,但当血压急骤升高时,可出现持续严重

的中枢神经系统症状,可发生子痫或脑出血。同样,子痫前期血小板计数减少可以导致脑卒中。血小板计数减少是子痫前期的早期症状之一,约 50% 的子痫前期患者可出现血小板计数减少,该征象亦为血压升高之先兆。血小板计数减少的机制是血管内皮细胞损伤引起血小板聚集和黏附,使得血小板消耗增加,并易在小动脉产生凝血酶^[28],从而导致脑卒中。另外,在妊娠期和产褥期,可逆性后部脑病综合征(PRES)和可逆性脑血管收缩综合征(RCVS)也可以导致脑卒中。子痫前期可出现可逆性后部脑病综合征,这是由血管内皮细胞功能障碍和高血压引起的一种血管源性脑水肿综合征。脑水肿是由以下两种因素共同造成的:(1)高血压引起的静水压升高。(2)血-脑屏障完整性破坏导致血管内皮细胞功能障碍。子痫前期/子痫脑血流自动调节能力降低,导致血管扩张和脑血流量增加,加剧脑水肿,可能导致出血性和缺血性卒中^[29]。子痫前期/子痫也与可逆性脑血管收缩综合征高度相关,后者主要是颅内血管张力改变引起的一种短暂性血管痉挛病变,主要表现为血管内皮细胞损伤和血管张力失调导致的病理性血管收缩。其典型临床表现为头痛和局部神经功能障碍,也可发生癫痫发作。可逆性脑血管收缩综合征最常见的病理表现是缺血性卒中,蛛网膜下腔出血和脑出血亦较常见,可能是由于血-脑屏障功能障碍所致^[23]。尽管上述两种综合征是可逆的,但仍然是妊娠期女性发生缺血性和出血性卒中的重要原因^[13]。

四、妊娠相关脑卒中的治疗

妊娠相关脑卒中一旦发生,应开启多学科诊疗模式(MDT)快速处理,但目前高质量的循证医学证据较少。2018年,加拿大心脏与卒中基金会(HSFC)基于当时的最权威文献和专家共识撰写并发布《妊娠期急性脑卒中管理指南》^[30],指出妊娠相关脑卒中发生后,需神经科、急诊科、产科、麻醉科、介入神经放射科和神经外科等多学科合作,共同快速评估并制定治疗方案。

1. 急性缺血性卒中 (1)rt-PA 静脉溶栓:rt-PA 相对分子质量较大,经静脉注射后不易透过胎盘,半衰期为 4~5 分钟,20 分钟后血药浓度可降至 10% 以下^[31]。截至目前,未见关于 rt-PA 能够透过胎盘的报道。生存胎儿的脑发育未发现异常迹象,无证据表明其具有致畸性^[32]。且经 rt-PA 静脉溶栓后患者预后良好^[32-34]。美国心脏协会(AHA)/美国卒中

协会(ASA)建议,当预期收益大于风险时应考虑对妊娠期女性进行静脉溶栓治疗,但产后行静脉溶栓尚无足够证据^[35]。(2)血管内机械取栓术:因存在照射剂量和动脉夹层风险,妊娠期行血管内机械取栓术一直受到限制,特别是妊娠后期^[36]。但目前已有多例妊娠期女性因急性缺血性卒中成功行血管内机械取栓术且预后良好的报道,孕妇和胎儿均未见相关并发症^[33,37-39]。最近一项针对 3 例妊娠期女性行血管内机械取栓术的研究显示,胎儿受到的平均照射剂量为 (0.024 ± 0.018) mGy,显著低于 50 mGy 的风险剂量,发生流产或胎儿畸形的风险与正常妊娠风险相比无明显差异^[40]。由此可见,血管内机械取栓术是一种有效的治疗方法^[41]。《妊娠期急性脑卒中管理指南》建议,考虑到不及时治疗大血管闭塞性缺血性卒中可严重危害胎儿和孕妇,当收益大于风险时建议行血管内机械取栓术^[30]。

2. 出血性卒中 妊娠期出血性卒中的处理与非妊娠期相似。任何类型的颅内出血初步处理均为防止再出血和血肿扩大。凝血功能障碍患者应纠正凝血功能,并及时通过 CTA 和(或)诊断性脑血管造影确定出血部位。脑出血一经诊断后应立即控制血压,严密进行胎心监测,及早发现是否存在胎盘灌注降低的迹象。拉贝洛尔、甲基多巴、尼卡地平和长效硝苯地平等药物均可用于妊娠期女性,安全有效^[30]。当妊娠期女性发生出血性卒中时,一旦确定颅内出血的原因为动静脉畸形时,应考虑病情有急速恶化的风险,立即进行外科和(或)血管内介入治疗。为确保胎儿安全,在进行脑血管造影检查和血管内介入治疗时应适当屏蔽照射^[42]。而对未破裂、无症状性颅内动静脉畸形的处理目前尚存争议^[43]。对于未破裂的颅内动静脉畸形,一项关于血管内介入治疗与保守治疗的随机对照试验由于介入治疗组的不良反应而停止,但是长期观察结果显示,保守治疗患者预后更佳^[44]。对于具有高风险的颅内动静脉畸形患者,如果位置较深、有深部引流、动静脉瘘或伴动脉瘤等,治疗方案应根据个体情况而定^[42]。妊娠期女性发生颅内动脉瘤破裂出血,应快速予以干预。在确定动脉瘤为出血病因后,应进行血管内介入治疗或开颅手术尽早处理动脉瘤。有学者认为,因可能的照射或对比剂带来的不良影响而延误处理或诊断,对孕妇和胎儿是不利的^[45]。大多数证据表明,女性在妊娠期颅内动脉瘤破裂的风险并未增加,大多数情况下建议对未破裂

的颅内动脉瘤进行保守治疗^[46]。

3. 妊娠相关高血压、可逆性后部脑病综合征和可逆性脑血管收缩综合征 妊娠期发生高血压相关脑出血应该以控制血压为重点^[47],有研究发现,血压 $\geq 135 \sim 140/85 \sim 90$ mm Hg 的患者目标血压为 $110 \sim 140/85$ mm Hg^[48]。子痫前期/子痫应按照目前的产科相关指南进行处理,包括硫酸镁治疗和快速胎儿分娩^[49]。当危及生命时应紧急清除颅内血肿或放置脑室外引流管。妊娠相关可逆性后部脑病综合征或可逆性脑血管收缩综合征可在 3 个月内完全消退,若出现相关缺血性或出血性卒中,可能导致患者发生不可逆性神经系统功能障碍^[50]。可逆性后部脑病综合征的治疗为,妊娠期和产后癫痫发作的女性可予以抗癫痫药物如地西洋或苯巴比妥控制发作;妊娠期合并子痫的女性先予以硫酸镁治疗,效果欠佳时再予以地西洋或苯巴比妥^[51]。可逆性脑血管收缩综合征的治疗包括去除病因、重症监护、缓解症状(如口服或静脉滴注尼莫地平)、控制血压以及预防癫痫发作。对发生严重血管痉挛的患者,应用侵入性血管内舒张剂和行球囊扩张术的适应证和有效性仍不明确^[52-54]。值得注意的是,为防止病情进一步恶化,可逆性后部脑病综合征或可逆性脑血管收缩综合征相关脑出血应避免使用皮质类固醇激素^[55-56]。

五、结论与展望

妊娠相关脑卒中是妊娠期和产褥期女性病死的重要原因,需产科、神经内科、神经外科等多学科合作。目前对于可能导致妊娠相关脑卒中的危险因素研究仍不充分,无法准确评估高危患者;此外,对于妊娠相关脑卒中的复发,特别是出血性卒中,亦未得到充分量化,使得临床医师难以向患者提出具体建议。子痫前期/子痫等复杂病理生理学机制及其对脑血流动力学的影响,尚待进一步研究。

利益冲突 无

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· 小词典 ·

中英文对照名词词汇(七)

细胞外信号调节激酶 extracellular signal-regulated kinase(ERK)	ordered subset expectation maximization(OSEM)
细胞因子释放综合征 cytokine release syndrome(CRS)	语义变异型原发性进行性失语 semantic variant primary progressive aphasia(svPPA)
小脑后下动脉 posterior inferior cerebellar artery(PICA)	语义性痴呆 semantic dementia(SD)
小脑前下动脉 anterior inferior cerebellar artery(AICA)	原发性进行性失语 primary progressive aphasia(PPA)
行为异常型额颞叶痴呆 behavioral variant frontotemporal dementia(bvFTD)	运动神经元病 motor neuron disease(MND)
Logopenic 型原发性进行性失语 Logopenic primary progressive aphasia (LPA)	载脂蛋白 E apolipoprotein E(ApoE)
兴趣区 region of interest (ROI)	早发性阿尔茨海默病 early-onset Alzheimer's disease(EOAD)
选择性雌激素受体调节剂 selective estrogen receptor modulators(SERMs)	早发性家族性阿尔茨海默病 early-onset family Alzheimer's disease(EOFAD)
血管紧张素 II angiotensin II (Ang II)	枕动脉 occipital artery(OA)
血管内皮生长因子受体 2 vascular endothelial growth factor receptor 2(VEGFR2)	枕动脉-小脑后下动脉 occipital artery-posterior inferior cerebellar artery (OA-PICA)
血管生成素-2 angiopoietin-2(Ang-2)	直接皮质电刺激 direct cortical stimulation(DCS)
血管性痴呆 vascular dementia(VaD)	直立性低血压 orthostatic hypotension(OH)
血管性血友病因子 von Willebrand factor(vWF)	中枢神经系统 central nervous system(CNS)
血-脑屏障 blood-brain barrier(BBB)	肿瘤电场治疗 tumor-treating fields(TTFields)
血压变异性 blood pressure variability(BPV)	肿瘤坏死因子-α tumor necrosis factor-α(TNF-α)
循环游离 DNA circulating free DNA(cfDNA)	肿瘤微环境 tumor microenvironment(TME)
循环肿瘤 DNA circulating tumor DNA(ctDNA)	蛛网膜下腔出血 subarachnoid hemorrhage(SAH)
循环肿瘤细胞 circulating tumor cells(CTCs)	椎动脉 vertebral artery(VA)
吲哚菁绿 indocyanine green(ICG)	总胆固醇 total cholesterol(TC)
吲哚菁绿荧光血管造影术 indocyanine green angiography(ICGA)	阻塞性睡眠呼吸暂停 obstructive sleep apnea(OA)
荧光素钠 fluoresceinsodium(FLS)	左旋多巴日等效剂量 levodopa equivalent daily dose(LEDD)
有序子集最大似然法	