

围绝经期女性伴发抑郁状态的诊疗进展

刘 婷, 熊正爱*

重庆医科大学附属第二医院妇产科, 重庆

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摘 要

围绝经期是女性卵巢功能衰退的关键阶段, 雌激素波动导致抑郁发生率显著升高。全球流行病学数据显示, 围绝经期抑郁(Perimenopausal Depression, PMD)患病率为33.9% (95% CI: 27.8%~40.0%), 我国门诊围绝经期女性抑郁症状检出率达37.9%。PMD不仅加重血管舒缩症状(VMS)及睡眠障碍, 还与心血管疾病风险升高相关。世界卫生组织(WHO)将PMD列为中老年女性健康管理的优先领域, 我国亦强调需关注PMD的早期识别。本文结合最新研究, 从筛查、诊断、生物标志物及治疗策略方面综述。

关键词

围绝经期抑郁, 筛查, 诊断, 治疗, 激素

Advances in the Diagnosis and Treatment of Depression in Perimenopausal Women

Ting Liu, Zhengai Xiong*

Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing

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Abstract

The perimenopausal period is a critical stage marked by the decline of ovarian function in women. Fluctuations in estrogen levels contribute to a significantly increased incidence of depression. Global epidemiological data indicate that the prevalence of perimenopausal depression (PMD) is 33.9% (95% CI: 27.8%~40.0%), with a detection rate of depressive symptoms reaching 37.9% among perimenopausal women in outpatient settings in China. PMD not only exacerbates vasomotor symptoms (VMS) and sleep disturbances but is also associated with an elevated risk of cardiovascular

*通讯作者。

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diseases. The World Health Organization (WHO) has identified PMD as a priority area for health management in middle-aged and older women, and China also emphasizes the need for early recognition of PMD. This article reviews the latest research, summarizing advances in screening, diagnosis, biomarkers, and treatment strategies for PMD.

Keywords

Perimenopausal Depression, Screening, Diagnosis, Treatment, Hormone

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1. 围绝经期抑郁的筛查与诊断

1.1. 筛查工具

筛查是早期识别 PMD 的关键环节,其准确性直接影响后续诊疗策略,自我报告的筛查量表是评估抑郁症状的重要工具[1] [2]。近几年针对围绝经期抑郁的特异性量表不断涌现,例如 2018 年 Kulkarni 等开发的“Meno-D”量表,以及 2023 年 Kim 等人开发的更年期情绪量表(MESQ)。此外,传统筛查量表如流行病学研究中心抑郁量表(CES-D)、汉密尔顿抑郁评定量表(HDRS)等仍在广泛应用,但研究者们不断对其在围绝经期女性中进行验证和优化。各种常用量表特点见表 1:

Table 1. Characteristics of commonly used scales
表 1. 常用量表特点

量表名称	条目数	适用场景	优势	局限性
CES-D [3]	20 项	流行病学调查	- 自评, 操作简便 - 内部一致性、可靠性和稳定性较高 (Cronbach's α 值约为 0.85)	- 不作为临床诊断工具
HAMD [4]	17/21 项	临床研究、 药物治疗评估	- 他评, 国际金标准 - 全面覆盖情感、躯体及认知症状 - 敏感性高(重症区分度好)	- 需至少两名专业人员进行评估 - 耗时长(15~30 分钟)
PHQ-9 [5]	9 项	初级保健筛查、快速 评估抑郁严重程度	- 自评, 耗时短(<5 分钟) - 与 DSM-IV 诊断一致性高	- 对重度抑郁症及其他情绪障碍 特异性低
SDS [6]	20 项	自评筛查、心理 健康初步评估	- 简单易行(10 分钟) - 文化适应性较强(多语言版本)	- 主观性强, 易受应答偏差影响 - 未区分抑郁亚型(如更年期 特异性症状)
Meno-D [7]	12 项	围绝经期特异性 抑郁评估	- 从五个维度评估围绝经期抑郁特异症状 - 5 个子量表内部一致性均较高 - 已在希腊人群验证[8]	- 尚未翻译成中文版本以及 在中国人群中验证
MESQ [9]	13 项	以情绪症状为主 的围绝经期抑郁	- 高度特异性(仅评估情绪症状, 能明确没有躯体症状的围绝经期抑郁)	- 仅在韩国人群中验证, 缺乏跨文化适应性研究

1.2. 诊断标准

诊断主要依据《美国精神疾病诊断与统计手册》(DSM-5)或《国际疾病分类》(ICD-11)中的标准: 1. 至少一项核心症状: 持续情绪低落或兴趣丧失 ≥ 2 周; 2. 大于等于四项附加症状: 睡眠障碍、疲劳、认

知功能下降等; 3. 鉴别诊断: 包括重度抑郁症、亚综合征抑郁症、适应障碍、心理困扰、丧亲、与双相情感障碍相关的抑郁发作和抑郁症的一般医学原因[10], 结合临床精神心理医生的结构化访谈[11]。近年来, 研究者们强调了对围绝经期抑郁症状特点识别, 如情绪波动、睡眠障碍等, 以提高诊断的准确性。

1.3. 生物标志物

PMD 的发生可能伴随某些生物标志物的升高, Hader 等人 2022 年发现高水平脑源性神经营养因子(BDNF)可能与急性细胞应激标志物热休克蛋白(HSP70)有关, 反映 BDNF 对细胞应激的代偿作用, 围绝经期女性抑郁发作时, 较高水平的 BDNF 提示近期存在细胞应激源, 由于衰老导致修复系统效率低, BDNF 的纠正效应未能在当前情绪评估中体现[12]。还有证据表明, 多环芳烃(PAHs)暴露与围绝经期女性抑郁风险呈剂量依赖性正相关, 提示环境污染物可能通过氧化应激或表观遗传机制影响神经内分泌功能[13]。最新研究发现, 围绝经期抑郁女性由于下丘脑垂体甲状腺轴负反馈调节功能障碍, 引起甲状腺激素水平的降低, 从而引起抑郁, 另外还提示同型半胱氨酸(Hcy)水平升高可能是症状加重的征兆[14]。

近年来, 围绝经期抑郁的诊断工具和标准不断更新, 特异量表的开发、生物标志物的发现以及对症状特点的深入研究, 为临床提供了更精准的诊断依据。未来, 结合诊断工具和生物标志物的综合诊断方法有望进一步提高诊断的准确性。

2. 围绝经期抑郁的治疗

围绝经期抑郁的治疗包括药物治疗、心理治疗和补充替代医学疗法。近年来, 治疗策略不断优化, 以下是对一些研究新进展的总结。

2.1. 药物治疗

2.1.1. 激素治疗

围绝经期女性出现抑郁症状的风险高于绝经前女性[15], PMD 的发病机制目前尚未明确, 但大多研究表明与雌激素波动密切相关, 例如, 有研究表明雌二醇水平波动会影响单胺氧化酶 A 的结合, 并通过影响大脑网络中的应激反应和情绪调节来增加女性患严重抑郁症的风险[16]。还能引起围绝经期症状如血管舒缩症状及睡眠障碍等间接导致情绪恶化[17], 开发治愈疾病的一种方法是确定发病机制, 然后根据根本原因进行治疗, 围绝经期抑郁的发生与雌激素波动关系紧密, 因此关于雌激素改善 PMD 的研究层出不穷。既往多项小型但设计严谨的临床试验表明, 对于明确诊断的围绝经期抑郁症患者, 雌激素治疗能显著改善其抑郁相关行为量表评分[18][19]。但一项基于韩国大型电子健康数据库的回顾性队列研究得出了不同结论, 该研究未发现激素治疗对抑郁、焦虑和睡眠障碍有显著的治疗效果, 甚至提示在更年期后期使用雌二醇可能对情绪产生负面影响。以上矛盾的内容可能反映了临床试验的理想环境与真实世界医疗实践的差异, 且研究结果受研究人群、研究时间等多种因素的影响[20]。相关指南如 2016 年加拿大情绪和焦虑治疗网络(CANMAT)成人重度抑郁症管理临床指南将透皮雌二醇推荐为 PMD 的二线治疗[21], 2018 年美国围绝经期抑郁的评估和治疗指南指出雌激素有抗抑郁的作用[10]。2023 版中国绝经管理与绝经激素治疗指南认为 MHT 可改善围绝经期女性的抑郁症状[22]。但传统认知中, 单用雌激素会增加子宫内膜癌、乳腺癌、血栓形成等风险[23]。但近期综述表明, 目前没有证据表明雌激素替代疗法会增加子宫内膜癌的风险, 且通过优化剂量、给药途径、治疗时长并把握合适的“治疗时间窗”, 可以显著降低甚至避免相关的乳腺癌及血栓形成风险[24]。

综上, 激素治疗对围绝经期抑郁的疗效并非对所有人均等。其效果在很大程度上依赖于“治疗时间窗”, 即对围绝经期早期(60 岁以下或绝经 10 年内)的女性效果最为显著[22], 对于绝经后期女性或非激

素相关性抑郁, 其疗效可能有限甚至无效, 这可能解释了部分真实世界研究出现阴性结果的原因。而且将激素治疗的副作用视为一个固定不变的概念是过时的。现代绝经管理的核心在于通过“个体化方案”将风险最小化。关键策略包括: 1. 选择经皮雌激素: 规避口服药物的血栓形成风险。2. 把握最佳“治疗时间窗”: 在窗口期内启动, 不仅不增加冠心病风险, 还可能带来心血管保护效益。3. 选用更安全的药物: 如替勃龙, 在保证疗效的同时, 兼顾了子宫内膜和乳腺的安全性[25]。

孕激素(也称黄体酮)是由卵巢黄体产生的类固醇激素, 被认为具有抗焦虑和抗抑郁作用, 其通过与孕酮受体或膜受体结合、代谢为 GABA 能神经递体、调节单胺类神经递质等途径来影响大脑中的情绪和行为回路[26]。围绝经期女性由于卵巢功能衰退, 导致分泌的孕激素减少, 容易引起焦虑和严重抑郁症状。Sovijit 等(2021)通过动物实验发现: 在卵巢切除(OVX)小鼠模型中, 黄体酮通过改变肠道微生物群组成来减轻抑郁和焦虑, 并显著增加肠道乳酸菌属丰度[27]。此外, Susser (2023)在综述中指出, 神经甾体别孕烯醇酮(Allopregnanolone)作为孕酮的关键代谢物, 通过调节 γ -氨基丁酸(GABA) A 受体活性, 在围绝经期生殖相关抑郁的改善中发挥核心作用[28]。还有研究表明, 微粉化孕酮口服给药时, 直接或通过其代谢物充当神经类固醇, 对大脑功能产生有益影响, 可缓解焦虑和抑郁症状, 缓解睡眠问题, 同时改善围更年期和更年期妇女的工作记忆[29]。以上研究表明, 孕激素通过神经内分泌、肠道菌群等多个途径改善抑郁, 未来单独用于治疗 PMD 的前景广阔。

近年来, 有研究还探索了其他激素治疗 PMD 的可能性。有研究表明, 对于单独使用标准激素替代治疗(HRT)仍有神经精神症状的围绝经期及绝经后女性, 加用经皮睾酮可以有效改善情绪症状, 可避免使用高剂量雌激素, 降低出现出血及乳房胀痛等雌激素副作用的风险[30]。FSH 与海马体上的促卵泡激素受体(FSHR)结合, 会诱发雄性小鼠抑郁行为; 并且通过敲低 FSHR 来选择性下调海马体中的 FSH 信号传导有助于预防 FSH 诱发的抑郁, 这些结果证实调节 FSH 的表达可能是预防经历激素波动的女性患抑郁症的一种潜在方法[31]。此外, 褪黑素可以通过阻断肠道内 *Alistipes inops* 导致的色氨酸-5 羟色胺代谢紊乱, 进而预防和缓解卵巢切除小鼠的抑郁样行为, 表明应用褪黑素抑制 *Alistipes inops* 可能是预防和缓解围绝经期抑郁症状的潜在策略[32]。

2.1.2. 传统抗抑郁药

当前指南一致推荐抗抑郁药为围绝经期抑郁的一线治疗, 包括: 选择性 5-羟色胺再摄取抑制剂(SSRIs)、5-羟色胺-去甲肾上腺素再摄取抑制剂(SNRIs)、非典型抗抑郁药、血清素调节剂、三环抗抑郁药和单胺氧化酶抑制剂(MAOIs), 其中 SSRIs 和 SNRIs 被推荐为首选用药[10][33][34]。目前的标准做法是开始使用 SSRI, 但如果在第一个月内没有充分(超过 50%)的反应, 则改用 SNRI [35]。既往两项为期 8 周的大型随机、双盲临床试验已证实去甲文拉法辛(SNRI) (50 mg/d 或 100~200 mg/d)能在短期显著改善围绝经期和绝经后妇女的抑郁症状[36][37]。有些抑郁药虽虽未经过大型临床试验验证, 但多项小型开放性标签试验已证实如艾司西酞普兰(10~20 mg/d)、度洛西汀(60 mg/d)、帕罗西汀(12.5~25 mg/d)等抗抑郁药在合适的剂量下对围绝经期抑郁有积极影响[38]-[40], 虽然单用抗抑郁药对不同基线水平的抑郁症都有效, 但其缓解率不同[35], 在重度抑郁症中, 已经提出了几种策略来增强对抗抑郁药的反应, 联合用药方案(如度洛西汀 60 mg/d 联合奥氮平 2.5~5 mg/d)在重度 PMD 患者中显示更优疗效, HDRS 评分降幅较单药组明显[41]。抗抑郁药联合心理治疗也被证实其疗效优于单独使用任何一种。还有研究发现, 对于伴有严重血管舒缩症状者, 短期联用透皮雌二醇可能增强抗抑郁效果[10]。

2.2. 补充和替代医学疗法

抗抑郁药物和激素虽然是围绝经期抑郁的主要治疗方法[10], 但二者带来的副作用促使许多围绝经

期女性考虑补充和替代医学疗法(CAMT), CAM 干预措施包括: 心身干预(如催眠、认知行为疗法[CBT]、放松、生物反馈、冥想和芳香疗法)和天然产品(如草药、维生素、矿物质和膳食补充剂)以及全系统替代医学方法(如中医、反射学、针灸和顺势疗法) [42]。

认知行为疗法通过结合认知干预和行为干预来改善患者的症状, 其核心在于教会抑郁症患者如何识别消极的思维模式, 并尝试用更健康、积极的想法来取代它们, 对轻中度抑郁尤其有效[43]。已有荟萃分析证实, CBT 能有效改善更年期女性抑郁症状, 但后续需进一步试验确定起效的最佳治疗次数[44]。针对难治性抑郁, 因患者症状过重, 通常无法配合心理治疗, 因此需要在药物治疗的帮助下才能起效[35]。基于正念的干预(MBI)是身心疗法的一种形式, 在西方国家越来越受到超过一半的女性的追捧, 为症状管理提供了更安全、更方便的选择[45]。早在 2021 年 Gordon 等人就通过一项为期 8 周的临床随机试验, 证实了基于正念的减压(MBSR)可防止更年期过渡期心境正常的女性出现抑郁症状[46]。一项纳入了 18 项研究的系统评价也验证了基于正念的干预能有效地改善围绝经期抑郁, 提出 MBI 未来可以作为辅助治疗[47]。

植物雌激素具有类似于哺乳动物雌激素的结构, 可以与雌激素受体结合以发挥各种有益作用, 例如抗氧化和抗炎活性[48]。类黄酮是人类饮食中最常见的植物雌激素, 其因为独特的药理活性和包括抗抑郁活性在内的有益健康作用而受到相当多的关注[49]。一项来自人群的随机对照试验和一项动物试验分别表明, 补充类黄酮可改善围绝经期妇女的抑郁症状和减轻围绝经期抑郁小鼠模型的抑郁样行为[50] [51]。槲皮素是一种类黄酮化合物, 是近些年研究较多的植物雌激素, 常见于许多蔬菜和水果中, 如洋葱、浆果和苹果, 多项动物实验通过研究不同机制均证实了槲皮素的抗抑郁作用[52]-[54], 其未来很有可能成为围绝经期抑郁症的有效预防和辅助治疗策略。

有研究表明 Amberen® (一种基于琥珀酸盐的非激素补充剂)联合 Smart B® (维生素 B)复合物可以改善睡眠和认知能力, 降低抑郁和焦虑, 改善情绪和健康状况, 并对生活质量产生积极影响[55]。还有证据表明, 膳食补充叶酸、维生素 B12 和 S-腺苷-L-蛋氨酸(SAMe)对轻度情绪障碍患者有益[56]。

近年研究表明, 中药对改善 PMD 有一定作用。一项随机对照试验证明, 与安慰剂组相比, 口服香芍颗粒(12 g/d)的研究组的抑郁症状明显缓解[57]。此外, 多项动物试验显示, 中药复方(如柴胡疏肝散、桃红四物汤、养阴宁神方、二仙汤)通过调节神经内分泌、神经递质及肠道菌群等途径, 对 PMD 表现出显著疗效[58]-[61]。但以上多数研究主要依赖动物模型, 临床转化证据不足, 且中药复方成分复杂, 作用机制尚未完全阐明, 缺乏标准化制剂及长期用药安全性评估。未来需结合现代技术(如脑成像、代谢组学)解析作用靶点, 开发标准化复方, 并通过多中心临床试验验证其疗效及安全性, 以推动中药在围绝经期抑郁治疗中的临床应用。

针灸在 PMD 患者中的有效性和安全性已经得到证实[62], 一项临床研究表明, 选穴“百会、太冲、三阴交”进行针灸, 每周 3 次, 8 周后 HDRS 评分降低 40% [63]。此外, 一篇系统综述已提供证据证明针灸在降低 HAMD 总体评分的效果优于或与抗抑郁药相当, 表明针灸可能对 PMD 有中长期治疗效果, 肯定了针灸独立治疗 PMD 的有效性及安全性[64]。相比单用针灸, 还有研究表明联合中药更能改善患者的抑郁症状[65] [66]。

其他的替代治疗方法包括瑜伽[67]、体力活动[68]、足部反射疗法[69]、太极拳训练[70]等均被证实可以改善围绝经期抑郁症状。

由于围绝经期抑郁机制和症状的特殊性, 其机制涉及性激素、神经内分泌系统及下丘脑-垂体-肾上腺(HPA)轴, 雌激素水平波动直接影响 5-HT、NE、DA 等神经递质系统, 同时激活 HPA 轴, 导致情绪障碍(焦虑、抑郁)与躯体症状(潮热、失眠)交织, 导致单一疗法难以全面覆盖, 因此近些年倾向于研究联合用药的疗效, 以期能达到增效及减少药物副作用的效果。已有临床随机对照试验表明传统抗抑郁药、

激素及心理治疗两两联合比单药或单用心理治疗对改善 PMD 的效果更佳[71][72], 而且使用微量激素及小剂量的抗抑郁药不仅增加药物疗效, 还能降低药物不良反应, 未来有望在临床广泛推广[73]。

3. 结论

PMD 的筛查主要依赖于自评量表, 但必须根据个体情况进行个性化选择, 甚至可能需要联合使用多种量表。诊断主要依靠《美国精神疾病诊断与统计手册》(DSM-5)或《国际疾病分类》(ICD-11)中的标准及临床医师结构化访谈。展望未来, 基层保健单位应配备专业的精神心理医师或者对妇产科医师开展专业培训, 加强临床医师对围绝经期抑郁的识别能力。目前, 主流的药物治​​疗包括 SSRIs、SSNRIs 及 HRT 等, 这些药物的单独使用或联合应用均显示出治疗效果。此外, 非药物治疗, 如认知行为疗法、正念干预、草药、维生素、中药以及针灸等, 已被证实对缓解 PMD 相关的抑郁症状同样有效, 未来有望得到更广泛的推广和应用。

4. 临床实施的挑战与展望

尽管围绝经期抑郁(PMD)的诊疗策略日益丰富, 但在中国临床实践中, 其有效实施仍面临诸多挑战。未来发展的关键在于推动筛查工具的本地化、构建高效的多学科协作模式, 并加强以患者为中心的共同决策。

目前, 国际上多个围绝经期抑郁特异性量表(如 Meno-D、MESQ)显示出良好的应用前景, 但其在我国人群中的适用性仍需系统验证[7][9]。直接翻译而不进行文化调适可能导致量表条目难以被准确理解, 影响筛查的信度和效度。因此, 未来的核心任务之一是遵循标准的跨文化调适流程, 对上述量表进行翻译、回译及文化调试, 并在此基础上开展大样本、多中心的流行病学调查, 以建立适用于中国围绝经期女性的常模和界值。同时, 在基层医疗机构中, 可考虑将经过充分验证的通用量表(如 PHQ-9)与更年期症状量表结合使用, 作为初步筛查的务实策略, 并逐步推广更具特异性的评估工具。

PMD 的病因涉及生理、心理及社会多个层面, 单一科室的诊疗模式难以满足其复杂需求。构建“妇产科-精神心理科-全科/基层医疗-社区支持”的多学科协作(MDT)网络至关重要。具体策略包括: 在综合医院层面, 建立 PMD 的联合门诊或诊疗绿色通道, 由妇产科医生负责内分泌评估与激素治疗, 精神科医生负责精神心理诊断、严重度评估及抗抑郁药处方, 心理治疗师提供规范的心理干预。在基层医疗层面, 应加强对全科医生和妇产科医生的专项培训, 提升其对 PMD 的识别与初步处理能力, 并建立清晰的双向转诊路径, 确保复杂病例能及时获得专科支持。

许多中国围绝经期女性对抑郁症状存在“病耻感”, 同时对激素治疗持有“致癌”等根深蒂固的恐惧观念[23][24]。这要求临床工作者必须将患者教育和共同决策置于核心位置。首先, 应开发基于循证证据、语言通俗易懂的患教材料(如手册、短视频), 明确解释 PMD 的生物学基础、各种治疗方案的获益与风险, 尤其要澄清现代 MHT 在“治疗时间窗”内及个体化方案下的安全性。其次, 在临床决策时, 医生应使用决策辅助工具, 与患者充分讨论其症状特点、个人价值观与治疗偏好, 共同制定治疗方案。例如, 对于伴有严重潮热、失眠且对传统抗抑郁药有顾虑的早期围绝经期女性, 可共同探讨经皮雌激素或替勃龙的治疗价值; 而对于主要诉求为心理支持的患者, 则应引导其接受认知行为疗法等干预。

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