

绝经后子宫内膜增厚的治疗进展

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摘要

超声检查是一种无创、方便、准确的检测技术, 临床上常将其用于筛查有无内膜病变。对于通过超声检查发现的绝经后子宫内膜增厚妇女进行进一步有创性检查的时机, 在绝经后有异常子宫出血和无症状患者中存在差异。在临床实践中, 对于绝经后有异常子宫出血的患者进行有创性检查的时机较为明确, 但对于绝经后无症状的内膜增厚及绝经后接受激素治疗的内膜增厚患者进行有创性检查的时机尚存争议。故本文就绝经后子宫内膜增厚的治疗进展做一综述。

关键词

绝经后期, 子宫内膜, 子宫出血, 激素替代治疗, 他莫昔芬

Treatment in Endometrial Thickening of Postmenopausal Women

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Abstract

Ultrasonography is a non-invasive, convenient and accurate detection technique, which is often used in clinical screening for endometrial lesions. The timing of further invasive testing for postmenopausal women with endometrial thickening detected by ultrasound varies between postmenopausal and asymptomatic patients with abnormal uterine bleeding. In clinical practice, the timing of invasive examination for postmenopausal patients with abnormal uterine bleeding is relatively clear, but the timing for postmenopausal asymptomatic endometrial thickening and post-

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menopausal hormone therapy patients with endometrial thickening remains controversial. Therefore, this article reviews the treatment progress of postmenopausal endometrial thickening.

Keywords

Postmenopause, Endometrium, Uterine Hemorrhage, Hormonal Replacement Therapy, Tamoxifen

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1. 引言

绝经后妇女因卵巢内分泌功能衰退, 子宫内膜呈菲薄状态, 当超声检查测量其子宫内膜厚度(endometrial thickness, ET) ≥ 5 mm 临床上诊断为子宫内膜增厚[1] [2]。绝经后子宫内膜增厚可见于子宫内膜息肉、黏膜下子宫肌瘤、宫腔粘连、子宫内膜炎、不典型增生(atypical hyperplasia, AH)及子宫内膜癌(endometrial cancer, EC)等病变[2], 也可能是卵巢内分泌功能一过性波动所致。绝经后子宫内膜增厚根据患者有无绝经后异常子宫出血在临床上常分为有症状者和无症状者。目前, 经阴道超声测量的绝经后妇女子宫内膜厚度已成为预测 EC 风险的重要筛查指标之一[3] [4]。当测量的 ET 达到一定的临界值, 可提示患者需进行侵入性检查(子宫内膜活检和刮宫)排除或诊断 AH 及 EC [5]。虽然有无症状的绝经后子宫内膜增厚患者内膜恶性病变发生率均低于良性病变, 且两者内膜恶性病变发生比例存在差异[6], 但在临床实践中, 无论其有无症状, 大多数被建议行进一步侵入性检查以诊断或排除 AH 及 EC。而临床上, 对于无症状或接受激素治疗的绝经后子宫内膜增厚患者是否应接受进一步有创性检查及其接受有创性检查的 ET 临界值等尚有争议[2] [7] [8]。因此, 本文就近年来关于绝经后子宫内膜增厚的治疗进展作一综述, 旨在阐述绝经后子宫内膜增厚妇女进行侵入性检查的时机, 以期减少临床工作中对这部分患者的过度诊疗和医疗资源的浪费。

2. 绝经后有症状的子宫内膜增厚患者特点及治疗

绝经后有症状的子宫内膜增厚患者多数为良性疾病, 少数为 AH 及 EC [9]。正如 Yao 等[6]研究表明, 在 202 例绝经后有症状的子宫内膜增厚患者中, AH 及 EC 的比例为 24.7%; 相似地, 李灿等[2]对 124 例绝经后有症状的子宫内膜增厚患者的临床病例资料进行分析指出, AH 及 EC 占 22.58%。2018 年美国妇产科协会(American College of Obstetricians and Gynecologists, ACOG)提出绝经后出现阴道流血需及时有效的进行评估以排除或诊断 AH 及 EC, 推荐将经阴道超声检查(transvaginal ultrasonography, TVS)作为评估初次绝经后阴道出血患者的首选方法[7]。TVS 测量 ET 可用来评估绝经后有症状患者是否需行进一步侵入性操作(如诊断性刮宫、子宫内膜活检、宫腔镜检查等) [10] [11] [12]。

为摸索在绝经后有症状患者中预测 AH 和 EC 风险的 ET 临界值, 国内外学者进行了大量研究。我国学者研究表明, 在 4383 例绝经后有症状患者中, ET 临界值为 3 mm、4 mm 和 5 mm 检测子宫内膜癌的敏感性分别为 97.0%、94.1%和 93.5%, 这些阈值对应的特异性分别为 45.3%、66.8%和 74.0%, 考虑其敏感性, 建议将预测绝经后有症状者子宫内膜恶性病变的 ET 临界值定为 3 mm [13]。然而除敏感性外, 还需考虑其特异性; 正如 Long 等[14]进行的一项包括了 44 项研究共纳入 17,339 名女性的荟萃分析发现, 对于绝经后有症状妇女, ET ≥ 5 mm 与 ET ≥ 3 或 4 mm 相比, 将降低 17%的侵入性检查率(如子宫内膜活

检、宫腔镜检查、诊刮等),在具有相似的敏感度的同时,对 EC 有更高的特异性(51.5% v.s 46.0% v.s 42%)。

然而多项研究表明,在绝经后有症状患者中,仅关注 ET 似乎是不恰当的。除内膜厚度外,年龄也是重要的参考因素;2020 年 Clarke 等[15]研究发现,在绝经后有症状者中,年龄 ≥ 60 岁且 $ET > 4$ mm, AH 及 EC 占 22.3%,年龄 < 60 岁, $ET > 4$ mm, AH 及 EC 比例为 8.4%;而年龄 ≥ 60 岁且 $ET \leq 4$ mm 的 48 例绝经后有症状者中 AH 及 EC 的发生率仍有 4.2%,而年龄 < 60 岁且 $ET \leq 4$ mm 的 74 例绝经后有症状者中未发现 AH 及 EC,由此建议对年龄 ≥ 60 岁,或年龄 < 60 岁且 $ET > 4$ mm 的绝经后有症状患者行进一步活检。此外,出血的持续时间和频率也是需要关注的;2018 年 AOCG 提示对于持续或反复的绝经后子宫出血者提倡行子宫内膜组织学检查,并且 $ET < 3$ mm 也可能存在子宫内膜癌(尤其是 II 型) [7];再此基础上,有学者认为对于 TVS 测量 $ET \leq 4$ mm 的绝经后有症状者无需进一步检查,除非存在反复出血,而 $ET > 4$ mm 的绝经后有症状者建议对子宫内膜进行取样[16]。

3. 绝经后无症状的子宫内膜增厚患者特点及治疗

随着女性健康意识的提高,临床上偶然发现无症状的绝经后子宫内膜增厚患者检出率增多。多项国内外研究表明,此类患者子宫内膜恶性病变发生率明显低于有症状者。正如,徐茜茜等[17]报道,在 117 例绝经后无症状的子宫内膜增厚妇女中 AH 及 EC 占 1.7%,明显低于 98 例绝经后有症状的子宫内膜增厚患者(21.4%)。相似地,在其他研究中,绝经后无症状的子宫内膜增厚者 AH 及 EC 发生率大多在 3.6%~8.5% [14] [18] [19] [20]。

绝经后妇女 ET 增加,患子宫内膜癌的风险增加[21] [22]。通过测量 ET 预测患 AH 及 EC 的风险,发现绝经后无症状患者的 ET 临界值比绝经后有症状者的明显升高。正如,2004 年 Smith-Bindtman 等[23]报道,ET 为 11 mm 的绝经后无症状患者与 ET 为 5 mm 的 PMB 者罹患 EC 的风险相当;在 $ET > 11$ mm 的绝经后无症状患者中 EC 的发生率约为 6.7%,而在 $ET \leq 11$ mm 的绝经后无症状患者中 EC 的发生率极低(0.002%),认为 11 mm 可作为绝经后无症状者判断患者是否需进行侵入性检查的 ET 临界值。后续研究也有相似结论[20] [24]。然而,有学者研究得出与此不同的 ET 临界值,分别为 8、9、10 及 12.5 mm [1] [18] [25] [26]。

除此之外,Gemer 等[27]研究发现,绝经后无症状子宫内膜增厚患者确诊为 EC 与有症状者相比生存率无明显差异;认为偶然发现的绝经后无症状的子宫内膜增厚患者不应接受侵入性检查,建议 3 个月复查超声,若患者出现异常子宫出血或持续性子宫内膜增厚,可进一步行侵入性检查,若无此类情况,可定期随访。而有学者提出了不同观点,建议 $ET \geq 10$ mm 的绝经后无症状妇女,行进一步子宫内膜活检或宫腔镜检查;而 ET 为 4~10 mm 的绝经后无症状妇女,需结合考虑其是否合并子宫内膜癌高危因素(如肥胖、不孕、糖尿病、高血压、无拮抗性雌激素等)和超声检查其余异常(如囊性子宫内膜、宫腔积液、疑似息肉或其他可疑特征) [28]。相似地,Li 等[8]研究指出,考虑到在绝经后无症状妇女中早期诊断子宫内膜癌与其更高的生存率无关,认为对无 EC 危险因素且 $ET < 10$ mm 的绝经后无症状的子宫内膜增厚妇女暂观察随访或许是可行的。

4. 绝经后接受激素治疗的子宫内膜增厚

4.1. 绝经后接受激素替代治疗的子宫内膜增厚

随着对更年期保健意识的提高,接受激素替代治疗(Hormone replacement therapy, HRT)的绝经后妇女增多。国外研究提出接受 HRT 出现异常子宫出血的妇女发生子宫内膜癌的风险明显低于未接受激素治疗的妇女[29]。此类妇女出血的常见原因是依从性差、肝病、药物相互作用、良性妇科疾病(如子宫内膜或宫颈息肉、宫颈炎)和非妇科疾病(如尿道或直肠等) [30]。1997 年 Hänggi 等[31]比较了三种激素替代治疗

方案(口服微量 17β -雌二醇/口服序贯地屈孕酮、经皮注射 17β -雌二醇/口服序贯地屈孕酮、口服替勃龙)和未接受激素替代治疗的患者的安全性,发现 TVS 检测的 ET 与子宫内膜活检结果有较好的相关性,ET < 5 mm 病检结果提示子宫内膜不活跃或萎缩、或是样本量不足以进行组织病理学诊断,未发现子宫内膜恶性病变,由此认为 5 mm 作为预测子宫内膜恶性病变的 ET 临界值,可避免 75%的无意义活检。而在 Mossa 等[32]调查了 587 例接受 HRT 妇女的研究中发现,接受 HRT 患者出现子宫内膜增厚(ET $\geq$ 5 mm)和出血发生率增加,但并不一定增加其子宫内膜癌的发病率;建议接受 HRT 有异常子宫出血的妇女,当 ET > 8 mm 时进行宫腔镜检查 and 活检。然而,2021 年国外学者[33]认为,在接受序贯方案的 HRT 妇女中,若服药过程中出现异常子宫出血,应本周期孕激素治疗结束后再进行超声检查;提出对于绝经后接受 HRT 的妇女,初次出现异常子宫出血且 ET $\leq$ 4 mm,不必急于行有创性检查;对于反复异常出血或 ET > 4 mm,建议进行侵入性检查(如宫腔镜检查和子宫内膜活检)。

4.2. 绝经后接受他莫昔芬的子宫内膜增厚

他莫昔芬(tamoxifen, TAM)是一种选择性雌激素(ER)受体调节剂。TAM 作为辅助治疗用于 ER 受体阳性乳腺癌的患者,可治疗转移性乳腺癌,也可降低存在乳腺癌高风险妇女的乳腺癌发病率[34]。研究表明,由于 TAM 具有子宫内膜的雌激素活性,与正常人群相比,TAM 治疗使患 EC 的相对风险增加[35]。1997 年国外学者[36]研究发现,在他莫昔芬治疗组与未治疗组就患子宫内膜癌危险因素无统计学显著差异的背景下,经 TAM 治疗的绝经后组的子宫内膜厚度和子宫大小分别显著大于未治疗组,经 TAM 治疗的绝经后患者的组织病理学明显异常(22/33, 66.7%),其中 4 例(12.1%)为子宫内膜癌前或恶性病变,因此认为 TAM 与绝经后子宫内膜癌前或恶性病变有关;建议将 TVS 作为使用他莫昔芬 2 年以上的绝经后妇女子宫内膜病变的筛查工具,即使是无症状者;且绝经后 ET 异常或有症状者应行刮宫或宫腔镜检查以发现子宫内膜病变。

2014 年美国妇产科医师协会提出,使用 TAM 的乳腺癌妇女应该在出现异常阴道出血或血性分泌物等情况下进一步检查,尤其是绝经后妇女应密切监测有无 EC 等相关症状[34]。相似地,2018 年国外学者研究发现,在至少接受 12 个月 TAM 治疗且 TVS 检查 ET $\geq$ 4 mm 的 31 例无症状绝经后女性中,AH 及 EC 的发生率为 6.5%;认为所有接受 TAM 治疗乳腺癌的绝经后女性都应该定期行 TVS 评估子宫内膜,如果出现子宫出血或内膜增厚,则需行宫腔镜检查[37]。2021 年我国抗癌协会肿瘤内分泌专业委员会提出,对于使用 TAM 的绝经后乳腺癌妇女,若有阴道出血或分泌物增多需积极行 TVS 评估子宫内膜;而无症状者,6~12 个月随访 TVS,若 ET $\geq$ 8 mm,则需进一步行宫腔镜等检查排除有无子宫内膜病变[38]。

5. 结语

综上所述,在绝经后子宫内膜增厚妇女的临床治疗中,需兼顾 ET 预测内膜病变风险的敏感度和特异度,并根据其个体情况及对疾病认知、依从性等综合制定诊疗方案。在诊治过程中,应考虑到有无症状的绝经后妇女患 EC 的风险差异及侵入性检查带来的医疗资源浪费及经济负担。对于绝经后有异常子宫出血的内膜增厚者,应积极进行有创性检查以排除 AH 和 EC。对于绝经后无异常子宫出血的内膜增厚患者,不建议常规进行有创检查,多数可随访超声检查;但当其 ET $\geq$ 10~11 mm,或存在以下任意一个或多个情况(如 EC 高危因素、出现异常子宫出血、持续子宫内膜增厚、超声检查内膜有其余异常等)需进行宫腔镜下子宫内膜活检等检查。对于接受 HRT 的绝经后子宫内膜增厚妇女,需结合考虑其接受的 HRT 方案综合分析,若存在异常子宫出血或 ET $\geq$ 5 mm,建议行子宫内膜活检。对于接受 TAM 的绝经后乳腺癌患者,常规 6~12 个月进行 TVS 监测子宫内膜,若 ET $\geq$ 8 mm,建议进一步行宫腔镜等检查,若随访期间出现异常子宫出血等症状,可随时进行 TVS。

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