

多囊卵巢综合征与桥本氏甲状腺炎共病的研究进展

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摘 要

多囊卵巢综合征(polycystic ovary syndrome, PCOS)和桥本甲状腺炎(Hashimoto's thyroiditis, HT)均为育龄期女性常见的内分泌代谢紊乱性疾病。临床观察发现, PCOS与HT具有相似的临床表现。近年来, 越来越多的研究证实, PCOS女性中HT的发生率明显高于一般人群, 二者共病将进一步加重生殖障碍和代谢紊乱。提示这两种疾病之间可能存在某种关联, 但内在的病理生理机制尚不清楚。探讨PCOS与HT之间的相互关系对PCOS的临床管理具有重要意义。

关键词

多囊卵巢综合征, 桥本甲状腺炎, 生殖代谢影响

Research Progress of Comorbidity of Polycystic Ovary Syndrome and Hashimoto's Thyroiditis

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Abstract

PCOS and HT are common endocrine and metabolic disorders in women of childbearing age. Clinical

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observations show that PCOS and HT have similar clinical manifestations. In recent years, more and more studies have confirmed that the incidence of HT in women with PCOS is significantly higher than that in the general population, and the comorbidity of the two further aggravates reproductive disorders and metabolic disorders. It is suggested that there may be some correlation between the two diseases, but the underlying pathological and physiological mechanism is still unclear. It is of great significance to explore the interrelationship between PCOS and HT for the clinical management of PCOS.

Keywords

Polycystic Ovary Syndrome, Hashimoto's Thyroiditis, Effects on Reproduction and Metabolism

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1. 引言

多囊卵巢综合征(polycystic ovary syndrome, PCOS)是一种高度异质性的生殖内分泌系统疾病,以稀发或无排卵、雄激素过多、卵巢多囊形态(polycystic ovarian monography, PCOM)为主要特征。据统计,PCOS影响10%~13%的女性[1]。甲状腺功能减退症(简称甲减)是育龄期女性的另一常见内分泌代谢性疾病,在碘充足地区,女性甲减最常见的病因是自身免疫性甲状腺疾病(autoimmune thyroid diseases, AITD)。桥本甲状腺炎(Hashimoto's thyroiditis, HT)为最常见的AITD类型,是一种以淋巴细胞浸润甲状腺组织、甲状腺自身抗体(ATA)水平升高为特征的器官特异性自身免疫疾病[2]。

HT与PCOS在临床表现上存在相似之处,都可能出现月经紊乱、不孕、孕产期母儿不良并发症、脂质代谢异常等情况。大量研究显示,PCOS患者易合并HT,然而共病是否影响PCOS女性的激素分泌和代谢健康,以及两种疾病内在的关联机制目前仍不清楚。因此,本文中我们将总结国内外近年来有关文献,对PCOS与HT共病的临床现状、对生殖和代谢等多方面的影响进行探讨。

2. PCOS与HT共病的临床现状

2004年,Janssen等人[3]的一项前瞻性多中心研究首次描述了PCOS与AITD的相关性,发现AITD在PCOS育龄期女性中的发生率约为非PCOS人群的三倍(26.9% vs. 8.3%);且PCOS组患者拥有更高的促甲状腺激素(TSH)水平,10.9%的PCOS组女性血清TSH超过正常参考范围上限,对比非PCOS组中仅为1.8%。PCOS不同表型之间甲状腺过氧化物酶抗体(TPOAb)阳性率尚未发现差异[4]。一项大型荟萃分析纳入了13项研究,包括1210例PCOS患者和987例健康受试者,结果显示,AITD在PCOS组和对照组中的发生率分别为26.03%和9.72%,PCOS患者发生AITD的风险增加(OR = 3.27, 95% CI: 2.32~4.63, $p = 0.07$);按照地区分布进行分析,发现亚洲PCOS女性中AITD的发生率高于欧洲和南美洲[5]。不同研究中共患率的差异可能受研究对象的种族、年龄以及PCOS和HT诊断标准不同的影响。近期,Benelli等人[6]发现,PCOS-A型和B型女性ATA阳性率高于其他表型,可能与该两种表型的患者体内更严重的雌、孕激素水平失衡有关。除PCOS患者中HT的患病率明显高于一般人群外,HT人群发生PCOS的风险同样增加[7]-[9]。在我国台湾一项大型研究中,纳入了1332名新诊断的HT女性,按照年龄和合并症以1:2匹配对照组,平均随访6.69年,结果显示,与对照组相比,HT组患者中PCOS的发生风险更高(HR = 2.37, 95% CI = 1.22~4.62; $p < 0.05$) [10]。上述研究结果为这两种疾病存在共患倾向提供了有力证据。

3. PCOS 与 HT 共病对女性生殖功能及激素水平的影响

如今我们已充分认识到 PCOS 影响女性生殖系统健康, 包括出现月经不规律、不孕、妊娠并发症, 以及子宫内膜增生甚至子宫内膜癌的风险增加等。此外, 心理障碍及代谢异常贯穿 PCOS 患者的生命全程, 共同导致生活质量下降[11]-[15]。HT 本身的自身免疫异常及潜在的甲减风险可能进一步恶化 PCOS 患者内分泌紊乱和生殖结局。

3.1. 生殖障碍及妊娠并发症

PCOS 是女性排卵障碍性不孕的最常见原因[16]-[18], 同时由于性激素比例失衡、胰岛素抵抗、黄体功能不全、血栓形成倾向等一系列复杂病理变化, PCOS 女性为自然流产及复发性流产高风险人群[19][20]。然而, PCOS 与妊娠丢失是否独立相关尚未得到证实[21]。即便成功妊娠, PCOS 女性发生妊娠期糖尿病(GDM)、高血压疾病和早产等妊娠并发症的风险增加, 并可能使后代更易患生殖代谢疾病[22][23]。

越来越多的证据表明, 自身免疫过程在多个层面影响女性的生殖结局[24]。HT 女性不孕症风险增加的病理生理机制尚未完全阐明[25]。除 PCOS 外, 甲状腺自身抗体与不孕症的其他多种原因同样具有相关性, 包括子宫内膜异位症、卵巢储备功能减少等[26]-[28]。近期一项研究通过检测接受体外受精治疗(IVF)的不孕女性(38 例 HT 患者, 23 例对照组)的卵泡液, 发现 HT 组患者卵泡液中多种代谢物水平显著高于对照组, 进一步生信分析表明这些差异代谢物通过 α -亚麻酸、鞘脂代谢等途径调节卵巢功能, 提示 HT 女性卵泡液的代谢特征发生变化[29]。HT 一方面可推迟受孕, 增加衰老相关的妊娠丢失; 另一方面通过 ATA 直接浸润卵巢, 或与其他自身免疫性疾病共存, 导致母体免疫耐受受损, 以及甲状腺激素相对缺乏, 共同导致 HT 女性不良妊娠结局的发生风险增加[30]。

已有研究证实合并 HT 可能进一步降低 PCOS 女性的生育能力, 对育龄期女性造成了极大的困扰。Serin 等人[31]的研究发现, 合并 HT 的 PCOS 组女性的生育率降低(17.4% vs 单纯 PCOS 组 43.5%)。目前关于合并 HT 对 PCOS 女性妊娠结局和母儿并发症影响的研究数据较少。我国一项研究对 486 名接受 IVF/ICSI(卵胞浆单精子注射)的 PCOS 女性进行回顾性分析发现, 母体孕前 TPOAb 水平与新生儿的出生体重存在相关性, 但在单胎妊娠和双胎妊娠中呈现出相反的趋势, 母体孕前 TPOAb 水平与单胎出生体重呈负相关, 与双胎出生体重呈正相关, 推测母体甲状腺自身免疫异常可能导致 PCOS 女性双胎妊娠的新生儿脂质蓄积[32]。甲状腺自身免疫状态是否影响及如何影响新生儿出生体重有待未来更广泛的研究。

抗苗勒氏管激素(AMH)是转化生长因子 β (TGF- β)超家族成员, 由窦前卵泡和小窦卵泡的颗粒细胞分泌, 是预测和评估卵巢储备功能的首选指标, 但国际上尚缺乏 AMH 正常参考值范围, 且 AMH 受年龄、BMI、种族、月经周期等多种因素的影响, 临床应用受限[33]。PCOS 患者血清 AMH 水平升高, 高水平 AMH 有助于成人 PCOS 的诊断[1]。多项研究结果显示, HT 女性的 AMH 水平低于健康对照组, 但真正影响 AMH 水平的是相对较高的 TSH 水平还是甲状腺自身免疫, 目前仍然存在争议。Weghofer 等人[34]的研究中, 调整 ATA 水平和年龄后, 高水平 TSH ($\geq 3.0 \mu\text{IU/ml}$)组不孕女性的 AMH 血清浓度仍显著低于低水平 TSH 组($p = 0.02$), 表明较低的 TSH 水平对卵泡募集有直接的有益作用, 该效应是甲状腺功能依赖性的, 而不是甲状腺自身免疫的结果。Tuten 的团队[35]报道了 HT 与 AMH 水平升高有关, 需要注意的是, 该研究的研究对象为接受左旋甲状腺素(L-T4)替代治疗的 HT 甲减女性, HT 组与健康对照组的 TSH、FT4 水平相当, HT 组女性具有更高的 FT3 水平。但是由于缺少 L-T4 治疗前甲功水平, 不能除外 HT 女性补充 L-T4 导致的 AMH 升高, 我们可以猜想 HT 女性 AMH 水平的下降可能在一定程度上是可逆的。事实上, 由于 TPOAb 与 TSH 水平密切相关[36], 区分甲状腺功能和自身免疫对 AMH 的独立影响存在困难, 甲状腺功能和甲状腺自身免疫可能通过不同的途径影响女性生育力。合并 HT 的 PCOS 女性具有相对较低的 AMH 水平。土耳其一项研究纳入了合并与未合并 HT 的 PCOS 患者各 46 名, 发现 PCOS-

HT 组患者 AMH 水平显著低于 PCOS-非 HT 组, 且在 PCOS-HT 组中, 血清 AMH 浓度与 TPOAb 水平呈负相关($r = -0.294$, $p = 0.047$); 根据 HT 病程长短进行亚组分析, 结果显示, HT 病程不足 2 年组患者的 AMH 水平高于 HT 病程超过 2 年者, 且 AMH 水平与 HT 持续时间呈负相关($r = -0.418$, $p = 0.004$) [31]。因此, 学者们推测甲状腺自身免疫进一步降低了 PCOS 患者的卵巢储备功能, 并且卵巢更多地暴露于甲状腺自身抗体可能导致卵巢破坏, 建议合并 HT 的 PCOS 患者应在进行全面评估后尽早确定生育治疗方案和控制卵巢早衰。

3.2. 性激素水平

PCOS 女性下丘脑 - 垂体 - 卵巢(HPO)轴功能失衡, 激素紊乱表现为黄体生成素(LH)/卵泡刺激素(FSH)比值增加、高雄激素血症, 以及持续无排卵所致的雌激素/孕激素比例异常。现已证实垂体 - 甲状腺轴和垂体 - 卵巢轴之间存在相互调节[37]。甲状腺自身免疫是否改善或加重 PCOS 女性的性激素紊乱, 目前尚缺少高质量研究。有研究报道, PCOS 女性中血清雌二醇浓度与 TPOAb 水平之间存在相关性[38], 表明高浓度雌二醇可能直接参与 PCOS 女性的甲状腺自身免疫过程。德国一项研究纳入了合并 HT 的 PCOS (PCOS-HT 组)女性 190 名, 单纯 PCOS 女性 637 名, 所有受试者甲功正常, 发现 PCOS-HT 组高雄激素血症、多毛症的患病率均低于单纯 PCOS 组, 同时具有较低的睾酮水平, 提示合并 HT 可能是 PCOS 患者高雄激素血症的保护因素[39]。本研究中 HT 的诊断标准更为严格, 要求至少满足以下三个标准中的两项, “TSH 高于正常参考值范围上限($2.5 \mu\text{IU/ml}$)、TPOAb 和/或 TGAb 滴度升高、甲状腺超声低回声性质”, 因此并不能明确是甲状腺自身免疫还是亚临床甲减实际影响的雄激素水平, 还需要我们进一步研究探索。

4. PCOS 与 HT 共病对代谢健康的影响

PCOS 的代谢改变一直是相关领域的研究热点。现已证实 PCOS 是早发 2 型糖尿病(T2DM)的重要危险因素[40]-[42]。澳大利亚一项基于人群的纵向研究(ALSWH)数据显示, PCOS 女性无论年龄和 BMI 水平, 患 T2DM 的风险均增加[12]。胰岛素抵抗(IR)和代偿性高胰岛素血症是 PCOS 症状和代谢并发症恶化的基础, IR 影响 75%~95%的 PCOS 女性[43]。目前甲状腺功能障碍(甲减或亚临床甲减)与糖脂代谢异常相关的证据已较为充分, 但甲功正常的 HT 是否影响患者代谢健康研究数据较少。一项研究纳入 91 例 HT (甲减组 42 例, 甲功正常组 49 例)、健康对照组 50 例, HT-甲减组、HT-甲功正常组和对对照组的总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)、空腹胰岛素(FINS)、稳态模型胰岛素抵抗指数(HOMA-IR)水平依次降低, 且差异均具有统计学意义($p < 0.05$), 而三组组间空腹血浆葡萄糖(FPG)和餐后 2 h 血浆葡萄糖(2h-PBG)水平未发现显著差异[44]。

Kim 等人[45]的研究共纳入 210 例甲功正常的 PCOS 女性(其中 13 例合并 HT, 197 例未合并 HT), 结果表明, PCOS 合并 HT 组女性的肥胖程度(BMI、腰围)显著高于未合并 HT 的 PCOS 患者。多项研究发现 PCOS-HT 组患者的胰岛素分泌和 HOMA-IR 指数均高于 PCOS-非 HT 患者, 且 TPOAb 和 TGAb 水平与口服糖耐量试验(OGTT)多个时间点测定的胰岛素水平呈正相关[45]-[47]。我国一项研究结果显示, 合并 HT 的 PCOS 患者具有更高水平的血清总胆固醇水平(4.88 vs. 单纯 PCOS 组 4.38 mmol/L , $p = 0.01$), 其他血脂指标与单纯 PCOS 组无显著差异[46]。一项旨在调查 HT 与 PCOS 共病是否会增加冠状动脉疾病(coronary artery disease, CAD)等合并症风险的研究发现, 以健康人群为对照组, 单纯 HT 组患者中高血压[校正比值比(aOR): 1.31 , 95% CI: $1.03 \sim 1.66$; $p < 0.05$]和高脂血症(aOR: 1.55 , 95% CI: $1.27 \sim 1.90$; $p < 0.001$)的患病风险增加, 而单纯 PCOS 组和 PCOS 合并 HT 组中高血压和高脂血症的风险未见增加。此外, PCOS 合并 HT 组中患 CAD 的风险高于单纯 HT 组(aOR: 5.92 , 95% CI: $1.32 \sim 26.53$ vs. 校正 OR: 1.51 , 95% CI:

1.11~2.06), 单纯 PCOS 组患者中无 CAD 发生[10]。但并非所有研究结果都支持合并 HT 对 PCOS 女性代谢有负面影响。Gawron 等人[48]的研究虽显示亚临床甲减是 PCOS 患者 IR 的独立危险因素, 但在合并亚临床甲减的 PCOS 患者中, 甲状腺自身免疫的存在并未加重代谢异常。大多研究的样本量均较小, 可能需要未来大规模的多中心研究提供更可靠的证据。

5. 合并 HT 对 PCOS 治疗的影响

PCOS 目前尚无针对病因的有效治疗方法, 主要是根据现阶段患者是否有生育需求选择适宜的干预措施[15]。有效促进 PCOS 不孕女性排卵、妊娠和活产的一线治疗药物包括来曲唑和克罗米芬[49]。有研究指出, 合并 HT 可能与 PCOS 女性促排卵治疗反应不佳有关。奥地利一项旨在评估患有 PCOS 的不孕女性中 HT 的发生是否与治疗反应相关的回顾性研究发现, 与柠檬酸克罗米芬(CC)联合二甲双胍(联合治疗)缓解组和二甲双胍单药治疗缓解组相比, 联合治疗耐药组中 TPOAb 阳性率显著更高, 各组间甲状腺激素水平差异无统计学意义。TPOAb 阳性对 CC 耐药有一定的预测价值, 但由于其特异性和阳性预测值较低(分别为 20.2%和 38.3%), 有待进一步研究探索更多优质预测模型[4]。

6. 小结

随着对 PCOS 发病机制的深入研究, 学者们认为自身免疫可能参与 PCOS 的发生发展[50] [51]。与此同时, PCOS 女性由于雌激素与孕激素比例失衡, 免疫系统处于过度刺激状态, 易于合并 HT 等自身免疫性疾病。尽管越来越多的证据表明 PCOS 与 HT 之间存在潜在联系, 但二者共病机制的相关研究进展较少。已经发现了一些可能的共同遗传背景。有研究表明, PCOS 相关基因原纤维蛋白 3 (FBN 3)、促性腺激素释放激素受体(GnRHR)和 CYP11B1 三种基因的多态性在 PCOS 和 HT 共病中发挥重要作用[52] [53]。此外, 自身免疫异常、内分泌紊乱、IR、维生素 D 缺乏、肠道菌群失调等也可能参与两种疾病的发生发展[54] [55]。

总之, PCOS 与 HT 之间密切相关。对这两种疾病存在共病趋势的内在关联机制进行深入探索, 可能为 PCOS 更好的临床管理提供依据。二者共病可能对 PCOS 女性的生殖结局和远期代谢健康造成不利影响, 因此, 在 PCOS 初诊时和随访中定期进行甲状腺疾病的筛查, 对早期发现及纠正甲状腺功能异常具有重要意义。

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