

中医药治疗多囊卵巢综合征高雄激素血症相关机制的研究进展

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[摘要] 多囊卵巢综合征(PCOS)是育龄期女性常见的内分泌代谢疾病,高雄激素血症(HA)是其核心病理特征之一,与疾病的临床表现及代谢并发症密切相关。目前,西医治疗PCOS-HA以抗雄激素和促排卵为主,如达英-35、优思明等口服短效避孕药,但长期服用存在增加肝功能损伤风险及加重脂代谢异常等不良反应,且单纯西药治疗远期疗效欠佳。而中医药治疗PCOS-HA具有整体观念与多靶点调控的独特优势,中医学认为PCOS-HA属于“月经后期”“闭经”“不孕”等范畴,病机以肾虚为本,肝郁、脾虚为标,痰瘀互结贯穿始终,现代研究表明中医药在改善患者雄激素水平、恢复排卵功能及改善胰岛素抵抗方面疗效显著,典型方剂如二仙汤、加味逍遥散、桂枝茯苓丸和苍附导痰汤等,通过调节下丘脑-垂体-卵巢轴(HPO)功能、降低卵巢雄激素合成酶活性、改善胰岛素信号通路、抑制炎症与氧化应激等多重机制,体现了中医药综合治疗的特色。基于此,该文从中医病因病机、现代医学认知、典型方药与作用机制等维度,总结了中医药治疗PCOS-HA的研究进展,以期为该领域的深入研究与临床应用提供参考。

[关键词] 多囊卵巢综合征; 高雄激素血症; 中医药; 作用机制; 研究进展

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Relevant Mechanism of Traditional Chinese Medicine in Treatment of Hyperandrogenism in Polycystic Ovary Syndrome: A Review

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[Abstract] Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder among women of reproductive age. Hyperandrogenism (HA), one of its core pathological features, is closely associated with the clinical manifestations and metabolic complications of the disease. Current western medical treatments for PCOS-HA mainly include anti-androgen therapy and ovulation induction, such as short-acting oral contraceptives like Diane-35 and Yasmin. However, long-term use of these medications may result in adverse reactions like increasing the risk of liver dysfunction and exacerbating lipid metabolism disorders, with unsatisfactory long-term efficacy when used alone. Traditional Chinese medicine offers unique advantages in the treatment of PCOS-HA due to its holistic approach and multi-target regulatory mechanisms. In the view of traditional Chinese medicine, PCOS-HA is classified under the categories such as "delayed menstruation", "amenorrhea", and "infertility", with kidney deficiency as the root, as well as liver stagnation and spleen deficiency as the manifestations. Phlegm and blood stasis are considered to be intertwined throughout the disease course. Modern studies have shown that traditional Chinese medicine is significantly effective in improving the androgen levels, restoring ovulation, and improving insulin resistance in PCOS-

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HA patients. Representative prescriptions, such as Erxian Tang, Jiawei Xiaoyaosan, Guizhi Fulingwan, and Cangfu Daotantang, exert therapeutic effects through various mechanisms including regulation of the hypothalamic-pituitary-ovarian axis, reduction of ovarian androgen synthase activity, improvement of insulin signaling pathways, and inhibition of inflammation and oxidative stress, which demonstrates the characteristics of comprehensive treatment with traditional Chinese medicine. Based on the perspectives of etiology and pathogenesis of traditional Chinese medicine, modern medical cognition, typical prescriptions, and action mechanisms, this paper reviewed the research progress of traditional Chinese medicine in the treatment of PCOS-HA, aiming to provide a reference for in-depth research and clinical applications in this field.

[Keywords] polycystic ovary syndrome; hyperandrogenism; traditional Chinese medicine; action mechanism; research progress

多囊卵巢综合征(PCOS)是育龄女性常见的生殖内分泌与代谢疾病,全球患病率约为11%~13%^[1],其特征为慢性无排卵、高雄激素血症(HA)、胰岛素抵抗(IR)及多囊样卵巢改变等,其中HA在PCOS诊断和病理机制中居核心地位^[2]。约40%~80%的PCOS患者存在临床或生化高雄激素表现^[3],HA不仅引发月经稀发、闭经、不孕、痤疮、多毛、肥胖等临床症状,还因促发卵泡过早闭锁导致排卵障碍^[4],且与IR呈正相关,形成代谢-内分泌恶性循环^[1]。长期雄激素过多显著增加了PCOS患者远期罹患2型糖尿病、心血管疾病及子宫内膜癌的风险^[5]。故而,HA既是PCOS的重要临床表现,也是推动疾病进展的危险因素。目前,西医治疗PCOS-HA以抗雄激素和促排卵为主,如达英-35、优思明等口服短效避孕药(COC),通过抑制下丘脑-垂体-卵巢(HPO)轴减少卵巢雄激素生成,改善月经紊乱、多毛、痤疮等症状^[6],但长期服用有体质量增加、血脂异常、肝功能损害及血栓风险上升等副作用^[7],且单纯西药治疗远期疗效欠佳。因此,如何更安全有效地降低高雄激素水平、改善患者症状成为临床面临的挑战之一。中医药因多靶点综合调节,在降低雄激素水平、恢复月经周期、减轻IR及辅助体质量控制等方面有较好疗效,不良反应明显低于西药^[8]。现从中医病因病机、现代医学认知、典型方药与作用机制等维度,总结中医药治疗PCOS-HA的研究进展,以期为该领域的深入研究与临床应用提供参考。

1 中医病因病机及治疗概况

1.1 病因病机 在中医学古籍中,并无“PCOS-HA”这一病名,根据其症状特点,可将其归属于“不孕”“闭经”“月经过少”“月经后期”“癥瘕”等范畴,中医诸家对PCOS-HA病因病机的认识,主要集中于肾虚、肝郁、脾虚及痰瘀互结等方面。

1.1.1 肾虚血瘀 肾为先天之本,主司生殖,与天癸、冲任二脉密切相关。若肾气不足,冲任失调,血海空虚,胞宫功能紊乱,便会诱发月经失调与排卵障碍。全国名老中医蔡连香^[9]认为,肾精亏虚,肾阳衰惫,可致卵泡发育迟缓;肾阳不足,推动无力,即便卵泡发育成熟,亦难以顺利排出。肾阳不足,命门火衰,寒凝血瘀;或肾阴亏虚,水不涵木,肝经郁火上扰,皆可致血瘀,瘀血阻滞冲任,胞宫失于濡养,生殖功能障碍加剧^[6],久瘀还可影响卵巢局部血液循环,干扰卵泡发育及激素转化过程,促使雄激素蓄积升高。基于名医经验与诸多临床研究表明,肾虚血瘀是PCOS-HA的主要病机^[10]。

1.1.2 肝失疏泄 女子以肝为用,肝主疏泄,调畅情志。韩

延华教授等^[11-12]亦认为,肝郁是PCOS的重要病机之一,情志不遂致使肝气郁滞,疏泄功能失常,肝藏血,冲脉为血海,气血运行受阻,进而导致冲任气血失序,血瘀胞宫。肝郁血瘀可致月经后期、闭经及不孕;肝郁化火,则毛发增生,出现多毛、痤疮等症状。明末清初医家傅山^[13]曾言:“子病而母必有顾复之情,肝郁而肾不无缱绻之谊”,强调肝与肾关系紧密,犹如母子,肝郁气结,气机不畅,有碍肾气摄纳,以致肾气虚弱,推动气血乏力,冲任血行迟滞,则月事延闭。故而,肝郁血瘀常与肾虚相互影响,成为PCOS-HA发病的重要环节。

1.1.3 脾虚痰湿 脾为后天之本,气血生化之源,主运化水湿。现代学者认为,脾虚则气血生成不足,肾精不得充养,血海无法按时满盈,从而引发月经后期、月经过少、闭经;脾虚土壅,肝失疏泄,影响肾中阴阳转化,导致排卵障碍;脾虚水湿不化,停聚为痰,壅滞胞宫,造成月经紊乱;痰湿壅盛于肌肤,可引发皮肤脂溢、肥胖、多毛、痤疮;脾虚无力运血,血滞成瘀,痰瘀搏结,扰乱激素代谢平衡,致使卵巢呈多囊性改变^[14-16]。侯丽辉教授指出,“痰瘀互结”是本病的重要病机^[17],痰湿凝聚与血瘀阻滞常同时存在,引发慢性炎症反应和代谢失调,诚如明代医家朱丹溪所言:“痰挟瘀血,遂成窠囊”,表明痰瘀交阻在本病发病过程中起着重要作用。

综上,PCOS-HA病机以肾虚为本,肝郁、脾虚为标,痰湿和瘀血作为病理产物贯穿始终。肾虚与痰瘀常互为因果,正虚与邪实并存,共同引发多层次、多靶点的病理改变,这与国医大师肖承棕所倡导的肾虚痰瘀理念高度契合^[18]。中医治疗注重辨证论治,针对肾、肝、脾同治,兼顾祛痰化瘀,以期标本兼治,恢复机体生殖内分泌平衡。

1.2 治疗概况 近年来,中医药治疗PCOS-HA取得诸多研究成果。根据中医辨证论治的特点,临床常用补肾、疏肝、健脾、化痰、活血等治法,且常与针灸、推拿等多种手段配合应用,可显著提高PCOS-HA患者的排卵率和妊娠率,降低雄激素及胰岛素水平^[6,8]。系统评价结果也在逐步积累,有研究分别对33项、72项和51项实验和临床研究进行分析后证实,部分中草药及中医综合疗法对PCOS-HA的内分泌紊乱具有确切的调节作用,并且在小样本试验中观察到降低雄激素水平和恢复月经周期的积极效果,在改善不孕等方面优于单纯西药治疗,体现出协同增效的作用^[19-21]。然而,由于研究质量参差不齐,Cochrane评价认为中医药治疗PCOS的循证医学证据仍不充分,需要开展更多高质量的随机对照试验(RCT)来验证其疗效^[22]。随着循证医学和实验技术的发展,

中医药治疗PCOS-HA的临床和基础研究不断深入,大量的动物实验和细胞实验聚焦于中药作用的分子机制研究,为阐释中医药治疗PCOS-HA的作用提供了依据。这些研究涉及从调节下丘脑促性腺激素释放激素(GnRH)分泌,到改善卵巢局部胰岛素信号通路、类固醇合成过程,再到抗炎抗氧化等多个层面。

2 现代医学认知及治疗概况

2.1 发病机制 PCOS-HA发病机制复杂,多因素交织。遗传易感性被认为是发病的重要基础,全基因组关联研究(GWAS)已发现29个与PCOS相关的易感基因位点^[23],其中,甲状腺腺瘤相关蛋白(THADA)基因被证实与PCOS密切相关^[24]。HIAM等^[25]对PCOS候选基因进行系统回顾后指出,THADA基因的变异可能通过干扰能量代谢及胰岛素分泌过程,从而推动HA的发生^[26]。此外,宫内环境和表现遗传因素在PCOS-HA发病中的作用备受关注,孕期雄激素过量可导致女性胎儿下丘脑-卵巢轴(HO)发生程序化改变,为成年后罹患PCOS埋下隐患^[27-28],相关研究结果也证实,母体高雄激素暴露是子代出现PCOS倾向的促进因素之一。从内分泌机制角度分析,促性腺激素与胰岛素的失衡被视为PCOS-HA的重要成因^[29]。高促黄体生成素(LH)及高胰岛素血症在PCOS患者中较为普遍,LH过多能够直接刺激卵巢卵泡膜细胞,使其雄激素合成量增加^[27,29];而IR通过提高胰岛素水平,协同促进卵巢和肾上腺合成雄激素,约30%的PCOS患者存在IR,且LH/促卵泡生成素(FSH)值升高,与HA的严重程度呈正相关^[30]。过量的雄激素反过来会抑制卵泡颗粒细胞中芳香化酶的活性,阻碍雌激素的合成,进而形成“LH-雄激素-芳香化酶抑制”的恶性循环^[27],长此以往,患者体内雄激素水平持续偏高,生殖内分泌轴紊乱愈加严重。

2.2 治疗概况 目前,PCOS-HA的西医疗手段主要包括药物和手术治疗^[31]。在药物治疗方面,常用的有抗雄激素药物和促排卵药物,含有雌激素和孕激素的COC是治疗HA的一线方案,其作用机制为抑制LH分泌、提高性激素结合球蛋白(SHBG)水平,进而降低游离睾酮(T)含量^[32]。胰岛素增敏剂,如二甲双胍,则通过改善IR,间接降低雄激素水平,并对恢复排卵具有促进作用。对于有生育要求的PCOS患者,可选用克罗米芬、来曲唑等促排卵药物。在手术治疗方面,腹腔镜卵巢打孔术(LOD)适用于药物治疗无效的顽固性无排卵患者,但需要权衡其对机体造成的创伤及对卵巢功能可能产生的损伤风险。总体而言,西药在控制PCOS-HA症状方面效果较为明确,但停药后易复发,且不良反应限制了其长期应用。因此,越来越多的研究将目光转向中医药干预在调节内分泌、改善HA和IR及恢复排卵功能等方面的潜在优势,将中医传统理论与现代作用机制进行对接,揭示其科学内涵,为探索更安全、长期有效的治疗策略提供了新方向。

3 典型方药研究

中医治疗PCOS-HA常依据证型选方用药,其中补肾、疏肝、活血、化痰四类治法应用最为广泛。近年来,报道较多的有效方药涵盖传统经方与经验方,本节聚焦几种代表性的

中药复方,探讨其在PCOS-HA治疗中的研究进展。

3.1 二仙汤及补肾类方 二仙汤由仙茅、淫羊藿等药物组方而成,原为张伯讷教授治疗更年期综合征之名方^[33],具有温肾阳、益肾精之效。在PCOS-HA治疗中,二仙汤及其加减方常用于肾阳不足兼阴亏之证,旨在温补肾阳,调节HPO轴功能,改善内分泌失调^[34]。LIU等^[35]通过网络药理学靶点富集分析发现,二仙汤干预PCOS的作用涉及磷脂酰肌醇3-激酶/蛋白激酶B(PI3K/Akt)、IR、丝裂原活化蛋白激酶(MAPK)等多条信号通路,其所含多种活性成分可作用于雄激素合成、糖代谢及炎症反应等关键环节,进而整体改善PCOS表型。另有学者通过实验表明,二仙汤能够提升模型大鼠的雌激素水平,降低LH和T水平,促进卵泡发育与排卵^[36-37]。丁莉等^[38]研究证实加味二仙汤通过改善IR,调节T、LH等性激素水平,调经促排,提升妊娠率且复发率较低。此外,本课题组传承李光荣教授学术思想以二仙汤及泽兰汤合方加减而成的补肾活血方^[39-40],既能补肾温阳以治其本,又可活血化瘀以治其标,患者经治疗,LH、T水平显著降低,妊娠率呈提升态势,其疗效与达英-35无明显差异。左归丸通过调控类固醇激素生物合成途径显著降低T水平,促进卵泡的生成与发育,进而改善卵巢功能,疗效优于西药对照组^[41]。寿胎丸加味方可降低PCOS高雄激素-胰岛素抵抗流产模型大鼠流产率,调控炎症因子的表达,抑制炎症反应,从而提高子宫内膜容受性和恢复子宫蜕膜化缺陷^[42]。毓麟珠通过激素调节、抗炎作用和神经保护有效改善月经规律并降低雄激素水平,且具有良好的安全性^[43]。由此可见,以二仙汤为代表的补肾类方在PCOS-HA治疗中,具有调节HPO轴、平衡雌雄激素、促进卵巢功能恢复之作用,且在现代研究中得到了一定程度的验证^[44]。具体见增强出版附加材料。

3.2 加味逍遥散及疏肝类方 加味逍遥散(又名丹栀逍遥散)源自宋代《太平惠民和剂局方》逍遥散,加入丹皮、栀子以增强疏肝解郁、清热调经之效,是临床治疗PCOS应用最为广泛的中药方之一^[45],方中柴胡、当归等药物可调节下丘脑GnRH的分泌,改善慢性应激引发的内分泌紊乱^[46]。汪碧云和ZHU等^[47-48]研究发现,丹栀逍遥散治疗PCOS的作用机制包括甾体激素合成、氧化还原等过程,涉及卵巢类固醇生成、PI3K/Akt、IR等多个信号通路。邓丽玲等^[49]通过实验表明,加味逍遥散可改善卵巢多囊样变,降低PCOS-HA大鼠血清雄激素、瘦素水平,减少瘦素受体在卵巢组织的阳性表达,从而减少瘦素的生物利用度,抑制雄激素分泌及活性,有助于卵泡正常生长发育和优势卵泡形成并排卵。ZHOU等^[50]系统评价了逍遥散联合常规西药治疗PCOS的结果,发现联合组排卵率和妊娠率显著提高,且胰岛素抵抗指数(HOMA-IR)下降更为明显。加味逍遥散能更迅速地降低血清雄激素水平,缓解痤疮、多毛等雄激素依赖症状,患者服药3个月后,月经周期趋于规律,疗效优于西药达英-35对照组,其作用机制可能在于疏肝清热药物调节下丘脑-垂体-肾上腺(HPA)轴的应激反应,减少肾上腺雄激素分泌,同时改善肝气郁结所致的IR和炎症因子升高^[51]。此外,楚雨杰^[52]研究表明,芍药甘草汤合调肝定癸方不仅能有效降低PCOS-HA

患者的T水平,还能调节体质量指数(BMI)、FSH、LH、LH/FSH、HOMA-IR等指标,减少痤疮,提高排卵率,改善中医证候,疗效显著。芍药甘草汤降低PCOS-HA大鼠血清T水平并升高E₂和FSH水平,降低核转录因子- κ B p65亚基(NF- κ B p65)的磷酸化并增加核因子- κ B抑制蛋白(I κ B)的表达,从而改善HA,其潜在机制可能与NF- κ B信号通路有关^[53]。总体而言,以加味逍遥散为代表的疏肝调经类方在缓解PCOS-HA患者精神压力、纠正内分泌失衡方面效果显著,是治疗肝郁血热型PCOS-HA的常用方剂。具体见增强出版附加材料。

3.3 桂枝茯苓丸及活血类方 桂枝茯苓丸见于汉代张仲景《金匮要略》,由桂枝、茯苓、丹皮、桃仁、芍药组成,功擅活血化瘀、消癥散结,促进胞宫血行,调经以利排卵,还可抗雄激素、调节IR等代谢异常,改善多毛和痤疮情况,在PCOS伴血瘀内阻的患者中应用广泛^[54]。ZHU等^[55]运用来曲唑诱导PCOS-IR大鼠模型,给予桂枝茯苓丸治疗能降低血清雄激素和胰岛素水平,降低致炎菌相对丰度,增加短链脂肪酸产生菌比例,从而减轻肠道来源内毒素引发的全身炎症,调节因高雄激素导致的肠道菌群紊乱,改善卵巢微环境,降低炎症因子TNF- α 、IL-6水平,进而提高胰岛素敏感性。另有学者通过实验证实,桂枝茯苓丸可上调miR-29b-3p、下调长链非编码RNA H19(RNA H19),从而降低自噬相关关键蛋白磷酸酶张力蛋白同源物(PTEN)、基质金属蛋白酶-2(MMP-2)及Bcl-2相关X蛋白(Bax)的表达水平,减少细胞过度自噬和凋亡,或激活PI3K/Akt/哺乳动物雷帕霉素靶蛋白(mTOR)、PI3K/Akt/NF- κ B和核因子E₂相关因子2(Nrf2)/血红素氧合酶-1(HO-1)信号通路促进颗粒细胞自噬,降低血清T、LH、空腹胰岛素(FINS)水平、LH/FSH和HOMA-IR,增强胰岛素敏感性,减轻炎症和氧化应激反应,提示其可能通过改善卵巢局部细胞生存环境,调节卵巢功能障碍,从而消除瘀血阻滞来发挥促排卵作用^[56-59]。王南苏和张丽芸等^[60-61]研究表明桂枝茯苓丸联合二甲双胍等西药治疗PCOS较单用西药能更有效降低血清T水平和多毛痤疮评分,取得更高的排卵率和更显著的代谢改善,支持其活血化瘀、调经种子的作用。有研究系统评价桂枝茯苓丸及其联合西药治疗可有效改善患者排卵率和妊娠率,获益机制可能与降低FSH、T及LH水平并改善IR相关^[62]。此外,化痰消癥汤可显著降低雄烯二酮(ASD)、LH、T、FINS水平,调节生殖激素分泌,控制糖脂代谢异常,改善卵巢功能^[63]。因此,桂枝茯苓丸等活血化瘀类方为伴发血瘀证的PCOS-HA提供了有效的治疗手段,在现代研究中体现出通过调控肠-卵巢轴和抗炎改善代谢的机制特色。具体见增强出版附加材料。

3.4 苍附导痰汤及化痰类方 苍附导痰汤出自清代叶天士《女科证治秘方》,由苍术、香附、半夏、陈皮等药物组成,功能健脾祛湿、理气化痰,改善体内代谢环境,促进卵巢功能恢复,适用于痰湿阻滞型PCOS患者^[64]。诸多学者临床研究表明,苍附导痰汤可显著改善患者月经周期,有效调节糖脂代谢和性激素指标,缩小卵巢体积,改善卵巢多囊状态,并降低痤疮体征评分和中医证候积分,提高妊娠率,降低不良反应

发生率,提示可能与调节外周血PI3K/Akt信号通路有关^[65-68],多项系统评价结果与上述一致^[69-70]。相关实验研究发现,槲皮素、橙皮苷、甘草苷、芹菜苷、柚皮苷、柚木芸香苷和半甲基异黄酮B是苍附导痰汤的关键成分,这些成分与MAPK3、Akt1、NF- κ B p65、叉头框蛋白K1(FoxK1)、表皮生长因子(EGF)、m6A甲基化、有机阴离子转运多肽(OATP)2B1和OATP3A1等有高度的相互作用,其治疗PCOS主要与Toll样受体4(TLR4)/NF- κ B、PI3K/Akt、凋亡信号调节激酶1/c-Jun氨基末端激酶(ASK1/JNK)、腺苷酸活化蛋白激酶(AMPK)/mTOR、Wnt/ β -连环蛋白(β -catenin)、MAPK信号通路相关,通过调节卵巢颗粒细胞凋亡与自噬、刺激细胞增殖和改善炎症微环境,减轻因痰湿导致的慢性炎症和代谢紊乱,恢复卵巢结构与功能,提升子宫内腔容受性,从根本上缓解PCOS-HA症状^[71-77]。此外,健脾祛湿化痰方可有效提高排卵率、改善患者月经情况,调节性腺激素水平,使血清LH、LH/FSH、T、硫酸脱氢表雄酮(DHEA-S)水平下降、SHBG水平上升,改善腰臀比、BMI、痤疮症状,减轻患者的焦虑和抑郁情绪,提升生活品质,提高性功能指数^[78]。总体而言,以苍附导痰汤为代表的化痰祛湿类方在治疗肥胖等代谢异常并存的PCOS-HA患者中具有独特优势,可以安全有效地提高排卵和妊娠率,同时改善其代谢健康。具体见增强出版附加材料。以上典型方药的研究进展表明,中医药通过辨证施治在PCOS-HA治疗中发挥多层次作用,补肾类方调整内分泌轴,疏肝类方缓解神经内分泌紊乱,活血类方促进卵巢局部血循环及抗炎,化痰类方改善代谢环境,若将这些治法有机结合,往往疗效更佳。可见,合理运用经典方药的配伍协同,可针对PCOS-HA复杂病机实现整体调节,这也是中医药治疗本病的重要经验和特色。

4 作用机制分析

中医药干预PCOS-HA的作用机制具有多层次、多途径的特点,是当下研究热点之一。借助分子生物学与系统药理学技术,诸多研究从内分泌调控、酶靶点、信号通路、炎症免疫等维度,阐释中药单体及复方的作用机制。基于近年来的典型研究成果,其作用机制可归纳如下。

4.1 调节HPO轴功能 PCOS-HA患者常表现为GnRH脉冲频率升高,LH分泌异常,促使卵巢过度合成雄激素,进而扰乱HPO轴功能^[79-80]。中药对HPO轴的调控展现出从中枢神经至卵巢局部的多级干预特性,其整体性调节显著优于靶向单一激素的西药治疗。在下丘脑层面,疏肝解郁类中药可通过调节中枢神经递质及GnRH脉冲释放起效。逍遥散用于治疗慢性应激所致PCOS大鼠时,可降低交感兴奋标志物及下丘脑去甲肾上腺素(NE)含量,进而减少GnRH过度分泌,对抗应激引发的内分泌失调^[81]。在垂体层面,针刺与中药均具有调控促性腺激素分泌的功效。针灸实验表明,其可降低PCOS模型大鼠垂体LH分泌,同时提高FSH分泌,以推动卵泡成熟^[82]。补骨脂、淫羊藿等中药单体,可通过类似GnRH样作用刺激垂体功能,此即“中药人工周期疗法”,为无排卵患者诱导周期性出血提供新思路^[83]。在卵巢层面,中药能够促进卵泡发育与排卵。仙茅、泽兰等补肾活血中药,

已被证实可促进卵巢颗粒细胞增殖,减少卵泡闭锁^[84-86];二仙汤、逍遥散等复方通过增加原始卵泡募集、抑制颗粒细胞凋亡等方式,改善排卵功能^[46,86]。此外,中药对子宫内膜容受性亦具正向影响,补肾活血化痰药能够改善子宫内膜血流与厚度,提高着床成功率^[87]。因此,调节HPO轴及生殖微环境是中药治疗PCOS-HA的关键机制之一,既可以上调中枢-垂体对卵巢的有益信号,如FSH分泌、GnRH节律,又可以下调异常信号,如过高的GnRH/LH释放,并直接促进卵巢和子宫局部功能恢复,这种多层次的神经内分泌调控能力,使中医药能够多方面调节PCOS患者的生殖功能障碍,从而缓解PCOS-HA的内分泌功能紊乱。

4.2 影响类固醇激素合成的酶和受体 影响类固醇激素合成的酶和受体在PCOS-HA的发生中起关键作用,其包括胆固醇侧链裂解酶(CYP11A1)、17 α -羟化酶/17,20-裂解酶(CYP17A1)、芳香化酶(CYP19A1)和雄激素受体(AR)等。CYP11A1编码胆固醇侧链裂解酶,催化胆固醇转化为孕烯醇酮,是类固醇生成的第一步^[88]。青蒿素作为综合治疗PCOS的潜在有效药物,可直接与线粒体蛋白酶LONP1结合,引发LONP1与CYP11A1之间的相互作用,进而促进CYP11A1降解,抑制卵巢雄激素合成并遏制PCOS进展,为靶向LONP1-CYP11A1相互作用干预PCOS开辟了新途径^[89]。CYP17A1编码17 α -羟化酶/17,20-裂解酶,负责将孕烯醇酮转化为雄激素前体,其活性增高可致使雄激素过量^[90]。中药中部分活性成分对CYP17A1具有下调作用,从而减少雄激素合成。丹参的主要活性成分为隐丹参酮,将其用于治疗PCOS模型大鼠后,卵巢组织中CYP17A1基因和蛋白表达明显降低,同时AR表达亦被下调,其直接效果为血清T和ASD水平下降,LH/FSH比值恢复正常,进而改善排卵功能,展现出了显著的抗雄激素作用,提示隐丹参酮通过抑制CYP17A1和AR,重塑了PCOS模型动物的激素平衡,因此被视为潜在新型治疗剂^[91]。另一代表性单体黄连的主要活性成分是黄连素(小檗碱),其干预PCOS-HA大鼠后,血清T水平明显下降,卵巢中类固醇生成急性调节蛋白(StAR)和CYP17A1表达受到抑制,提示其抑制了胆固醇向雄激素转化的速率限制步骤^[92-93]。而含丹参、当归的活血复方可部分通过降低类固醇合成酶活性发挥抗雄激素功效^[94-95]。此外,中药对CYP19A1编码芳香化酶的作用亦受关注,其负责将雄激素转化为雌激素^[88],如益母草可能上调其活性,促进雄激素转化,从而间接降低HA的不良影响^[96]。然而,目前关于中药调控CYP19A1的研究结果尚不统一,仍需更多研究加以证实。因此,靶向类固醇合成关键酶和受体是中药治疗PCOS-HA的重要机制之一,通过下调CYP17A1、AR等,可有效抑制过多雄激素的产生与作用。

4.3 调节胰岛素信号通路与卵巢糖代谢 胰岛素信号与糖代谢通路的异常调节是PCOS-HA发病机制的重要组成部分,一方面高胰岛素水平通过PI3K/Akt信号通路增强卵巢膜细胞中P450c17 α 酶的活性,促进雄激素合成,形成“选择性IR”现象,即代谢通路受阻而类固醇合成持续活跃;另一方面,其还可通过MAPK/ERK信号通路影响HPO轴,增加

促性腺激素释放,进一步加重高雄激素状态^[97-99]。在此“失调”状态下,靶向调节PI3K/Akt成为治疗切入点。黄连素不仅可降低雄激素,还能提高肝脏和肌肉对胰岛素的敏感性,减少IR相关炎症因子^[100]。肉桂、黄芪等补脾化湿药提取物可降低PCOS患者空腹血糖和血脂水平,纠正代谢紊乱^[101-102]。补肾健脾方能显著减轻T诱导的颗粒细胞IR,提高细胞对葡萄糖的摄取和利用,其机制涉及激活PI3K/Akt信号通路、抑制胰岛素信号下游重要调节蛋白叉头框蛋白O1(FoxO1)转录因子过表达,从而减轻颗粒细胞的自噬与凋亡,提高其对胰岛素的反应性^[103]。二仙汤有效成分可作用于胰岛素受体底物和PI3K,从而激活下游Akt,增强卵巢对胰岛素的敏感性^[35]。由此可见,中药复方能够多途径改善IR,既有降低肝糖异生、促进周围组织葡萄糖利用的作用,也通过细胞信号调节减轻IR对卵巢的刺激。而在卵巢局部,PCOS-HA患者常出现某些关键信号通路紊乱,除PI3K/Akt信号通路外,MAPK信号通路与类固醇生成和卵泡发育密切相关,AMPK是细胞能量感受器,活化AMPK可促进葡萄糖摄取和脂肪酸氧化。黄连素通过激活AMPK和调节过氧化物酶体增殖物激活受体 γ (PPAR γ)、MAPK等关键信号通路,达到降低血糖和T、调节脂代谢的作用^[92-93],而含有此成分的中药复方亦可降低PCOS患者HOMA-IR指数并提高胰岛素敏感性^[104]。此外,Notch信号通路(Notch)、河马信号通路(Hippo)、Nrf2/HO-1等信号通路也在PCOS卵巢功能调控中发挥作用^[105],目前通过这些通路干预PCOS的研究尚不多见,但中药多成分、多靶点的特点非常契合此类复杂网络的调控,有望成为未来研究热点。因此,通过调节PI3K/Akt和MAPK等胰岛素信号通路,中药能有效打破IR驱动的雄激素合成正反馈,逆转内分泌-代谢异常联动进程。

4.4 抑制炎症反应与氧化应激 PCOS-HA患者常伴慢性低度炎症及氧化应激状态,促炎因子(如TNF- α 、IL-6)和活性氧升高可促进雄激素合成,干扰卵泡发育,通过干预炎症与氧化应激通路,有助于缓解HA,改善卵巢功能^[106]。NF- κ B是调控炎症因子转录的核心通路,许多中药通过抑制NF- κ B通路活性,实现抗炎效应。芍药甘草汤可降低PCOS模型大鼠卵巢中的TLR4受体和下游NF- κ B p65的表达,减少炎症因子TNF- α 、IL-6的产生,还能重塑肠道屏障,增加肠黏膜紧密连接蛋白的表达,防止细菌内毒素LPS移位入血,有效抑制其介导的NF- κ B信号通路活化,从源头上阻断炎症级联反应^[107]。同样,桂枝茯苓丸通过调整肠道菌群而间接抑制NF- κ B介导的炎症反应,表现为降低胚胎着床环境中的炎症水平,提高PCOS模型大鼠的胰岛素敏感性,也可通过调控miRNA和长链非编码RNA(lncRNA),减少卵巢组织过度自噬,从而减轻由炎症和应激诱导的细胞损伤^[55-56]。滋肾清热利湿化痰方可降低IL-6、CRP等炎症指标和血液中T、LH、胰岛素水平,改善痤疮和肥胖症状,其可能机制为促进卵巢颗粒细胞增殖,还涉及卵巢颗粒细胞自噬、类固醇生成、氧化应激及炎症相关的通路和基因^[108]。在巨噬细胞极化方面,部分中药可促进M2型抗炎巨噬细胞增多,抑制M1型促炎巨噬细胞,如补脾化痰活血方药干预PCOS模型小鼠后,

卵巢和脂肪组织中M1型巨噬细胞比例下降、M2型增加,局部TNF- α 等炎症因子水平下调,这从免疫学角度印证了中医“化痰祛瘀”法可以消除慢性炎症环境,为卵巢功能恢复创造了有利条件^[109]。在抗氧化方面,补益肾精和养阴清热中药富含多酚、黄酮类成分,如中药单体姜黄素、白藜芦醇等被证实具有清除自由基、抑制NF- κ B的作用,可减少卵巢组织的氧化应激损伤,保护卵泡发育环境^[110-111],而葛根素在PCOS大鼠中显示出提高超氧化物歧化酶活性、降低卵巢氧化应激损伤的效果^[112]。因此,抗炎和抗氧化是中药改善PCOS-HA的重要机制,通过作用于TLR4/NF- κ B等炎症信号通路,降低了炎症介质水平,改善了因炎症导致的卵巢反应异常和IR加剧,这对于缓解PCOS-HA的症状和降低远期并发症风险具有积极意义。

4.5 对合并症和靶器官的保护作用 PCOS-HA与多种代谢性和心血管合并症密切相关,包括IR、2型糖尿病、非酒精性脂肪肝、心血管疾病及子宫内膜病变等,高雄激素状态可加剧IR和脂质代谢紊乱,增加靶器官损伤风险,故而针对HA的干预不仅有助于改善生殖功能,还可能对心血管、肝脏

和子宫等靶器官产生保护作用^[31]。中药在这些方面的作用也有所涉及,如隐丹参酮能通过调控雌激素受体信号,改善PCOS模型大鼠子宫内膜的增殖状态,提高子宫内膜容受性^[113]。此外,补肾活血中药可逆转PCOS小鼠卵巢中出现的早期纤维化病变,并调节肠道菌群失衡,推测其可能对卵巢间质纤维化、棕色脂肪功能减退等PCOS新近关注的病理改变也有影响,这些效应拓宽了中医药治疗PCOS的视野^[114-115]。因此,早期识别和治疗HA对于降低PCOS相关合并症的发生和保护靶器官有重要意义,是治疗PCOS-HA的重要方面,中医药通过多系统、多途径的协同调节,不仅直接作用于高雄激素状态本身,还对PCOS相关的代谢及器官并发症起到一定的防治作用。以上机制剖析表明,中医药通过多通路、多靶点协同作用,实现对PCOS-HA复杂病理环节的干预,既改善IR等代谢异常,又抑制炎症氧化应激损伤;既调整激素合成与反馈,又促进卵泡发育与排卵。正因如此,中药在PCOS-HA治疗中表现出西药单靶治疗难以比拟的综合疗效。不同中药及方剂偏重的作用途径有所不同,与中医辨证施治、针对不同证型选方用药的理念相吻合。见图1。

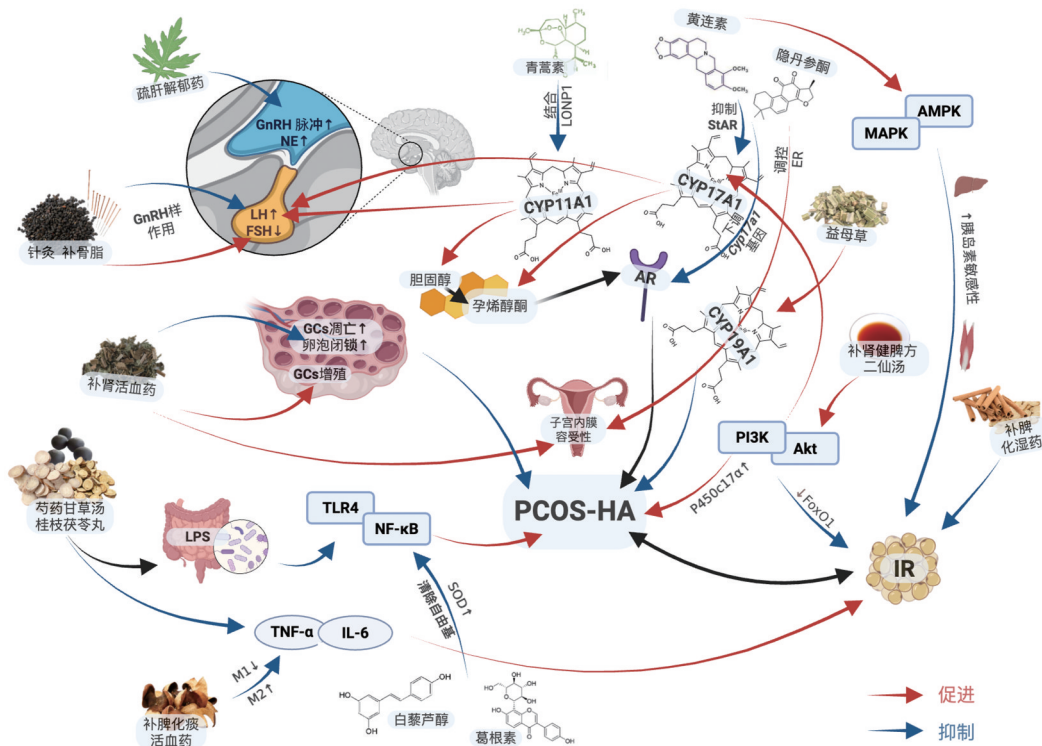


图1 中医药调控PCOS-HA的相关作用机制
Fig. 1 Mechanisms of traditional Chinese medicine in regulating PCOS-HA

5 总结与展望

综上所述,中医药在PCOS-HA治疗领域取得了可喜进展,已彰显出整体调节、多靶点干预的独特优势,形成了“临床疗效+作用机制”研究双轨并行的发展格局,为PCOS这一复杂综合征的治疗提供了有价值的思路 and 有效的手段。然而,现阶段研究仍存在诸多不足与挑战,亟待在后继研究予以攻克和完善:①现有中医药疗效研究以小样本临床观察或动物实验为主,高质量RCT与Meta分析相对有限,部分系

统评价指出,纳入研究普遍存在偏倚风险,证据质量有待提升。因此,亟需开展大规模、多中心的RCT,以更为客观地评价中医药对PCOS-HA的疗效和安全性。这包括严格的随机盲法设计、统一的疗效评价指标及充分的随访观察,为中医药纳入PCOS-HA循证医学指南提供有力依据;②当前中医药机制研究多基于动物模型,且多数未区分中医证型,这可能致使实验结果与临床实际存在偏差。未来应探索基于辨证分型的动物模型,如结合肾阳虚、痰湿型等特征构建模型,

以更契合不同PCOS患者亚型。此外,研究范畴需拓展,不应仅局限于卵巢本身,还应关注下丘脑、胰岛、骨骼肌、脂肪组织等在PCOS-HA发病中的作用,结合中医理论深入发掘对应的干预途径。随着分子生物学进展,PCOS-HA相关的新型信号通路和生物标志物不断涌现,如前述Notch、Hippo、Nrf2/HO-1信号通路及miRNA、生殖道微生物群等。由于中药成分复杂,其在这些新兴靶点上的作用尚有待研究,未来可运用网络药理学、转录组学、代谢组学等技术手段,系统剖析复方中各成分对应的潜在靶点,预测中药作用网络,并通过实验验证关键节点,有望揭示中药“多成分-多靶点-多通路”作用的内在规律,突破既往单一靶点研究的局限;③PCOS-HA患者往往病程长、症状复杂,单纯运用中药或西药有时难以全面收效,中西医结合治疗已展现出优势,如中药联合克罗米芬促排卵、针刺结合减重治疗等,但如何优化组合方案、明确最佳时机和剂量,仍需深入探究。应在确保中药主导地位的同时,融入现代医学优势,实现“优势互补,协同增效”。例如,可考虑将中药治疗与生活方式干预、营养补充剂(如肌醇、维生素D等)相结合,以提升胰岛素敏感性和促排卵效果。此外,借助人工智能和大数据分析,构建PCOS-HA患者中医证候与西医指标的关联模型,实现治疗方案的个性化推荐,亦是未来发展方向;④PCOS-HA的发生,除遗传因素外,与不良生活方式密切相关。中医“治未病”理念注重早期干预和综合调摄,展望未来,应将中医药干预前移至PCOS-HA高风险人群,如有家族史、青春月经失调者,通过中药调理、针灸、饮食起居指导等方式,预防或延缓PCOS-HA的发生发展。同时,中医药可作为西医治疗的有益补充,应用于PCOS-HA围孕期管理和并发症防治,如孕前中药调周以提高受孕率,孕期辨证用药以降低流产风险,长期调养以减少代谢并发症等。通过关口前移、全程干预,中医药将在PCOS-HA的全生命周期管理中发挥更大效能。

[利益冲突] 本文不存在任何利益冲突。

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