·综 述·

降糖药在多囊卵巢综合征治疗中的应用进展

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【摘要】多囊卵巢综合征是女性最常见的内分泌疾病之一,以雄激素分泌过多、排卵障碍为特征,可引起育龄期女性不孕不育。近年研究获知其健康风险已超出多毛、影响生育等而扩展到代谢等长期共病。尽管其病因尚不清楚,治疗主要基于症状和经验,但目前应用降糖药可改善症状、防范风险,已获得大量临床研究的证实。本文梳理了降糖药特别是二甲双胍在多囊卵巢综合征综合治疗中的应用。

【关键词】降糖药;多囊卵巢综合征;应用进展
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Application progress in hypoglycemic medications in the treatment of polycystic ovary syndrome

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【**Abstract**】Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases in women. It is characterized by excessive androgen secretion and ovulation disorders, causing infertility in women of childbearing age. In recent years, studies have showed that the health risks of PCOS have expanded beyond to cardio-metabolic long-term complications. Although its etiology is unknown and treatment is based on symptoms and experience, hypoglycemic medications can improve symptoms and prevent risks at present, which have been proven in numerous clinical studies. This paper discussed the characteristics of hypoglycemic medications, especially on Metformin in comprehensive treatment of PCOS.

【**Key words**】hypoglycemic medications; polycystic ovary syndrome; application progress

多囊卵巢综合征(polycystic ovary syndrome,PCOS)是女性最常见的内分泌疾病之一,以雄激素分泌过多、排卵障碍和多囊卵巢为特征,是引起育龄期女性不孕不育的重要原因。依照美国国立卫生研究院(National Institutes of Health,NIH)、欧洲人类生殖与胚胎学会(European Society of Human Reproduction,ESHRE)和美国生殖医学学会(American Society for Reproductive Medicine,ASRM)、美国高雄激素-多囊卵巢综合征协会(Androgen Excess and Polycystic Ovary Syndrome Society,AE-PCOS)分别提出的诊断标准,PCOS患病率分别为6%、10%和10%;多毛、高雄激素血症、多囊卵巢和少排卵无排卵的比例分别为13%、11%、28%和15%[1]。PCOS病因尚不清楚,治疗主要基于症状和经验,因40%~85%的PCOS患者超重或肥胖[2]和(或)因血清雄激素水平升高而存在代谢危险因素,其健康风险已扩展到一系列较长期的共病,如糖尿病、高血压、血脂异常、非酒精性脂肪性肝病(non-alcoholic fatty liver disease,NAFLD)和睡眠呼吸暂停、心境障碍和进食障碍等。二甲双胍最早被研究用于PCOS,在降低PCOS患者胰岛素抵

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抗、减轻体质量的同时，可增加排卵和怀孕的可能性。随着人们对胰岛素抵抗在PCOS病理生理中作用的深入认识，如何通过真实世界的研究了解降糖药治疗PCOS和改善代谢综合征等方面的有效性、安全性和经济性成为临床关注的热点之一[3-4]。本文梳理了以二甲双胍为代表的降糖药在PCOS治疗中的应用，以期为临床合理用药提供参考。

1 降糖药的增敏作用改善多囊卵巢综合征患者的胰岛素抵抗

1.1 双胍类降糖药

二甲双胍是2型糖尿病的首选药物，因其增加周围组织对胰岛素的敏感性、非胰岛素依赖的组织对葡萄糖的利用等，自20世纪90年代起即被超说明书用于PCOS的临床治疗。单用或与氯米芬、来曲唑合用，均能降低PCOS患者的胰岛素抵抗，并增加排卵和怀孕的可能，但由于病例数量相对较少、早期一些研究没有设立对照组，其治疗地位证据有限[5]。2000年，Moghetti等[6]利用糖钳夹试验研究服用二甲双胍6个月后，与空白对照相比，PCOS患者血清胰岛素和睾酮水平明显降低，胰岛素敏感性增加，月经周期调整。Ng等[7]通过测定内脏脂肪量、胰岛素抵抗水平，研究中国PCOS患者内脏脂肪与心血管代谢疾病风险的关系，190例PCOS患者与416名糖耐量正常的健康女性相比，内脏肥胖者具有更强的胰岛素抵抗问题，可优选二甲双胍，既可降低胰岛素水平，减少雄激素的产生并恢复正常月经周期[8]，又可预防妊娠糖尿病的发生。

1.2 噻唑烷二酮类降糖药

Zhao等[9]利用网络荟萃分析口服二甲双胍、噻唑烷二酮类药物、肌醇和小檗碱改善PCOS患者内分泌和代谢的效果，共纳入1079例患者，结果显示肌醇+二甲双胍+噻唑烷二酮类联合给药在降低雄激素水平和改善胰岛素抵抗上优于二甲双胍单药治疗。

1.3 二肽基肽酶4抑制剂

Tao等[10]对75例新诊断为2型糖尿病的PCOS患者进行比照研究，接受二甲双胍或沙格列汀或联合治疗24周。3组用稳态模型（homeostasis model assessment，HOMA）指数、胰岛素抵抗指数（HOMA-insulin resistance index，HOMA-IR）均显著降低、处置指数（disposition index，DI）提高，但组间差异无统计学意义；联合治疗组糖化血红蛋白下降明显优于单药治疗组，还可显著降低体质指数（body mass index，BMI）和超敏C反应蛋白水平。

1.4 钠-葡萄糖协同转运蛋白2抑制剂

Elkind-Hirsch等[11]通过单盲方式应用艾塞那肽、达格列净、艾塞那肽/达格列净、达格列净/缓释二甲双胍、苯丁胺/托吡酯缓释制剂治疗非糖尿病PCOS患者，研究纳入119例患者，治疗24周后结果显示，单方或复方制剂都可降低空腹血糖、平均血糖水平，提高胰岛素敏感性，降低雄激素、血压和体脂水平，艾塞那肽/达格列净的联合治疗临床获益优于单药或其他联合用药。

2 降糖药的减重作用降低多囊卵巢综合征患者的代谢风险

2.1 双胍类降糖药

减重可恢复排卵性月经周期并改善代谢风险，是多数PCOS患者的一线干预措施。Gangale等[12]用二甲双胍500 mg每日3次治疗140例超重PCOS患者，12个月后发现NAFLD和高胰岛素血症的发病率显著降低。Yang等[13]进行前瞻性队列研究二甲双胍对PCOS的长期影响，共119例患者，每日给予二甲双胍，连续治疗24个月后可改善超重和正常体质量的PCOS女性月经周期和大部分激素水平。与基线相比，6个月时月经频率增加，体质指数（body mass index，BMI）、睾酮和黄体生成素水平下降，进一步分层分析发现正常体质量组的女性激素水平6个月时达到最大幅度改善并维持稳态，而超重组患者则需12个月。

Harborne等[14]进行前瞻性随机对照队列研究，给予超重和肥胖PCOS患者每日1500 mg或2550 mg二甲双胍4~8个月，两组剂量均可显著减重，且肥胖亚组显示剂量相关性。仲晓荣等[15]研究不同剂量二甲双胍对超重和肥胖PCOS患者BMI和外周血炎性反应指标水平的影响，127例患者接受二甲双胍1500 mg每日3次治疗，6个月后将HOMA指数≥2.5的患者纳入高剂量组，即每日2500 mg持续治疗6个月，超重组仍维持原剂量。结果超重（25 kg/m^2<BMI

≤30 kg/m²)组常规剂量即可显著改善各项指标,而肥胖(BMI>30 kg/m²)组则需服用高剂量二甲双胍。有关二甲双胍的治疗剂量,生殖内分泌专科医师多处方1500 mg[16]。高剂量的二甲双胍是否有助于其他疾病的改善还需有待研究。

2.2 胰高血糖素样肽1受体激动剂

利拉鲁肽已在美国被批准用于BMI≥30 kg/m²的个体减重,但尚未批准用于PCOS。目前有限的数据提示,与安慰剂比较,利拉鲁肽在使患者减重的同时,肝脏、内脏脂肪组织含量分别降低了44%和18%,NAFLD患病率降低了2/3,游离睾酮水平下降19%,糖化血红蛋白、空腹血糖和瘦素水平降低[17-18]。但需注意的是,动物实验证明过多的雄激素会降低胰高血糖素样肽1(glucagon-like peptide-1,GLP-1)受体激动剂的降压作用,在改善女性心血管危险因素的同时可能需要额外的治疗控制血压升高[19]。2021年6月,美国食品药品管理局(Food and Drug Administration,FDA)批准司美格鲁肽注射液(周制剂)用于BMI≥30 kg/m²的患者减重。Siamashvili等[20]建议对超重或肥胖的PCOS患者给予GLP-1受体激动剂。

3 二甲双胍诱导排卵及降低卵巢过度刺激综合征风险

一线诱导排卵药为芳香酶抑制剂氯米芬和来曲唑,氯米芬应用多年,而来曲唑可进一步提升活产率[21],但亦为超说明书用药。Morin-Papunen等[22]对320例PCOS患者进行多中心随机双盲安慰剂对照研究,结果显示二甲双胍+标准不孕治疗使妊娠机会增加1.6倍,肥胖女性经二甲双胍预治疗3个月后联合常规促排卵治疗效果明显。对于氯米芬耐药的患者,联合二甲双胍序贯治疗是更好的选择[23]。Fleming等[24]的随机安慰剂对照试验结果表明,二甲双胍可显著改善卵巢功能和异常的排卵频率,延长治疗还可改善心血管危险因素。

诱导排卵和体外受精存在卵巢过度刺激综合征(ovarian hyperstimulation syndrome, OHSS)风险,期间使用二甲双胍可降低PCOS患者OHSS风险[25]。Wu等[26]的荟萃分析也证实此点。

4 二甲双胍在多囊卵巢综合征治疗中的安全性和经济性研究

4.1 二甲双胍对多囊卵巢综合征孕妇和子代的影响

Cao等[27]的系统评价研究表明,与安慰剂对比,1229例PCOS患者使用二甲双胍可降低早产风险、增大新生儿头围,但对新生儿体长和出生体质量无影响。Scherneck等[28]利用Embryotox药物警戒库2004—2014年的孕妇数据,纳入336例孕妇样本及1011例匹配的对照组,妊娠前3个月使用二甲双胍组的重大出生缺陷和自然流产发生率均未显著增加。Zhao等[29]荟萃分析了二甲双胍用于PCOS孕妇的安全性和有效性,共纳入17项研究、2899例患者,与对照组相比,二甲双胍明显降低早产率、早期流产率、妊娠糖尿病率和先兆子痫、孕期胰岛素的需求,并能控制孕妇的体质量增加。

二甲双胍可通过胎盘,在胎儿脐带血中的浓度与母体血中浓度接近。Hanem等[30]随访182例PCOS患者的子代,探讨二甲双胍宫内暴露对子代生长发育至4岁的影响,从妊娠早期到分娩分别给予二甲双胍1700 mg每日1次或2000 mg每日1次或安慰剂,在未行干预措施下测量子代4岁时的身高差异无统计学意义;但用药组体质量、BMI和超重/肥胖儿童数高于安慰剂组。Hanem等[31]进一步分析,在儿童基线可比的情况下,3.5年内子代BMI有明显增加的趋势,并得到了动物研究的支持。虽然BMI增加对未来健康的影响尚不确定,但该结果不应被忽视,可视为广泛使用二甲双胍的警示信号。2022年美国糖尿病学会(American Diabetes Association,ADA)指南提示,当二甲双胍治疗PCOS并诱导排卵时,应在妊娠第3个月末停用[32]。

基于动物研究,英国、美国药品说明书提示二甲双胍可能分泌进入乳汁,如果乳母在用药期间准备哺乳,需要考虑潜在的影响风险。Briggs等[33]研究测定了哺乳期女性血液和乳汁中的二甲双胍浓度,发现二甲双胍在乳汁与血清中的平均浓度比为0.63,估计婴儿体内平均剂量占母亲体质量调整剂量的0.65%。虽然数据有限,但表明婴儿的平均二甲双胍暴露量很低,对其血糖无不良影响。

4.2 二甲双胍早期介入多囊卵巢综合征治疗具有成本-效果优势

在美国，与PCOS相关生殖内分泌失调的初始诊治费用已从2004年的26亿美元升至2020年37亿美元[34]。如果考虑妊娠相关和长期疾病（妊娠期糖尿病、高血压等）的治疗费用，则PCOS相关经济负担总额达80亿美元，其中对症处置和长期治疗费用各占一半。Alenzi等[35]利用决策树模型评估了二甲双胍降低PCOS妊娠期糖尿病风险的成本-效果，假设10 000例PCOS孕妇进入队列，应用二甲双胍平均可节省759.34万美元，表明早期用药具有成本-效果优势。

综上所述，基因组学研究发现，PCOS涉及神经-内分泌、代谢和生殖系统，为此，PCOS患者的治疗需要包括内分泌、皮科、妇产科、心理医学科、儿科、营养科和药剂科等多学科团队的管理[36]。各类降糖药在真实世界中研究性用于PCOS治疗，不仅有益于纠正PCOS患者的胰岛素抵抗和雄激素过多问题，还可改善生育、降低代谢综合征的风险。但目前多属于超说明书用药，进一步探寻其治疗PCOS的最佳剂量、发现PCOS引发代谢风险的人群（某特定亚型、种族和发生的时间段[37]）、考察用药对其子代生长发育的影响等，需要在真实世界中不断收集证据。药师在关注降糖药用于PCOS治疗基础、转化和临床应用的同时，也要开展相关药品的综合评价，为进一步修订说明书、改善临床代谢并发症为终点，共同应对PCOS之未满足的治疗需求。

【参考文献】

[1] Bozdag G, Mumusoglu S, Zengin D, et al. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and Meta-analysis[J]. Hum Reprod, 2016, 31(12): 2841-2855.

[2] 中华医学会妇产科学分会内分泌学组及指南专家组. 多囊卵巢综合征中国诊疗指南[J]. 中华妇产科杂志, 2018, 53(1): 2-6.

[3] Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome[J]. Fertil Steril, 2018, 110(3): 364-379.

[4] Yanes Cardozo LL, Romero DG. Management of cardiometabolic complications in polycystic ovary syndrome: unmet needs [J]. FASEB J, 2021, 35(11): e21945.

[5] Practice Committee of the American Society for Reproductive Medicine. Role of Metformin for Ovulation Induction in Infertile Patients with Polycystic Ovary Syndrome (PCOS): a Guideline [J]. Fertil Steril, 2017, 108(3): 426-441.

[6] Moghetti P, Castello R, Negri C, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation [J]. J Clin Endocrinol Metab, 2000, 85(1): 139-146.

[7] Ng NYH, Liu KH, Tam CHT, et al. The relationship between visceral adiposity and cardiometabolic risk in Chinese women with polycystic ovary syndrome[J]. Obes Res Clin Pract, 2021, 15(6): 593-599.

[8] Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome[J]. J Clin Endocrinol Metab, 2005, 90(7): 4068-4074.

[9] Zhao H, Xing C, Zhang J, et al. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network Meta-analysis [J]. Reprod Health, 2021, 18(1): 171.

[10] Tao T, Wu P, Wang Y, et al. Comparison of glycemic control and β-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment[J]. BMC Endocr Disord, 2018, 18(1): 14.

[11] Elkind-Hirsch KE, Chappell N, Seidemann E, et al. Exenatide, dapagliflozin, or phentermine/topiramate differentially affect metabolic profiles in polycystic ovary syndrome[J]. J Clin Endocrinol Metab, 2021, 106(10): 3019-3033.

[12] Gangale MF, Miele L, Lanzone A, et al. Long-term metformin treatment is able to reduce the prevalence of metabolic syndrome and its hepatic involvement in young hyperinsulinaemic overweight patients with polycystic ovarian syndrome [J]. Clin Endocrinol (Oxf), 2011, 75: 520-527.

[13] Yang PK, Hsu CY, Chen MJ, et al. The efficacy of 24-month metformin for improving menses, hormones, and metabolic profiles in polycystic ovary syndrome [J]. J Clin Endocrinol Metab, 2018, 103(3): 890-899.

[14] Harborne LR, Sattar N, Norman JE, et al. Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses [J]. J Clin Endocrinol Metab, 2005, 90(8): 4593-4598.

[15] 仲晓荣，王秀美，刘娅，等. 不同剂量二甲双胍对超重和肥胖多囊卵巢综合征患者体质指数和外周血炎性反应指标水平的影响[J]. 临床药物治疗杂志, 2022, 20(5): 21-26.

[16] Ma RL, Zou Y, Wang W, et al. Obesity management in polycystic ovary syndrome: disparity in knowledge between obstetrician-gynecologists and reproductive endocrinologists in China[J]. BMC Endocr Disord, 2021, 21(1): 182.

[17] Frøssing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: a randomized clinical trial [J]. Diabetes Obes Metab, 2018, 20 (1): 215-218.

[18] Lamos EM, Malek R, Davis SN. GLP-1 receptor agonists in the treatment of polycystic ovary syndrome[J]. Expert Rev Clin Pharmacol, 2017, 10(4): 401-408.

[19] Torres Fernandez ED, Huffman AM, Syed M, et al. Effect of

GLP-1 receptor agonists in the cardiometabolic complications in a rat model of postmenopausal PCOS [J]. Endocrinology, 2019,160(12):2787-2799.
[20] Siamashvili M, Davis SN. Update on the effects of GLP-1 receptor agonists for the treatment of polycystic ovary syndrome [J]. Expert Rev Clin Pharmacol,2021,14(9):1081-1089.
[21] Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome[J]. N Engl J Med, 2014,371(7):119-129.
[22] Morin-Papunen L, Rantala AS, Unkila-Kallio L, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial [J]. J Clin Endocrinol Metab,2012,97(5):1492-1500.
[23] George SS, George K, Irwin C, et al. Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: a randomized, controlled trial[J]. Hum Reprod,2003,18(2):299-304.
[24] Fleming R, Hopkinson ZE, Wallace AM, et al. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial [J]. J Clin Endocrinol Metab, 2002, 87(2): 569-574.
[25] Palomba S, Falbo A, Carrillo L, et al. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial [J]. Fertil Steril ,2011,96(4):1384-1390.
[26] Wu Y, Tu M, Huang Y, et al. Association of metformin with pregnancy outcomes in women with polycystic ovarian syndrome undergoing in vitro fertilization: a systematic review and Meta-analysis [J]. JAMA Netw Open, 2020, 3 (8): e2011995.
[27] Cao Q, Hu Y, Fu J, et al. Gestational metformin administration in women with polycystic ovary syndrome: a systematic review and Meta-analysis of randomized control studies[J]. J Obstet Gynaecol Res, 2021,47(12):4148-4157.
[28] Scherneck S,Schlinke N, Beck E,et al. Pregnancy outcome after first-trimester exposure to metformin: a prospective cohort study [J]. Reprod Toxicol,2018,81(10):79-83.
[29] Zhao Q, He J. Efficacy and safety of metformin in pregnant women with polycystic ovary syndrome: a systematic review with Meta-analysis of randomized and non-randomized controlled trials [J]. Gynecol Endocrinol,2022,38(7):558-568.
[30] Hanem LGE, Stridsklev S, Júlíusson PB, et al. Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs[J]. J Clin Endocrinol Metab,2018,103(4):1612-1621.
[31] Hanem LGE, Ødegård R, Vanky E. Response to letter to the editor: "metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs" [J]. J Clin Endocrinol Metab,2018,103(9):3521.
[32] American Diabetes Association.Introduction: Standards of Medical Care in Diabetes-2022[J].Diabetes Care, 2022, 45(Suppl): S1-S2.
[33] Briggs GG, Ambrose PJ, Nageotte MP, et al. Excretion of metformin into breast milk and the effect on nursing infants [J]. Obstet Gynecol, 2005,105(6):1437-1441.
[34] Riestenberg C, Jagasia A, Markovic D, et al. Health care-related economic burden of polycystic ovary syndrome in the United States: pregnancy-related and long-term health consequences[J]. J Clin Endocrinol Metab,2022,107(2):575-585.
[35] Alenzi EO. Cost-effectiveness analysis of polycystic ovary syndrome management and the risk of gestational diabetes in pregnant women: a decision-tree model[J]. Expert Rev Pharmacoecon Outcomes Res,2021,21(5): 995-999.
[36] Del Pup L, Cagnacci A. IMPROVE lifestyle in polycystic ovary syndrome: a systematic strategy[J]. Gynecol Endocrinol, 2021, 37(10):875-878.
[37] Allen LA, Shrikrishnapalasuriyar N, Rees DA.Long-term health outcomes in young women with polycystic ovary syndrome: a narrative review [J]. Clin Endocrinol (Oxf), 2022, 97(2): 187-198.

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