

肌醇类药物应用对助孕技术结局的影响

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近年来,我国不孕症发病率逐年上升,成为继心血管疾病、肿瘤的第三大疾病^[1]。辅助生殖技术(assisted reproductive technology, ART)是解决不孕症的最终治疗手段,即采用医疗辅助技术使不孕夫妇实现妊娠。ART包括人工授精和体外受精-胚胎移植(in vitro fertilization and embryo transfer, IVF-ET)及其衍生技术。随着ART的不断发展,为提高配子质量及ART妊娠率,临床上开始应用一些辅助药物如叶酸、维生素、辅酶Q10、生长激素、肌醇等。其中,肌醇作为一种胰岛素增敏剂和抗氧化剂,可能具有降糖、抗氧化^[2-3]等治疗作用,目前该类药物在辅助生殖领域的应用还处于探索阶段,本文就目前已有文献,对肌醇类药物在ART中的应用情况进行综述。

1 肌醇的概念

肌醇是一种饱和环状多元醇,化学结构(环己烷-1,2,3,4,5,6-己醇)与葡萄糖相似,是具有9种异构体的六羟基环己烷,属于碳水化合物^[4],目前已发现4种存在的肌醇异构体分别为肌肉肌醇(myo-inositol, MI)、D-手性肌醇(D-chiro-inositol, DCI)、L-手性肌醇、鲨肌醇,其中最常见的是MI和DCI,在水果、豆类、玉米、坚果等食物中肌醇含量较高。MI(MI-顺式1,2,3,3,5-反式4,6-环己烷己醇)是人体内含量最丰富的肌醇异构体,主要来源于各种食物,包括全麦、种子、水果,并且MI可以在人体中合成,从6-磷酸葡萄糖变成6-磷酸肌醇,随后被肌醇单磷酸酶1脱磷酸,产生游离的MI^[5]。DCI(DCI-顺式-1,2,4-反式-3,5,6-环己烷己醇)是MI的C1羟基的异构化产物,在自然界中以化合物形式存在于大豆、

荞麦等植物中,在人体内能通过胰岛素依赖性差向异构酶将MI转换为DCI^[6],大多分布于脂肪、肌肉和肝脏内^[7]。临床上肌醇类药物主要指MI和DCI,具有促进肝脏脂肪代谢、胰岛素增敏、调节糖代谢、抗氧化、抗炎等功能^[8-11]。

肌醇也是人体内一种重要的多功能化合物,能通过脂质依赖和非依赖途径磷酸化产生多种衍生物,主要以游离形式或磷脂酰肌醇的形式存在于细胞内^[12],在调节离子通道开放、细胞内Ca²⁺信号传导、细胞骨架重排、葡萄糖代谢、调节细胞增殖等方面发挥着重要作用^[13-16]。其衍生物肌醇三磷酸作为第二信使,通过胞浆扩散并与内质网表面的肌醇三磷酸受体结合,触发细胞内Ca²⁺释放,可参与包括受精、细胞生长、转化、分泌、平滑肌收缩、感觉感知及神经元信号传递等在内的许多生理过程^[17]。并且,肌醇也是磷脂的前体,可参与哺乳动物卵母细胞中重要的细胞内信号的产生、参与多精子的抑制、减数分裂的完成及随后的胚胎发育等过程^[18]。有文献报道卵巢组织中,MI主要参与糖的吸收和促性腺激素信号通路,DCI主要参与胰岛素调节及睾酮生物合成^[19]。

2 肌醇类药物与多囊卵巢综合征

多囊卵巢综合征(polycystic ovary syndrome, PCOS)是一种育龄女性常见内分泌疾病,在我国妇女中该病的发病率约为5.6%^[20]。PCOS患者会出现排卵障碍、月经不调、肥胖、多毛、痤疮等表现,常伴有胰岛素抵抗(insulin resistance, IR)、高胰岛素血症,部分患者会导致不孕。一些学者认为补充肌醇可帮助PCOS患者改善症

状,每次 2 mg、每天 2 次服用肌醇可使其生物利用度达到 24 h 全覆盖^[21]。有研究报道 PCOS 患者每日补充 1.75 g MI、0.25 g DCI 和 4 g 葡甘露聚糖治疗 3 个月后,治疗组与自身相比体质量指数明显下降^[22]。另一研究显示每日补充 2 g 肌醇与 0.5 mg 的 L-酪氨酸、0.2 mg 叶酸、55 ug 硒、40 ug 铬联合使用 3~6 个月,可帮助 PCOS 妇女减轻体重并恢复正常的月经周期和排卵^[23]。有学者认为 IR 可能是 PCOS 发病机制中的核心环节^[24],肌醇可促进 PCOS 患者卵母细胞成熟,改善 IR^[25-27],并改善糖代谢、增加获卵率^[28]。其具体机制可能是肌醇类药物通过激活控制葡萄糖代谢的酶,在糖代谢中起重要作用,进而改善 PCOS 患者的 IR 来纠正代谢参数^[29]。

另外,对于二甲双胍、克罗米芬耐药的 PCOS 患者,肌醇可能具有更高的临床应用价值。多项研究表明,使用肌醇和二甲双胍治疗 PCOS 患者时,其糖代谢水平及性激素水平改善情况无明显差异,但对于脂代谢紊乱或不能耐受二甲双胍治疗的患者,肌醇可起到更好的疗效^[17,30-32]。一项临床随机、单盲、对照试验也表明,对于体质量指数正常但对来曲唑耐药的 PCOS 患者,添加肌醇和二甲双胍可改善卵巢功能,并且肌醇比二甲双胍更有效^[33]。此外,MI 还能降低克罗米芬的耐药率,提高 PCOS 患者对克罗米芬的敏感性^[34]。

对于行 ART 助孕的 PCOS 患者来说,补充肌醇也可能有积极的作用。有研究发现 MI(550 mg/d)与高剂量 DCI(300 mg/d)结合使用可改善接受胞浆内精子注射(intracytoplasmic sperm injection, ICSI)的 PCOS 妇女的卵母细胞胞质质量,而 MI(550 mg/d)与高剂量 DCI(150 mg/d)的组合可提高接受 ICSI 的 PCOS 女性妊娠率并降低卵巢过度刺激综合征(ovarian hyper-stimulation syndrome, OHSS)的风险^[35-36]。另一项研究对接受 ICSI 治疗的 PCOS 患者,从促性腺激素(gonadotrophin, Gn)启动当天开始接受肌醇(2 g/bid)联合叶酸(400 ug/d)连续治疗,结果肌醇组消耗重组卵泡刺激素(recombinant follicle-stimulating hormone, rFSH)总剂量和 Gn 天数显著减少,且人绒毛膜促性腺激素(human chorionic gonadotropin, hCG)扳机日雌二醇的峰值水平显著降低,可降低 OHSS 的风险,同时未成熟卵母细胞和退化卵母细胞的平均数量显著减少,但不会降低获卵总数,MI 卵母细胞比例也有增加的趋势^[37]。Yaylal A 等^[29]回顾性分析了 109 例 IVF 第一周期拮抗剂方案的 PCOS 患者,结果显示实验组应用 3 个月肌醇(4 g/d)要比对照组异常卵母细胞的数量少,但在其他卵泡及胚胎发育参数的差异没有统计学差异。Wdowiak A 等^[38]在为接受 ICSI 助孕的 PCOS 患者进行 3 个月肌醇(4 g/d)和叶酸(400 mg/d)预处理,结果显示肌醇组妊娠率高于对照组,并且可提高胚胎发育动力学并加速胚泡期到达时间,缩短养成囊胚的时间。另外一项前瞻性观察研究显示,MI(1.1 g/d)和 DCI(27.6 mg/d)联合使用可改善接受 IVF-ET 的 PCOS

妇女的卵母细胞和胚胎质量以及妊娠率^[39]。但也有学者认为,尚没有足够有力的证据表明肌醇对卵巢储备标志物有影响,不能支持在 PCOS 妇女行 IVF/ICSI 助孕前将其用作预处理^[40]。综上,肌醇类药物对于 PCOS 患者的治疗可能具有积极的作用,但在 ART 助孕时是否添加肌醇,还需要更深入的探讨。

3 肌醇类药物与卵子质量

各种原因导致的卵子质量下降,可导致受精能力及胚胎发育潜能的降低、反复种植失败、流产率及出生缺陷率的增加^[41],从而导致女性不孕症的发生。在利用 ART 帮助这部分患者制定个体化方案的同时,辅助药物的应用也是不容忽视的一部分。研究者们对于肌醇是否能改善卵子质量进行了探讨,发现卵泡液中的 MI 水平与雌二醇含量及胚胎质量呈正相关,提示高浓度 MI 可能在卵泡成熟中发挥作用,并可成为潜在优质卵母细胞标志物^[42]。在小鼠模型中,DCI 治疗能改善老年小鼠和 PCOS 小鼠模型卵母细胞质量、提高着床率、改善胚胎发育^[43]。动物研究表明 MI 可能通过增强细胞内 Ca^{2+} 振荡来影响小鼠 GV 期卵母细胞的减数分裂进程,在培养基中补充 MI 可能对人卵母细胞的成熟有用^[44]。

Unfer V 等^[45]学者认为 PCOS 患者排卵减少及卵母细胞质量变差可能是由于卵巢中差向异构酶活性增加导致局部 MI 缺乏,进而引起 MI 和 DCI 比例失调,所以补充合适比例的 MI 和 DCI 可能对改善卵巢功能有作用。目前部分研究结果支持肌醇类药物的应用能改善卵子质量、提高生育能力,在进入 IVF 周期的患者中应用可产生积极影响,但具体用法用量尚未统一,需进一步研究。对进入 IVF 周期的患者进行 3 个月 MI(4 g/d)加褪黑素(3 mg/d)预处理,成熟卵母细胞数、受精率、可移植胚胎数及优质胚胎数均显著高于前一周期,且卵子质量得到较好的改善^[46]。一项对 562 例 PCOS 妇女的随机对照双盲研究也有相似结论,从进入 IVF 周期第 1 天给予 MI(4 g/d)和褪黑素(3 mg/d)一直持续到胚胎移植后 14 天,结果显示二者联合使用可协同增强卵母细胞和胚胎的质量^[47]。另一项随机对照试验显示,PCOS 患者每日补充 2 g MI 和 200 ug 叶酸可通过减少退化和未成熟卵母细胞的数量来改善卵母细胞的质量,从而提高胚胎的质量^[48]。而对非 PCOS 的超重或肥胖女性在进入 IVF 周期前 3 个月补充 MI(2 g/d)、 α -硫辛酸(800 mg/d)和叶酸(400 mg/d),对卵母细胞和胚胎形态可能产生有益的影响,提高临床妊娠率和活产率^[49]。此外,在多次接受促排卵的非 PCOS 患者中,补充叶酸(400 ug/d)和 MI(4 mg/bid)可减少成熟卵母细胞的数量和 rFSH 的剂量,同时保持临床妊娠率^[18]。总的来说,补充肌醇可能对提高胚胎质量、减少促排卵药物的用量、同时可改善行 IVF-ET 或 ICSI 的不孕患者的临床妊娠率有利,但具体的机制还需要进一步探索。

4 肌醇类药物与卵巢低反应

在控制性促排卵方案使用中,卵巢储备减少的患者对外源性促性腺激素低反应,是目前生殖领域中最具挑战的难题之一^[50]。对于卵巢反应功能低下的患者,补充肌醇类药物是否能够改善此类患者助孕结局,仍有待进一步研究。一项前瞻性研究中,以 72 例卵巢低反应患者为研究对象,在 ICSI 前 3 个月服用 MI (4 g/d) 和叶酸 (400 μ g/d) 预处理,结果显示治疗组的促排卵药物用量减少,且 MII 卵母细胞获得率显著升高,卵巢对促性腺激素敏感性得到改善,且两组间的雌二醇水平无显著性差异^[51]。另一项研究用上述剂量的 MI 和叶酸对接受 ICSI 的卵巢低反应患者从 ICSI 前 1 个月开始服用到取卵日当天,结果也表明 MI 可提高受精率和胚胎质量,并可提高卵巢低反应患者的累积妊娠率^[52]。但目前有关肌醇类药物与卵巢低反应患者的研究较少,补充肌醇对于这类人群改善助孕结局是否有效,还需要大量对照研究进行进一步论证。

5 肌醇类药物与精子质量

根据世界卫生组织的数据,男性不育患者中精子因素几乎占有所有病例的 50%,较高的精子质量将对 ART 助孕成功率产生积极影响^[53]。目前,抗氧化剂疗法是治疗少、弱精子症应用较广泛的方法,而 MI 作为典型的抗氧化剂可降低氧化应激对不育男性精子质量及生育能力的影响,改善精液参数,降低精子 DNA 碎片率^[14,32,54-55]。少、弱精子症患者口服 MI 可显著改善其精液参数^[56]。有研究对这类患者补充 MI、 α -硫辛酸、叶酸、甜菜碱和维生素组成的营养物质治疗 90 天后的精液进行了分析,结果显示精子浓度、精子数量、精子前向性运动、活动精子总数和正常精子形态增加均有统计学意义,可改善低生育力男性的精子参数^[57]。另一项研究对少、弱精子症患者口服包含 MI 的营养保健品并在体外精子培养时上添加用 MI,结果表明在体外和体内治疗后,精子的活动性、活力均增加,MI 的应用可改善精子的体外和体内性能^[58]。此外, Montanino OM 等^[59]发现使用 MI 阴道栓剂的夫妇其精子活力、宫颈黏液质量得到改善,宫颈粘液的黏度下降,从而提升了妊娠率,并且其使用对母婴均具有安全性。

另一方面,除了可口服肌醇类药物改善少、弱精子症患者精子质量外,多项研究证明体外补充 MI 对于冷冻保存的精液的存活率有着积极的作用,MI 可通过增加精子线粒体膜电位来增加少、弱精子症患者的精子活动性,从而提升受精率^[52,60-62], Abdolsamadi M 等^[61]用添加了 MI (2 mg/mL) 的培养基冷冻精液样本,与对照组相比,冻融精子的精子活动力、精子前向运动力都能得到明显的改善,总抗氧化能力更高,能降低冻融后精子的 DNA 断裂,表明 MI 可作为精子冷冻的良好补充剂。Condorelli RA 等^[63]比较了少、弱精子症患者和健康男性

加入 MI 前后精液样本的精子活力,结果显示加入 MI 孵育后对精子运动性产生积极的影响。总之,肌醇作为抗氧化剂在改善少、弱精子患者精子质量方面具有一定的潜力,并且可成为潜在的精子冷冻保存的辅助添加剂。

6 小结与展望

综上所述,在辅助生殖领域,临床各项研究表明肌醇类药物在提高卵子与精子质量、改善 PCOS 患者的卵母细胞质量、增加患者对促排卵药物的敏感性以及减少促排卵药物的使用剂量上具有很大潜在优势,未来是否能够将这类药物应用于助孕的辅助用药,还需要对其有效性及安全性进行更多高质量的大数据研究,并对其使用剂量和方法进行规范,以更好地帮助不孕夫妇改善助孕结局。

利益冲突:所有作者均声明不存在利益冲突。

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