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高尿酸血症对女性生殖系统影响的研究进展

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摘　要

高尿酸血症(HUA)是因人体内嘌呤代谢紊乱所引发的一种疾病。尿酸水平升高会诱发人体多种系统性疾病，对身体健康构成严重威胁。已有大量证据显示，高尿酸血症会损害心血管和肾脏。近年来，越来越多的研究发现，高尿酸水平与女性生殖系统疾病紧密相关。本文旨在从多囊卵巢综合征(PCOS)、子宫内膜异位症(EM)和不孕症等方面入手，系统探究高尿酸血症对女性生殖功能的影响及其可能机制，从而为高尿酸血症的早期预防与治疗、保护女性生殖健康提供全新的理论依据和临床策略。

关键词

高尿酸血症，女性生殖系统，综述

Research Progress on the Effects of Hyperuricemia on Female Reproductive System

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Abstract

Hyperuricemia (HUA) is a disease caused by a disorder of purine metabolism in the human body. Elevated uric acid levels can induce a variety of systemic diseases in the body, posing a serious threat to health. It has been well documented that hyperuricemia damages the cardiovascular and renal organs. In recent years, more and more studies have found that high uric acid levels are strongly associated with female reproductive disorders. The aim of this paper is to systematically investigate the effects of hyperuricemia on female reproductive function and its possible mechanisms,

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starting from polycystic ovary syndrome (PCOS), endometriosis (EM) and infertility, so as to provide a brand-new theoretical basis and clinical strategy for the early prevention and treatment of hyperuricemia and the protection of female reproductive health.

Keywords

Hyperuricemia, Female Reproductive System, Review

1. 引言

尿酸作为嘌呤代谢的终产物，70%经肾脏排泄，30%则通过肠道排出，若尿酸生成过多或排泄减少，均可能引发高尿酸血症[1]。流行病学显示[2]，高尿酸血症在发展中国家和发达国家正愈发常见。2018 年依据美国国家健康与营养调查开展的一项研究显示，14.0%的中国成年人患有高尿酸血症(HUA)，约 20%的美国成年人患有 HUA，估计全球普通人群中约有 8.9%至 24.4%的人患有 HUA。近年来，HUA 已成为一个重要的全球公共卫生问题。HUA 与多种健康问题相关，包括糖尿病、高血压、心血管疾病(CVD)、痛风、代谢综合征、肝功能障碍和肾功能障碍等。研究表明[3]-[5]，尿酸在正常生理水平下具有保护性抗氧化作用，占血浆总抗氧化能力的三分之二，是一种重要的抗氧化有机化合物，在清除氧自由基和调节免疫系统以促进发育方面发挥着不可或缺的作用，并且在人体中扮演着重要角色，然而，过高的尿酸水平可以诱发氧化应激、炎症反应、异常脂质代谢等过程，是肾病、心血管疾病和代谢综合征的危险因素。近年来有不少文献发现一些女性生殖系统的疾病与尿酸水平密切相关，一项美国 2013 年至 2020 年的 NHANES 数据库调查显示，血清尿酸水平升高与女性不孕症之间存在正相关[6]，另有一项研究指出血液中的尿酸水平可以作为预测患有妊娠高血压综合征的女性及其胎儿并发症的指标[7]，本文将全面综述 HUA 对女性生殖系统的影响，并梳理其可能的作用机制，从而为后续研究提供理论依据。

2. 高尿酸血症与女性生殖系统疾病

高尿酸血症作为一种常见代谢疾病，其对女性生殖系统的损害不容忽视，尿酸可通过多种途径参与女性生殖系统疾病的过程，目前研究指出，高尿酸与多囊卵巢综合征、子宫内膜异位症、不孕症的发展密切相关，而胰岛素抵抗、炎症小体激活及激素水平代谢失衡是连接高尿酸血症与女性生殖疾病交叉的核心枢纽。

2.1. 高尿酸血症与多囊卵巢综合征

多囊卵巢综合征(PCOS)是育龄妇女的常见病。主要特征为月经稀少、排卵不规律及卵巢形态多囊等临床症状，并伴有多种代谢异常，包括高雄激素、高胰岛素血症、血脂异常和内脏肥胖。多囊卵巢综合征是最常见的内分泌疾病之一，影响着 4%~21%的育龄妇女[8] [9]。既往研究表明，PCOS 患者易出现一定程度的高尿酸血症，许多患有多囊卵巢综合征(PCOS)的女性存在生殖激素失衡问题，高水平的雌激素和雄激素会导致血清尿酸(SUA)水平降低。研究表明，高尿酸血症可能并非多囊卵巢综合征(PCOS)的唯一诱因，但与胰岛素抵抗(IR)、高雄激素水平以及肥胖等因素相互作用时，可能会加剧该综合征的发展[9] [10]。

胰岛素抵抗(IR)已被认为是多囊卵巢综合征(PCOS)发病机制和病情进展的主要致病因素[11] [12]。现有研究[13]指出，胰岛素可能通过双重作用机制增强肾脏尿酸重吸收：一方面直接激活尿酸转运蛋白URAT1，另一方面刺激肾近端小管刷状缘膜上的钠依赖性阴离子共转运系统，这两种协同作用显著提升了肾小管对尿酸的重吸收效率。一项前瞻性研究调查了低能量饮食或胰岛素增敏剂对超重高血压患者胰岛素抵抗的影响，结果显示，干预措施显著改善了胰岛素抵抗，进而致使血清尿酸水平下降[14]。另有观点认为，一旦胰岛素抵抗得到改善，胰岛素增强的肾小管尿酸重吸收作用将相应减弱，从而降低体内血清尿酸水平。

研究表明，中国人群中 SUA 水平与患者肥胖率也许存在显著正相关性[15]。一项回顾性研究发现，患有高尿酸血症的 PCOS 患者比非高尿酸血症组表现出更高的体重和体重指数(BMI)。此外，内脏脂肪组织(VAT)质量、体积和面积的上升模式与血清尿酸(SUA)水平显示出统计学显著相关性[16]。一项针对 2 型糖尿病合并世界卫生组织 II 级或以上肥胖患者的研究显示，手术诱导的减重可使血尿酸水平出现具有临床意义的下降[17]。而体重减轻导致血尿酸水平下降机制并不明确，但普遍认为该机制受多重因素影响[14] [18]，包括胰岛素抵抗改善和活性氧(ROS)水平降低。这一推论基于以下病理生理学前提：肥胖相关高尿酸血症的发病机制受胰岛素抵抗、脂质过氧化及活性氧生成的影响。

研究数据还证实，睾酮水平与 SUA 水平之间存在很强的相关性：绝经后妇女补充睾酮会导致 UA 血浆水平显著增加[19]。由于高雄激素血症是多囊卵巢综合征的一个核心特征，并与多种病理生理过程有关，其增加尿酸水平的能力可能会在多囊卵巢综合征和高尿酸血症之间架起一座桥梁。Mumford 团队的一项重要研究中还发现，月经周期中尿酸(UA)水平的波动规律——卵泡期达到峰值后黄体期逐渐下降[20]，此外，还发现 SUA 水平与促卵泡激素(FSH)呈正相关，而与雌二醇和孕酮浓度呈负相关。

2.2. 高尿酸血症与子宫内膜异位症

子宫内膜异位症是一种典型的妇科疾病，约影响 10%~15%的育龄女性，主要症状包括疼痛、月经异常和性交不适[21] [22]。而炎症反应是疾病发展的关键之一。患者体内的炎症细胞因子水平的升高，尤其是白细胞介素-1β (IL-1b)、白细胞介素-6 (IL-6)、白细胞介素-8 (IL-8)、血管内皮生长因子、CCL2、CCL5 以及肿瘤坏死因子-α (TNF-a)。这些促炎因子通过激活 NF-kB、PI3K 和 Akt 信号通路加剧炎症反应[23]-[25]。美国国家健康与营养调查(NHANES)数据库表明，血清尿酸水平与患子宫内膜异位症的风险呈线性正相关，提示子宫内膜异位症风险随尿酸水平升高而持续增加，多项研究表明[5]，尿酸水平升高与炎症反应存在直接关联，尿酸水平升高有助于炎症小体形成，促进 pro-IL-1 向 IL-1β 转化，尿酸浓度升高会导致细胞周围形成尿酸钠(MSU)结晶，进而激活 ASC 接头蛋白、募集人半胱氨酸蛋白酶-1，并通过和 NLR 家族吡啶结构域蛋白 3 (NLRP3)结合形成 NLRP3 炎症小体。这一过程将 MSU 诱导产生的 pro-IL-1 转化为 IL-1β，从而触发炎症反应[26] [27]。该过程通过多重途径加剧炎症反应，进而促使子宫微环境改变及坏死性凋亡，最终参与子宫内膜异位症的病理生理过程[28]-[30]。值得注意的是，IL-1b 还能通过上调 MMP12、MMP1、PAI2 等细胞因子和生长因子来放大炎症反应，促进新生血管形成及基质重塑[31]，这些机制均与子宫内膜异位症的发展密切相关。

2.3. 高尿酸血症与不孕症

不孕症是指育龄夫妇在有规律且无任何避孕措施的性行为持续至少一年后，依旧未能自然受孕的情况。据研究，不孕症可影响高达 15%的育龄夫妇。目前，不孕症的发病率正急剧上升，波及全球范围内日益增多的人群。不孕症不仅对夫妇身心健康造成伤害，还对许多国家的生育率产生负面影响[6]。据报道，33%~41%的不孕症仅由女性因素引起，最常见病因包括排卵功能障碍和输卵管疾病。此外，生活方

式、环境因素以及多囊卵巢综合征、子宫内膜异位症等内分泌疾病也有可能导致女性不孕[32]。

上文提及了高尿酸血症与子宫内膜异位症之间的关联，约有半数的子宫内膜异位症女性患者面临不孕问题[5]。一项基于美国国家健康与营养调查(NHANES)数据的研究显示，血清尿酸水平较高与女性不孕症呈正相关，并且血清尿酸水平与不孕症之间存在非线性联系[6]。研究表明，当高浓度尿酸诱发炎症反应时产生的白细胞介素-1β，可能抑制排卵并阻碍子宫内膜化生，进而影响胚胎着床导致不孕[33] [34]。

3. 高尿酸血症对女性生殖系统疾病作用机制

目前医学界对尿酸影响女性生殖系统疾病的具体机制尚未阐明，但普遍认为 UA 可能参与了体内氧化应激、炎症反应和脂质代谢紊乱的关键环节，从而引发多种病理状态。

3.1. 氧化应激

尿酸是一种已知的抗氧化剂，也是体内抗氧化潜力的主要贡献者。尿酸不仅能清除单线态氧和自由基，还能减少过氧亚硝酸盐对蛋白质的损伤，这些作用参与了体内近半数的抗氧化效应[3]。研究表明，尿酸在人体多种情况下都表现出抗氧化效果，并能通过抗坏血酸的作用迅速恢复其抗氧化状态。然而当抗坏血酸等抗氧化剂含量不足时，尿酸会转变为氧化剂，参与体内以氧化应激为主导的各种病理过程的发生[35]。

氧化应激是一种以病理状态下促氧化剂超过抗氧化剂为特征的状况。这种状态与多种疾病的发病机制相关，包括多囊卵巢综合征、高血压、代谢综合征等病症，有文献报道女性多囊卵巢综合征与氧化应激水平升高呈正相关[9] [36]。黄嘌呤氧化还原酶活性增强以及胰岛素抵抗和血脂异常，在氧化应激背景下具有相当重要的意义。根据现有证据推测，高尿酸血症诱导的氧化应激可能是导致多囊卵巢综合征女性活性氧水平升高的部分原因。研究表明，细胞内尿酸只能通过激活 NADPH 氧化酶和随后产生活性氧(ROS) [37] [38]，以及通过各种其他途径(包括但不限于：降低内皮细胞中的抗氧化一氧化氮水平、激活过亚硝酸盐介导的脂质氧化和刺激促炎症生物标志物)来发挥促氧化作用[39]。NADPH 氧化酶参与 ROS 的生成，可导致促炎信号通路的激活，而这是由丝裂原活化蛋白激酶介导的[39]。此外，在脂质过氧化物存在的情况下，尿酸的促氧化效应表现得尤为显著[40]，从而直接参与代谢综合征的发病机制。

3.2. 炎症作用与血管内皮损伤

研究表明，血液中高浓度的尿酸可激活白细胞对血管内皮细胞的粘附，破坏内皮细胞的结构和功能，进而促进 IL-1β、IL-6、TNF-α 等炎症因子和 ICAM-1 等粘附分子的释放，导致炎症连锁反应和血管内皮损伤的恶性循环。一项关于青少年高尿酸血症的研究发现，血清尿酸浓度与 IL-6 和 TNF-α 等炎症标志物呈正相关，证实高尿酸血症会引发年轻患者的炎症反应[41]。

曾有研究表明促炎细胞因子白细胞介素-1β (IL-1β)是自发性早产的重要介质[42]。体外实验表明，IL-1β 可促进人宫颈成纤维细胞局部孕酮代谢[43]。尿酸这一损伤相关分子模式(DAMP)已被证实可直接激活 NLRP3 炎症小体[44]。内源性尿酸介导的 NLRP3 炎症小体激活现象，此前已在抗磷脂抗体[45]或高糖环境[46]条件下的滋养细胞模型中得到验证。妊娠晚期血清尿酸水平升高与子痫前期孕妇发生早产临产风险增加相关[47]。进一步研究表明，使用黄嘌呤氧化酶抑制剂别嘌呤醇(可通过降低尿酸和活性氧生成)能抑制高糖暴露环境下的 IL-1β 产生。

3.3. 脂质代谢异常

尿酸水平升高不仅与肥胖和血脂异常的发生发展相关[1]，还会通过抑制脂蛋白酶的活性来干扰正常脂质代谢过程，同时改变调控脂肪合成的脂肪细胞因子表达[48]。临床数据研究显示，血清尿酸浓度与血

脂参数存在显著相关性：其中甘油三酯(TG)、总胆固醇(TC)和低密度脂蛋白胆固醇(LDL-C)水平与尿酸具有正相关，而高密度脂蛋白胆固醇(HDL-C)则呈现负相关关系[49]。在机制研究方面，有学者发现尿酸能刺激肝细胞 HepG2 中 NADPH 氧化酶亚型 NOX4 的表达上调，并随后增强该亚型向线粒体的转运，这一过程促进了线粒体超氧化物的生成增加，进而导致乌头酸酶活性降低，乌头酸酶活性的下降引起柠檬酸积累，后者作为新生脂肪生成的底物，最终刺激了脂肪生成[49]。为验证这一假说，已有研究证明，使用别嘌呤醇药物抑制尿酸生物合成可有效减轻果糖的促脂肪生成作用。

此外，细胞内尿酸的病理性蓄积会扰乱生理稳态，促进脂肪组织沉积和糖异生，该效应通过激活 AMP 脱氨酶并同时抑制 AMP 活化激酶来实现[50]。AMPK 通过抑制乙酰辅酶 A 羧化酶 1 活性和丙二酰辅酶 A 向线粒体的转运[51]，以及激活过氧化物酶体增殖物激活受体(PPAR)-α 及其下游靶基因，在脂肪氧化代谢中起关键作用。

4. 小结

尿酸在正常生理水平下具有保护性抗氧化作用，然而，过高的尿酸水平则可以通过氧化应激、炎症反应、血管内皮损伤、异常脂质代谢等过程影响机体健康，在女性生殖系统中，高尿酸血症可导致多囊卵巢综合症、子宫内膜异位症和不孕症。高尿酸血症对女性生殖系统的健康构成威胁：在多囊卵巢综合症患者中，尿酸结晶会引发胰岛素抵抗和高雄激素血症的恶性循环；而在子宫内膜异位症患者中，尿酸结晶会通过激活 NLRP3 炎性体促进炎症反应；在不孕症方面，HUA 引发的氧化应激和炎症微环境可干扰卵泡发育和胚胎着床，此外，还有研究说明尿酸升高对子痫前期及妊娠早产的相关性[52]，其中 NADPH 氧化酶激活、促炎因子释放及脂蛋白酶活性抑制是核心环节。希望此研究结果能够为潜在的预防、治疗和预后评估提供帮助。

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