·综述·

幽门螺杆菌与男性不育的关系

刘晋阳[1]，吴志平[2,3]
(1. 贵州医科大学附属医院泌尿外科，贵阳 550001；2. 贵州省黔南州人民医院泌尿外科，都匀 558000；3. 贵州医科大学临床医学院，贵阳 550001)

摘　要：幽门螺杆菌(Hp)是一种革兰阴性、螺旋型杆菌，是目前医学所知唯一能在胃中生活的细菌，在人群中的感染率较高。幽门螺杆菌与消化性溃疡、慢性胃炎等疾病有着密切的关系，近几年还发现幽门螺杆菌与许多胃外疾病也有关联，甚至与男性不育都有关。由于男性因素所导致的不孕不育的发生率逐年上升，且其中有一部分仍病因不明，为了进一步讨论幽门螺杆菌与不育的关系，本文总结了国外近几年关于幽门螺杆菌和不育的研究，旨在推测和探讨二者之间可能的关系。

关键词：幽门螺杆菌；胃外疾病；男性不育
中图分类号：R698+.2　　**文献标志码**：A　　**文章编号**：1672-3554(2023)04-0601-06
DOI：10.13471/j.cnki.j.sun.yat-sen.univ(med.sci).20230712.001

Relationship between Helicobacter Pylori and Male Infertility

LIU Jin-yang[1], WU Zhi-ping[2,3]
(1. Urology Surgery, the Affiliated Hospital of Guizhou Medical University, Guiyang 550001, China; 2. Urology Surgery, Qiannan People's Hospital of Guizhou Province, Duyun 558000, China; 3. School of Clinical Medicine, Guizhou Medical University, Guiyang 550001, China)
Correspondence to: WU Zhi-ping; E-mail: gzwzp@foxmail.com

Abstract: *Helicobacter pylori* (*H.pylori*) is a gram-negative, spiral-shaped bacillus and it is the only bacteria known in medicine that can live in the stomach, with a high infection rate in the population. Besides its confirmed link to peptic ulcer and chronic gastritis, *H.pylori* has recently been found to be associated with many extragastric diseases, including male infertility. The incidence of male factor infertility keeps rising, but some reasons remain unclear. This paper summarized the research on *H.pylori* and infertility abroad in recent years in order to speculate and explore the possible relationship between them.

Key words: *Helicobacter pylori* (*H. pylori*); extragastric diseases; male infertility
[J SUN Yat-sen Univ(Med Sci), 2023, 44(4): 601-606]

幽门螺杆菌(*Helicobacter pylori*，*H.pylori*)在全球范围内人群当中的感染率超过50%[1]，甚至在一些落后地区感染率可超过90%[2]，它的感染途径有粪-口、口-口等两种，如前所述，幽门螺杆菌的感染已证明与发生在胃和十二指肠的大量疾病有关，并且其感染也同样参与了许多胃外疾病，例如：动脉粥样硬化[3]、特发性血小板减少性紫癜、慢性结肠炎、神经系统疾病、肺癌等疾病，然而在众多胃外疾病中，甚少讨论幽门螺杆菌与男性不育的关系。夫妇双方在未采取任何避孕措施的情况下进行性生活，但在一年内不能自然妊娠称之为不孕不育，不孕不育被世卫组织(WHO)列为21世纪影响人类生活和健康的第三大疾病[4]，由于男方因素导致的女方不孕称之为男性不育，并且有研究表明男方

收稿日期：2022-11-07
基金项目：贵州省卫生健康委科技技术基金(gzwkj 2022-521)；贵州医科大学附属医院马歇尔基金
作者简介：刘晋阳，E-mail：806840133@qq.com；吴志平，通信作者，主任医师，教授，E-mail：gzwzp@foxmail.com

因素所导致的不孕不育占总病例的一半[5]。男性不育发病机制复杂,迄今为止仍有大量患者病因不明。近几年,有国外学者认为幽门螺杆菌的感染与男性不育有关[6],在幽门螺杆菌感染的人群中精子活力、浓度和生育指数都有降低[7],但具体机制还未探清。为指导男性不育的多维度治疗、研究幽门螺杆菌对胃外疾病的致病机制和追踪溯源男性不育的具体病因,本文系探讨幽门螺杆菌与男性不育的二者之间可能的关联的一综述。

1 男性不育的概述

男性不育的病因可分为睾丸前、睾丸性和睾丸后三类(表1),此外,约有50%的男性找不到具体病因[8],临床上称之为特发性男性不育。男性不育的特点有:①精子理化特性异常:例如精子液化、粘度、PH值和体积等异常,都被世界卫生组织列为诊断不育的数据指标[9];②男性生殖系统活性氧(reactive oxygen specie,ROS)水平异常:生理状态下ROS能促进精子成熟,其异常可引发精子蛋白质和DNA的损伤[10];③精子DNA损伤和片段化:精子DNA结构的改变已成为诊断男性不育的重要分子指标。

目前临床上男性不育常用的治疗有:基础治疗(纠正不良生活方式,戒烟、戒酒等)、抗氧化治疗、内分泌治疗、中医治疗和手术治疗等。如前所述,男性不育病因复杂,这使得多数治疗与前期研究疗效有差异,并且有研究指出男性不育造成的社会心理压力会使罹患癌症风险增加、男性健康水平下降[11]。因此,分析患者具体病因、综合考虑患者病情,才能制定合理、科学的治疗方案。

表1 男性不育的病因

Table 1 Etiology of male infertility

Pre-testicular conditions	Testicular problems	Post-testicular factors
Abuse of androgen steroids	Cryptorchidism	Vascular obstruction
Gonadotropin deficiency	Chromosome abnormality	Hypolibido
Pituitary insufficiency	Testicular atrophy	Sperm dysfunction
Hypothyroidism	Orchitis	Sexual life factors

2 幽门螺杆菌对肠道-睾丸轴的影响

2.1 肠道与睾丸的联系

肠道当中存在大量菌群,这些菌群具有调节宿主免疫力和保护肠道完整性等功能,近几年在《*Gut*》上有研究报道了肠道菌群对生育能力的影响[12],研究指出:肠道菌群失衡会导致T淋巴细胞和巨噬细胞在睾丸固有层中浸润,使得炎症因子例如:白细胞介素、单核细胞趋化蛋白和肿瘤坏死因子增多,其中肿瘤坏死因子TNF-a不仅会诱导生殖细胞凋亡还会诱发睾丸炎症从而影响男性生育能力[13];反之,改善肠道菌群失调后,精子的质量也会得到相应的改善[14],并且肠道菌群失调可影响人体维生素A的吸收,从而使精子在减数分裂过程发生异常(即生精功能障碍)诱发男性不育[15]。上述发现将肠道菌群与睾丸功能联系起来,称之为肠道-睾丸轴。

2.2 幽门螺杆菌破坏肠道菌群平衡

幽门螺杆菌虽然通常只在胃、十二指肠造成感染并引发一系列疾病。但有研究报道:幽门螺杆菌的感染会加重儿童肠道菌群的失调[16],幽门螺杆菌可诱导高氯血症改变肠道微生物群[17],还有研究发现幽门螺杆菌产生的细胞毒素相关蛋白CagA可诱导果蝇肠上皮细胞增殖和双氧化酶的过度表达从而破坏肠道菌群平衡[18]。除了感染阶段,在幽门螺杆菌的治疗阶段也有可能会导致或加重肠道菌群失衡:抗生素在根治幽门螺杆菌的过程中会使肠道菌群失衡[19],这种菌群失调要在根治幽门螺杆菌一年后才能恢复正常[20],肠道菌群失衡所带来病理生理变化也有可能会相应延迟恢复,所以现在有学者建议使用靶向药物治疗幽门螺杆菌,缓解炎症和修复胃黏膜的同时,避免诱发或加重肠道菌群失衡[21]。综上所述,幽门螺杆菌有可能通过肠道-睾丸轴:影响肠内菌群,从而间接对男性生育力造成影响,但上述结论还需更多中心性的研究去论证。

2.3 利用肠道-睾丸轴辅助治疗男性不育

幽门螺杆菌感染的患者其肠道菌群会发生改变,并且PPI与抗生素的联合使用有可能会加重这一现象[22],鉴于肠道-睾丸轴对男性生育的重要作用[12],治疗感染或未感染幽门螺杆菌的男性不育患者可联合服用益生菌,通过改善肠道菌群,不仅起到提高精液质量、辅助治疗男性不育的作用[23],还可增强抗生素疗效、减少幽门螺杆菌复发的可能性[24]。

3　幽门螺杆菌与雄激素的关系

3.1　幽门螺杆菌对雄激素的影响

当男性进入青春期后，睾丸开始分泌雄激素，而随着年龄的增长，雄激素的分泌也随之下降。雄激素具有：促进第二性征发育、维持男性性功能和促进精子形成等功能，对于男性生殖有着必不可少的作用。雄激素受到下丘脑和垂体的调控，也受生理和病理因素调节，近几年有研究表明幽门螺杆菌对雄激素也有影响。发表于《*Gut*》上的一篇文章指出[25]：幽门螺杆菌感染后，男性体内雄激素代谢产物3a-雄烷二醇葡萄糖苷酸明显降低，猜测幽门螺杆菌可以调节雄激素的产生。此外，来自台湾的一项关于“幽门螺杆菌感染的前列腺癌去雄治疗患者死亡率降低”的研究表示：幽门螺杆菌的感染可能会影响雄激素活性[26]。

3.2　幽门螺杆菌影响雄激素的可能机制

糖尿病系以葡萄糖水平慢性增高为特点的代谢性疾病，根治幽门螺杆菌后可使糖尿病病人的血糖情况得到改善[27]，甚至还有研究发现幽门螺杆菌的感染会使罹患糖尿病的风险增大27%[28]和增加机体的胰岛素抵抗[29]。当患上糖尿病后，有可能会导致性腺功能减退[30]，还有可能使雄激素水平降低[31]，猜测有可能与糖尿病患者下丘脑对促性腺激素释放激素的敏感性降低有关[32]。故幽门螺杆菌可诱发或加重糖尿病，影响雄激素水平，但具体糖尿病对雄激素的的影响成程度有多大尚无定论。除此之外，上文中所提及到的幽门螺杆菌通过肠道-睾丸轴，也可影响雄激素水平。

3.3　针对幽门螺杆菌对雄激素影响的思考

感染幽门螺杆菌能使接受去雄治疗前列腺癌的患者死亡率降低[26]，表明幽门螺杆菌可影响体内雄激素水平，在前列腺癌起到一定作用[25-26]。探究幽门螺杆菌对雄激素的具体影响机制需要更多大样本、中心性的实验，明确其具体机制不仅可提供前列腺癌去雄治疗的新思路，还能辅助治疗雄激素紊乱所引起的疾病。

4　幽门螺杆菌对精子的影响

4.1　幽门螺杆菌与精子产生交叉免疫反应

对于病原微生物引起男性不育的这一观点并不陌生，有学者认为细菌通过多信号通路诱导机体发生过度氧化应激[33]，过度氧化应激导致体内过氧化物堆积和抗氧化酶消耗，从而导致睾丸间质细胞凋亡和睾丸功能障碍[34]，最终影响精子的活性和质量。对于感染幽门螺杆菌的患者精子质量下降[7]这一现象，有学者将目光投向“交叉免疫反应”上。

幽门螺杆菌与大多数自身免疫疾病的关系归结于幽门螺杆菌的毒力因子与宿主自身蛋白具有抗原相似性，例如CagA$^+$的幽门螺杆菌菌株可刺激多克隆淋巴细胞活化诱导自身免疫反应[35]，这种交叉免疫反应同样存在于幽门螺杆菌与男性精子的关系中。有研究发现精子鞭毛的主要成分微管蛋白与幽门螺杆菌的鞭毛蛋白、CagA和VacA存在部分结构同源性，这表明幽门螺杆菌有可能刺激人体产生交叉免疫反应[36]，诱导机体产生抗精子抗体使患者精子质量下降（图1），甚至抗CagA抗体可阻断精子顶体反应从而影响受精[37]。但来自浙江大学的一项研究表明：感染或未感染幽门螺杆菌的患者其精子的浓度与活力无明显差异[38]。鉴于上述各研究中人种差异较大，值得进一步在我国各地域不同民族间进行探索与调查。

4.2　阴道内幽门螺杆菌是否影响受精

女性阴道中存在大量微生物，这些微生物及其代谢产物不仅对宿主的免疫调节有着一定影响，甚至可影响生育[39]，而幽门螺杆菌与不孕症的关系也是研究热点。近几年有研究报道了女性阴道中的念珠菌内存在幽门螺杆菌[40]，念珠菌作为“特洛伊木马”充当幽门螺杆菌的储存库并提供保护，在念珠菌内的幽门螺杆菌同样能释放CagA于念珠菌之外[41]，而CagA可引起机体交叉免疫反应降低精子活性并阻止精子顶体反应[36-37]，故阴道中念珠菌内的幽门螺杆菌是否可通过该途径干扰受精？此外《*The BMJ*》早年便提出过幽门螺杆菌是否能通过性传播的猜测[42]，后续也有研究证实性伴侣之间幽门螺杆菌感染率更高[43]，故建议：①备孕女性应当根治体内幽门螺杆菌并可同时检测CagA抗体。②备孕夫妻双方中的一方感染幽门螺杆菌，另一方应当尽早筛查病原体。这个观点虽缺乏大量实验数据，但可为临床提供防治幽门螺杆菌和辅助治疗不孕不育的新思路。

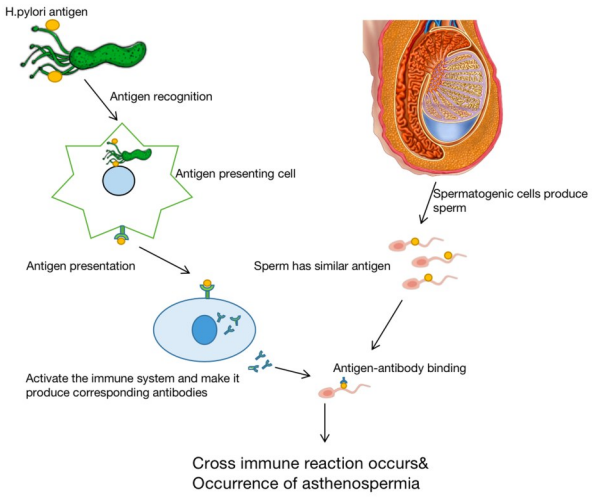

图1　幽门螺杆菌与精子的交叉免疫反应

Fig.1　Cross immune reaction between Helicobacter pylori and sperm

5 治疗幽门螺杆菌的药物对男性生殖系统的影响

根据《2022年中国幽门螺杆菌治疗指南》,建议治疗幽门螺杆菌选用药物为四联方案联合益生菌:质子泵抑制剂+铋剂+两种抗生素+益生菌,但在治疗过程中,使用上述某些药物对男性生殖系统有着一定的影响作用。

5.1 质子泵抑制剂

质子泵抑制剂(proton pump inhibitors, PPI)系通过与胃壁细胞膜上的H^+-K^+-ATP酶结合来减少胃酸分泌从而增强抗生素疗效的一类药物,常用的PPI包括:奥美拉唑、泮托拉唑和雷贝拉唑等药物,在长期使用这类药物的过程中,其风险及副作用也慢慢暴露出来,例如:①长期使用PPI会增大骨质疏松性骨折的风险[44];②来自英国的一项数据表明:长期使用PPI会与结肠恶性肿瘤的发生有关[45]。除此之外,其副作用也同样涉及男性生殖方面。

质子泵除了在胃壁细胞中有分布,也存在于胃外组织和细胞中,在胃外的质子泵称之为非胃H^+-K^+-ATP酶,近期在精子中也发现了非胃H^+-K^+-ATP酶[46],已有研究证明PPI对非胃H^+-K^+-ATP酶也有抑制作用[47],考虑到H^+和K^+等离子浓度对精子活力的影响[48],推测PPI可通过该途径影响精子正常生理功能。其次,有体外实验表明:泮托拉唑可增加精子蛋白质磷酸化和阻止精子细胞膜电位超极化从而抑制精子获能[49],埃索美拉唑作为新一代的PPI,同样有研究发现在服用60 min后,减少了活动精子的总数[50]。

5.2 抗生素

抗生素是治疗幽门螺杆菌有效且使用广泛的的方法,一般选用喹诺酮类、头孢类、青霉素类和硝基咪唑类两种,除了抗生素的耐药性,抗生素的副作用也是待攻克的一大难题。有研究发现:环丙沙星会降低动物血清睾酮和损害其精原细胞[51]。此外,阿莫西林[52]和甲硝唑[53]可通过增加氧化应激对小鼠睾丸产生损伤,降低精子活力。

除了直接影响,抗生素的联合使用会使宿主肠道菌群失衡[22],引起肠道屏障功能障碍,通过上文中提到的肠道-睾丸轴[12],间接影响男性生育能力。

5.3 治疗幽门螺杆菌药物的选择

综上,某些药物会诱发或加重男性不育,故建议正在治疗男性不育和短期内有生育需求的患者在根治幽门螺杆菌时选择药物避免使用泮托拉唑、埃索美拉唑、阿莫西林、甲硝唑和环丙沙星等药物,但上述药物具体剂量与男性生育能力的影响还需进一步研究。

6 总结与展望

综上所述,幽门螺杆菌即可通过肠道-睾丸轴,也可通过直接影响雄激素水平从而影响男性生殖系统,幽门螺杆菌还可介导机体免疫反应导致男性不育,甚至在治疗幽门螺杆菌的过程中对男性生殖也有一定的危险因素。故在治疗男性不育的患者时可考虑检测幽门螺杆菌,或是对于幽门螺杆菌感染的男性患者若近期有生育需求对其治疗方案需“量体裁衣”。上述潜在机制有助于打开临床思路,提供幽门螺杆菌与男性不育的下一步研究方向,但这些机制仍不明朗,针对上述结论,还需更多科学的、严谨的和高质量的深入探索,为治疗和预防男性不育提供更多角度。

参考文献

[1] Ding SZ, Du YQ, Lu H, et al. Chinese consensus report on family-based helicobacter pylori infection control and management(2021 Edition)[R]. Gut, 2022, 71(2): 238-253.

[2] Sun Y, Zhang J. Helicobacter pylori recrudescence and its influencing factors[J]. J Cell Mol Med, 2019, 23(12): 7919-7925.

[3] He J, Liu Y, Ouyang Q, et al. Helicobacter pylori and unignorable extragastric diseases: mechanism and implications [J]. Front Microbiol, 2022, 13: 972777.

[4] World Health Organization. International classification of diseases 11th revision[S]. Geneva: World Health Organization, 2018.

[5] Agarwal A, Baskaran S, Parekh N, et al. Male infertility[J]. Lancet, 2021, 397(10271): 319-333.

[6] El-Garem Y, El-Sawy M, Mostafa T. Seminal helicobacter pylori treatment improves sperm motility in infertile asthenozoospermic men[J]. Urology, 2014, 84(6): 1347-1350.

[7] Moretti E, Figura N, Campagna MS, et al. Infectious burden and semen parameters[J]. Urology, 2017, 100: 90-96.

[8] Chehab M, Madala A, Trussell JC. On-label and off-label drugs used in the treatment of male infertility[J]. Fertil Steril, 2015, 103(3): 595-604.

[9] Björndahl L, Kirkman Brown J; other Editorial Board Members of the WHO Laboratory Manual for the Examination and Processing of Human Semen. The sixth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen: ensuring quality and standardization in basic examination of human ejaculates[J]. Fertil Steril, 2022, 117

(2): 246-251.
[10] Villaverde AISB, Netherton J, Baker MA. From past to present: the link between reactive oxygen species in sperm and male infertility[J]. Antioxidants (Basel), 2019, 8(12): 616.
[11] Sun H, Gong TT, Jiang YT, et al. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990-2017: results from a global burden of disease study, 2017[J]. Aging, 2019, 11(23): 10952-10991.
[12] Ding N, Zhang X, Zhang XD, et al. Impairment of spermatogenesis and sperm motility by the high-fat diet-induced dysbiosis of gut microbes[J]. Gut, 2020, 69(9): 1608-1619.
[13] Wang F, Liu W, Jiang Q, et al. Lipopolysaccharide-induced testicular dysfunction and epididymitis in mice: a critical role of tumor necrosis factor alpha[J]. Biol Reprod, 2019, 100(3): 849-861.
[14] Zhang P, Feng Y, Li L, et al. Improvement in sperm quality and spermatogenesis following faecal microbiota transplantation from alginate oligosaccharide dosed mice[J]. Gut, 2021, 70(1): 222-225.
[15] Zhang T, Sun P, Geng Q, et al. Disrupted spermatogenesis in a metabolic syndrome model: the role of vitamin A metabolism in the gut-testis axis[J]. Gut, 2022, 71(1): 78-87.
[16] Yang L, Zhang J, Xu J, et al. Helicobacter pylori infection aggravates dysbiosis of gut microbiome in children with gastritis[J]. Front Cell Infect Microbiol, 2019, 9: 375.
[17] Parsons BN, Ijaz UZ, D'Amore R, et al. Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of helicobacter pylori-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use[J]. PLoS Pathog, 2017, 13(11): e1006653.
[18] Jones TA, Hernandez DZ, Wong ZC, et al. The bacterial virulence factor CagA induces microbial dysbiosis that contributes to excessive epithelial cell proliferation in the drosophila gut[J]. PLoS Pathog, 2017, 13(10): e1006631.
[19] Wang L, Yao H, Tong T, et al. Dynamic changes in antibiotic resistance genes and gut microbiota after helicobacter pylori eradication therapies[J]. Helicobacter, 2022, 27(2): e12871.
[20] Zhou Y, Ye Z, Wang Y, et al. Long-term changes in the gut microbiota after triple therapy, sequential therapy, bismuth quadruple therapy and concomitant therapy for helicobacter pylori eradication in Chinese children[J]. Helicobacter, 2021, 26(4): e12809.
[21] Cao R, Xu Y, Weng Z, et al. Metal-organic-framework-based hydrogen-release platform for multieffective helicobacter pylori targeting therapy and intestinal flora protective capabilities[J]. Adv Mater, 2022, 34(2): e2105738.
[22] Olekhnovich EI, Manolov AI, Samoilov AE, et al. Shifts in the human gut microbiota structure caused by quadruple helicobacter pylori eradication therapy[J]. Front Microbiol, 2019, 10: 1902.
[23] Hao Y, Feng Y, Yan X, et al. Gut microbiota-testis axis: FMT improves systemic and testicular micro-environment to increase semen quality in type 1 diabetes[J]. Mol Med, 2022, 28(1): 45.
[24] Ji J, Yang H. Using probiotics as supplementation for helicobacter pylori antibiotic therapy[J]. Int J Mol Sci, 2020, 21(3): 1136.
[25] Schooling CM, Dowd JB, Jones HE. Helicobacter pylori is associated with lower androgen activity among men in NHANES III[J]. Gut, 2013, 62(9): 1384-1385.
[26] Liu JM, Wu CT, Hsu RJ, et al. Association between helicobacter pylori infection and mortality risk in prostate cancer patients receiving androgen deprivation therapy: a real-world evidence study[J]. Cancer Med, 2021, 10(22): 8162-8171.
[27] Song X, Cai C, Jin Q, et al. The efficacy of helicobacter pylori eradication in diabetics and its effect on glycemic control: a systematic review and meta-analysis[J]. Helicobacter, 2021, 26(2): e12781.
[28] Mansori K, Moradi Y, Naderpour S, et al. Helicobacter pylori infection as a risk factor for diabetes: a meta-analysis of case-control studies[J]. BMC Gastroenterol, 2020, 20(1): 77.
[29] Azami M, Baradaran HR, Dehghanbanadaki H, et al. Association of helicobacter pylori infection with the risk of metabolic syndrome and insulin resistance: an updated systematic review and meta-analysis[J]. Diabetol Metab Syndr, 2021, 13(1): 145.
[30] Dhindsa S, Ghanim H, Batra M, et al. Hypogonadotropic hypogonadism in men with diabesity[J]. Diabetes Care, 2018, 41(7): 1516-1525.
[31] Zhong O, Ji L, Wang J, et al. Association of diabetes and obesity with sperm parameters and testosterone levels: a meta-analysis[J]. Diabetol Metab Syndr, 2021, 13(1): 109.
[32] Baccetti B, La Marca A, Piomboni P, et al. Insulin-dependent diabetes in men is associated with hypothalamo-pituitary derangement and with impairment in semen quality[J]. Hum Reprod, 2002, 17(10): 2673-2677.
[33] Wang S, Zhang K, Yao Y, et al. Bacterial infections affect male fertility: a focus on the oxidative stress-autophagy axis[J]. Front Cell Dev Biol, 2021, 9: 727812.
[34] Strycharz J, Rygielska Z, Swiderska E, et al. SIRT1 as a therapeutic target in diabetic complications[J]. Curr Med Chem, 2018, 25(9): 1002-1035.
[35] Youssefi M, Tafaghodi M, Farsiani H, et al. Helicobacter py-

lori infection and autoimmune diseases; Is there an association with systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophy gastritis and autoimmune pancreatitis? a systematic review and meta-analysis study[J]. J Microbiol Immunol Infect, 2021, 54(3): 359-369.

[36] Figura N, Piomboni P, Ponzetto A, et al. Helicobacter pylori infection and infertility [J]. Eur J Gastroenterol Hepatol, 2002, 14(6): 663-669.

[37] Ponzetto A, Holton J. Extragastric diseases correlated with helicobacter pylori[J]. Helicobacter, 2019, 24(1): e12549.

[38] Feng C, Lv PP, Huang CC, et al. Sperm parameters and anti-Müllerian hormone remain stable with helicobacter pylori infection: a cross-sectional study [J]. BMC Urol, 2020, 20(1): 188.

[39] Vitale SG, Ferrari F, Ciebiera M, et al. The role of genital tract microbiome in fertility: a systematic review[J]. Int J Mol Sci, 2021, 23(1): 180.

[40] Sánchez-Alonzo K, Matamala-Valdés L, Parra-Sepúlveda C, et al. Intracellular presence of helicobacter pylori and its virulence-associated genotypes within the vaginal yeast of term pregnant women[J]. Microorganisms, 2021, 9(1): 131.

[41] Hiengrach P, Panpetch W, Chindamporn A, et al. Helicobacter pylori, protected from antibiotics and stresses inside Candida albicans vacuoles, cause gastritis in mice[J]. Int J Mol Sci, 2022, 23(15): 8568.

[42] Head S. Helicobacter pylori infection: a sexually transmitted disease?[J]. BMJ, 2008, 337: a2077.

[43] Sgambato D, Visciola G, Ferrante E, et al. Prevalence of helicobacter pylori infection in sexual partners of H. pylori-infected subjects: role of gastroesophageal reflux[J]. United European Gastroenterol J, 2018, 6(10): 1470-1476.

[44] Lespessailles E, Toumi H. Proton pump inhibitors and bone health: an update narrative review[J]. Int J Mol Sci, 2022, 23(18): 10733.

[45] Abrahami D, McDonald EG, Schnitzer ME, et al. Proton pump inhibitors and risk of colorectal cancer[J]. Gut, 2022, 71(1): 111-118.

[46] Favia M, Gerbino A, Notario E, et al. The non-gastric H^+/K^+ ATPase (ATP12A) is expressed in mammalian spermatozoa [J]. Int J Mol Sci, 2022, 23(3): 1048.

[47] Wang G, Guo Y, Zhou T, et al. In-depth proteomic analysis of the human sperm reveals complex protein compositions[J]. J Proteomics, 2013, 79: 114-122.

[48] Cooray A, Kim JH, Chae MR, et al. Perspectives on potential fatty acid modulations of motility associated human sperm ion channels[J]. Int J Mol Sci, 2022, 23(7): 3718.

[49] Escoffier J, Arnaud B, Kaba M, et al. Pantoprazole, a proton-pump inhibitor, impairs human sperm motility and capacitation in vitro[J]. Andrology, 2020, 8(6): 1795-1804.

[50] Kumar A, Kumar R, Flanagan J, et al. Esomeprazole reduces sperm motility index by targeting the spermic cholinergic machinery: a mechanistic study for the association between use of proton pump inhibitors and reduced sperm motility index[J]. Biochem Pharmacol, 2020, 182: 114212.

[51] Hou L, Fu Y, Zhao C, et al. Ciprofloxacin and enrofloxacin can cause reproductive toxicity via endocrine signaling pathways[J]. Ecotoxicol Environ Saf, 2022, 244: 114049.

[52] Karaman M, Budak H, Çiftci M. Amoxicillin and gentamicin antibiotics treatment adversely influence the fertility and morphology through decreasing the Dazl gene expression level and increasing the oxidative stress [J]. Arch Physiol Biochem, 2019, 125(5): 447-455.

[53] Hassan MH, Awadalla EA, Ali RA, et al. Thiamine deficiency and oxidative stress induced by prolonged metronidazole therapy can explain its side effects of neurotoxicity and infertility in experimental animals: effect of grapefruit co-therapy [J]. Hum Exp Toxicol, 2020, 39(6): 834-847.

(编辑 余 菁)