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环境有害因素致生殖损伤研究进展与展望

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［摘要］ 环境有害因素导致的生殖损伤是生育力下降的重要原因,也是目前全球性重大公共卫生问题。阐明环境有害因素暴露与生殖系统损伤的因果关系、揭示其分子作用机制、构建精准生殖损伤评估与防治体系对于维护人口生殖健康具有重要意义。本综述简要概述了近3年环境新污染物、重要的物理有害因素和生物因素致生殖损伤的研究进展,总结了新的替代模型、暴露组学及人工智能等新技术在本领域中的应用,并对环境有害因素生殖健康评估、预防与干预等潜在研究方向进行了初步探讨。

［关键词］ 环境有害因素;生殖损伤;新技术方法

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Research progress and prospect on reproductive damage caused by environmental hazards

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［**Abstract**］ Environmentally-induced reproductive toxicity is one of the important causes of fertility declines and has become a significant global public health challenge. Elucidating the causal links between exposure to environmental hazards and reproductive damage, unraveling the underlying molecular mechanisms, and establishing precise reproductive injury assessment systems are crucial for development of targeted interventions and safeguarding human reproductive health. In this article, we systematically review the research progress on reproductive toxicity caused by emerging environmental chemical pollutants, common physical factors, and biological factors in the recent 3 years. We summarize the new technologies in the field of toxicology, including novel experimental models, exposomics, and artificial intelligence. We also discuss the potential research directions in risk assessment, prevention and intervention of environmental factors-induced reproductive damage.

［**Key words**］ environmental hazards; reproductive damage; new technologies

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根据最新国家统计局数据,2024年我国育龄人口30 777万人,出生人口954万人,总和生育率为1.085,远低于1.5的人口安全警戒线,而60岁以上人口首次突破3亿人[1]。生育率持续低下、老龄化程度不断加深,使生殖健康问题愈加成为我国人口安全的战略问题[2]。在我国工业化与城市化进程加速过程中,全氟烷基替代物、微塑料等新污染物,电离辐射、噪声等物理因素,以及昼夜节律紊乱等生物应激因素正通过多种途径影响大众的生殖健康。另一方面,暴露组学与高通量多组学技术的融合发展、类器官和器官芯片、以及计算毒理学与人工智能(artificial intelligence, AI)等前沿技术在生殖毒理学中逐渐广泛使用,又为环境有害因素致生殖损伤的研究提供了新的手段,也推动了生殖毒性评估从传统的病理生理等观察终点向分子事件及早期预警转型。现就近3年环境有害因素致生殖损伤相关研究与最新生殖毒性评估技术进行综述,并对本领域未来研究方向进行初步展望。

1 环境有害因素致生殖损伤效应与机制研究

1.1 新污染物致生殖损伤研究

新污染物是指排放到环境中的具有生物毒性、环境持久性、生物累积性等特征,对生态环境或者人体健康存在较大风险,但尚未纳入管理或现有管理措施不足的有毒有害化学物质;其包括持久性有机污染物[如多氟/全氟烷基化合物(poly/per-fluoroalkyl substance, PFAS)]、内分泌干扰物[如双酚类化合物(bisphenols, BPs)和阻燃剂]、抗生素及微塑料四大类。

PFAS广泛用于食品包装、电子产品等领域,其中全氟辛酸和全氟辛烷磺酸等传统的PFAS已被限制使用,但其替代品,如六氟环氧丙烷二聚体酸(hexafluoropropylene oxide dimer acid, HFPO-DA,商品名称GenX)等使用日益增多[3]。雄性生殖系统对GenX高度敏感,胚胎期暴露即可引发子代雄性小鼠青春期延迟、血清睾酮水平降低等性发育异常,同时精液质量降低及精子畸形率升高[4]。在雌性生殖系统方面,短期和亚慢性GenX暴露可致胎盘结构受损并影响胎儿发育[5]。GenX对雄性的生殖毒性主要机制是通过诱发氧化应激导致支持细胞衰老,从而破坏血睾屏障并造成精子发生障碍与激素分泌失调[4]。基于单细胞测序分析,发现GenX会特异性干扰精原干细胞分化轨迹,激活睾丸内体细胞的炎症应答,破坏体细胞与生殖细胞间的信号互作网络[6]。此外,GenX暴露会引起雌性小鼠胎盘血管生成相关因子血管内皮生长因子A(vascular endothelial growth factor A,VEGF-A)、血管生成素1(angiopoietin-1,ANGPT1)和Tie2等表达失衡,造成血管网络异常[5]。

双酚类替代物双酚S(bisphenol S,BPS)、双酚F(bisphenol F, BPF)等随着使用增加在人体中的检出率激增,且成年男性尿液中BPS和BPF的浓度与精液质量呈显著负相关[7]。基于围产期孕妇队列研究表明,双酚A(bisphenol A,BPA)替代物会通过损伤胎盘功能,增加子代发育风险[8];接受辅助生殖技术(assisted reproductive technology, ART)治疗的不孕妇女,BPS和BPF会抑制子宫内膜基质细胞增殖,并影响内膜蜕膜化[9]。BPS导致的生殖损伤与其导致的睾丸/卵巢组织中自由基与抗氧化系统失衡、内分泌干扰与激素失调有关;同时,BPS可影响DNA甲基转移酶(DNA methyltransferases, DNMTs)导致精子基因印记异常,进一步影响子代生殖功能[10]。此外,BPF、双酚G(bisphenol G,BPG)和4,4′-联苯酚(4,4′-biphenol, BPBP)等暴露可通过卵母细胞的减数分裂周期阻滞、纺锤体/染色体的排列异常导致雌性生殖损伤[11]。

传统的氯系阻燃剂、溴代阻燃剂,包括多溴联苯醚、六溴环十二烷等已逐渐淘汰且列入管控清单。有机磷酸酯(organophosphate esters, OPEs)阻燃剂作为溴系阻燃剂的替代品,被大规模应用于家具、电子产品、纺织品和建筑材料中[12]。最新的人群流行病学研究发现,不同种类OPEs单独与联合暴露会影响男性精子活力、密度、总数、正常形态和精子线粒体DNA拷贝数,且精子在附睾成熟阶段对OPEs阻燃剂的暴露最为敏感[13]。孕产妇OPEs暴露与流产、低出生体质量、母体和新生儿甲状腺功能障碍、儿童代谢失调和异常生长、神经发育受损等不良健康结局相关[14]。OPEs具有典型的持久性有机污染物(persistent organic pollutants, POPs)和内分泌干扰物的特征,可与生殖相关核受体(reproduction-related nuclear receptors, ReNRs)结合,尤其是雌激素受体α,通过调控类固醇合成相关基因,如*CYP11A1*、*HSD3B*、*CYP19A1*的表达,来干扰性激素稳态介导生殖损伤[15]。

近年来,抗生素在医疗、水产养殖业等的大量使用已引发全球公共卫生担忧。孕前暴露于大环内酯类、磺胺类药物、甲氧苄啶等抗生素,可显著降低受精率、增加自然流产及先天性畸形率风险[16]。在低出生体重儿的最新随访队列研究中发现,围产期抗生素的多次暴露与早产儿学龄早期肺功能受损高度相关[17]。斑马鱼亲代雌雄个体暴露于15种常用抗生素后,F1

代胚胎出现不同程度的生殖与发育损伤,而F2代尽管未检出抗生素残留,仍出现生殖细胞发育异常和胚胎畸形等毒性效应[18]。抗生素暴露会通过干扰睾酮合成与代谢酶的活性,如四环素可降低小鼠睾丸中CYP11A1、CYP17A1和17β-HSD等类固醇生成相关酶的表达水平,导致睾酮合成减少[19]。一些新的研究发现,抗生素暴露还可通过诱发母体菌群失衡致雌激素代谢紊乱,造成卵巢功能异常;同时,相关菌群还可通过母婴传递导致婴儿菌群失调以及生殖疾病[20]。

微塑料(microplastics,MPs)及纳米塑料(nanoplastics,NPs)是能通过食物链、空气和饮用水等多种途径进入生殖系统,并在睾丸、卵巢等组织中蓄积,引发生殖损伤[21]。MPs暴露会导致小鼠睾丸生精小管结构紊乱、支持细胞损伤及精子发生阻滞[22]。MPs/NPs对雌性生殖系统的损害主要集中于卵巢功能抑制与子宫微环境失衡[23]。MPs/NPs能进入胎盘并导致胎盘代谢异常、胎盘结构受损,并通过胎盘屏障进入子代体内,对子代的神经和生殖系统产生不良影响[24]。机制方面,以往研究表明MPs/NPs生殖毒性机制主要与氧化应激、炎症反应和细胞凋亡等有关[25]。最新研究发现,MPs/NPs暴露会激活mTORC1/RPS6/MMP-9和ERK1/2/mTOR/EIF4EBP1信号通路,造成生殖细胞功能紊乱[26]。MPs也可通过扰乱肠道微生物群,介导炎症反应和代谢异常,间接影响生殖系统[27]。

1.2 物理因素致生殖损伤研究

电离辐射(ionizing radiation, IR)作为广泛暴露的物理因素,可通过直接损伤DNA、诱导氧化应激及激活细胞凋亡通路等多种途径损伤生殖细胞功能,进而导致生育力下降或丧失[28]。男(雄)性睾丸对IR高度敏感,单次高剂量6.4 Gy全身急性γ照射可导致雄鼠生育能力丧失[29]。低剂量电离辐射(low-dose ionizing radiation, LDIR)能够诱导雄性生殖细胞DNA损伤和表观遗传修饰改变,影响精子质量、生育力,增加跨代健康风险[30]。对于女(雌)性,放疗中的辐射暴露可诱导卵母细胞和卵泡颗粒细胞的DNA损伤和凋亡,导致卵巢功能不全甚至过早衰竭[31]。手机等电子产品、基站、电力系统等使用过程产生的电磁辐射(electromagnetic radiation, EMR)也可能会影响生殖健康。妊娠阶段暴露于手机辐射会减少大鼠卵巢激素分泌,使卵巢损伤的风险增加[32]。5G手机辐射对小鼠精子质量无显著影响,但可导致性激素水平紊乱[33]。暴露于极低频磁场(extremely low frequency magnetic field, ELF-MF)可能对精子产生不同的影响,具体取决于波形、磁通量密度、频率和暴露持续时间,但科学界目前仍存在争论[34]。

近年来,全球极端热浪频发,热应激对生殖健康损害引起高度关注。男性生殖系统对高温极为敏感,阴囊维持精子生成的最佳温度是34~35 ℃,阴囊温度每上升1 ℃,精子总活力降低0.11%、精液量减少0.007 8 mL、运动活力降低0.15%,精子DNA碎片率(DNA fragmentation index, DFI)升高0.13%和不活动率升高0.12%[35-36]。基于广东省人类精子库2016–2021年的最新队列数据研究也证实,环境温度升高与精子浓度、精子总数、总活力等质量指标呈显著负相关[37]。对于女性,高温对孕期影响较大,可显著增加流产、早产及妊娠高血压等并发症风险,特别是从事纺织、冶金等高温作业的孕妇,其不良妊娠结局和出生缺陷风险显著升高[38]。热应激导致生精细胞死亡,精子质量下降主要与氧化-抗氧化平衡、线粒体/Fas/JNK-p53等凋亡通路激活等有关[36]。高温暴露会减少母体子宫胎盘血流,降低胎儿葡萄糖、氨基酸等营养物质的供应;同时,高温会激活母体应激反应系统,引发内分泌紊乱与免疫失调,干扰胎儿的发育进程[39]。

噪声是现代社会不容忽视的一种物理因素。长期暴露于交通噪声(Lden≥60 dB)可使>35岁女性的不孕风险增加35%,且噪声强度每升高10 dB,风险相应递增13%;年轻男性群体虽未观察到显著关联,但37~45岁男性暴露于交通噪声后不孕风险增加6%[40]。噪声可引起circRNA表达异常、凋亡信号通路激活等途径诱导生精细胞程序性死亡[41]。持续噪声暴露还会激活下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal axis, HPA)轴,导致皮质醇和儿茶酚胺水平异常升高,干扰下丘脑-垂体-性腺(hypothalamic-pituitary-gonadal axis, HPG)轴,诱导氧化应激、炎症反应和昼夜节律失调[42],以及干扰褪黑素分泌,进一步影响生殖内分泌的稳态[43]。

1.3 生物因素致生殖损伤研究

睡眠不足与昼夜节律紊乱作为当今社会普遍存在的健康风险因素,可通过干扰人体的内分泌系统、免疫系统和神经系统等,降低女性和男性生育力。最新一项基于20~40岁的育龄妇女睡眠质量的横断面研究发现,睡眠不佳组女性血清促卵泡生成素(follicle-stimulating hormone, FSH)水平较高,而抗苗勒管激素(anti-müllerian hormone, AMH)和总窦卵泡计数(antral follicle count, AFC)水平显著降低,提示睡眠质量差与育龄妇女卵巢储备减少有关[44]。睡眠剥夺和昼夜节律紊乱可直接影响睾丸屏障功能和精子发生

过程[45],昼夜节律紊乱还会导致激素分泌异常、免疫功能紊乱及细胞周期调控失衡,从而影响子宫内膜的状态和胚胎着床过程[46]。

另一重要的生物有害因素是病毒感染。最近一项基于育龄男性的研究发现,人乳头瘤病毒(human papillomavirus, HPV)感染组精子数量、浓度、活力和正常形态率显著降低,而精子DFI则明显高于未感染组;乙型肝炎病毒(hepatitis B virus, HBV)、丙型肝炎病毒(hepatitis C virus, HCV)、人类免疫缺陷病毒(human immunodeficiency virus, HIV)以及严重急性呼吸系统综合征冠状病毒2(severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)同样会损害男性生育能力[47]。实验表明,男(雄)性在感染戊型肝炎病毒(hepatitis E virus, HEV)后,其精液中能够持续检测到该病毒的存在,且可能引发睾丸结构畸变、血睾屏障完整性破坏、局部炎症应答及精子形态异常等损伤[48]。SARS-CoV-2病毒感染同样可通过破坏血睾屏障、干扰性激素平衡并影响精子发生[49]。对女性而言,病毒感染的危害同样严重,HBV感染不仅降低受孕概率,还可能影响母源性基因的甲基化状态[50];妊娠期感染SARS-CoV-2可能引发胎盘局部氧化应激和DNA损伤并影响胎儿发育[51]。

2 生殖损伤研究中的新技术与方法

2.1 新型替代模型

类器官模型是体内动物实验最佳的替代模型。随着睾丸组织体外培养和睾丸细胞重聚类器官技术的建立和发展,使睾丸类器官在毒性评估及男性生育力保存方面展现良好的应用潜力。最近,通过时序调控分化方法结合3D悬浮培养与生长因子组合培养系统,成功从人类诱导多能干细胞(human induced pluripotent stem cells, hiPSC)中培养出具有正常基因表达特征和功能特征的人类睾丸类器官。该模型已成功应用于评估胰高血糖素样肽-1受体激动剂(glucagon-like peptide-1 receptor agonist, GLP-1 RA)索马鲁肽对睾丸功能的影响[52]。而利用干细胞定向分化与细胞外基质(extracellular matrix, ECM)工程构建功能性卵巢类器官,在模拟卵巢微环境及其生物功能评价方面提供了可能,但其减数分裂效率仍待提升[53]。类器官芯片平台可通过动态建模模拟人类生殖系统的复杂状态,用于评估生殖器官对药物或环境的反应,以及研究环境污染物致妊娠并发症与胎儿发育异常的分子机制[54]。斑马鱼作为模式生物,单日产卵量高达200枚,特别适用于环境污染物的生殖发育毒性高通量初筛;而人-斑马鱼嵌合体技术的建立,可弥补斑马鱼与哺乳动物在代谢通路与器官功能上的差异,提升其在生殖毒性机制研究中的重要作用[55]。诚然,这些新型替代模型还有一些局限,比如类器官的批次间细胞组成差异,器官芯片则受限于血管网络成熟度不足及多器官耦合的流体控制复杂性等[56],未来都还需进一步从自动化、标准化、表型分析等方面加以改进。

2.2 多组学技术的交叉融合

整合多维组学数据的暴露组学,在揭示复杂环境暴露与生殖健康结局之间的动态因果关联中提供了新的可能[57]。早期的动物和前瞻性出生队列研究表明,多组学技术联合分析,可捕获早期生命暴露引发的DNA甲基化、转录组、蛋白质组及代谢物等分子印记的变化,进而揭示其与儿童期乃至成年期有害结局的时空关联[58]。例如,孕期多种化学混合物(含有机氯农药、全氟化合物、酚类物质)暴露与新生儿精细运动功能下降相关,提示发育早期暴露可能干扰神经行为发育轨迹[59]。不同生命阶段的暴露会留下独特的生物学"指纹"。妊娠期母体吸烟、镉和钼环境暴露主要影响后代DNA甲基化模式,而儿童期暴露则呈现多组学层面的扰动;特异性标志物可反映饮食模式、毒物接触、微量元素代谢及气候适应等多重暴露特征[60]。将多组学信息融入全生命周期的暴露组学研究,将使健康评估从静态"快照"转变为动态"连续剧",真正实现从子宫到"坟墓"的全程监控。

2.3 基因编辑技术与生殖损伤靶向治疗

CRISPR-Cas9基因编辑技术的成熟与普及,极大促进了基因编辑在生殖损伤修复与机制研究中的应用,为解决人类不孕症和遗传性疾病提供了可能。例如,利用CRISPR-Cas9技术已在小鼠精原干细胞中实现对于人类不育相关的Tex15基因的靶向编辑[61]。同时,CRISPR-Cas9技术可用于靶向修复生殖细胞的DNA损伤,如减数分裂错误或环境毒素诱发的基因突变[62]。此外,基因编辑、小分子抑制剂、抗体和外泌体靶向策略可作用于特定基因、蛋白质或信号通路,从而对生殖损伤进行精准干预[63],如利用胎盘间充质干细胞外泌体,可通过其携带的miRNA靶向抑制TGF-β/Smad信号通路,逆转纤维化,恢复子宫功能并提高受损动物的生育率[64]。靶向治疗在精准生殖损伤修复和个性化治疗方面具有独特优势,但其安全性和有效性仍需进一步提升。

2.4 AI与计算毒理学

AI的快速发展正影响毒理学在内的众多学科发展,并可能改变生殖毒性的安全评估策略和体系。最近,由意大利比萨大学开发的VenomPred 2.0计算毒理学平台,采用沙普利可加性解释技术(shapley additive explanations, SHAP),可直接定位小分子中导致毒性的关键结构基团,能进行多维度解析与可视化归因分析,该模型对于大量生殖损伤因素的效应评估和机制解析提供了新的手段[65]。华南师范大学研究团队开发的一种深度神经网络模型(androgen receptor deep neural network, AR-DNN),以化学指纹作为输入层,通过5层网络模拟雄激素受体(androgen receptor, AR)诱导的AOP构建而成。运用该AR-DNN模型对塑料添加剂清单(n=7 112)和中国现有化学物质名录(n=17 741)中的化学物进行分析,分别识别出1 477种和2 448种可能导致雄性不育风险的化学物质,并揭示了潜在毒性途径[66]。当然,AI模型对环境因素与生殖损伤的可解释性、数据偏差和透明度等问题,还需要跨学科合作来进一步完善。

3 未来研究趋势展望

3.1 潜在生殖危险因素评估

随着科技的日新月异,新材料、新药物、新的营养补剂和新型替代物正快速涌入人类日常生活,而解析它们是否具有生殖毒性仍然是当下及未来生殖毒理学的重要研究内容。新型纳米材料、新型农药等导致的生殖损伤已经引起高度关注,如二氧化硅纳米颗粒(SiO_2NPs)暴露会破坏减数分裂[67],草不隆的代谢产物会加速卵泡闭锁、降低卵母细胞质量等[68]。另一持续关注的因素是气候因素,极端高温或高寒天气直接与生殖健康损伤密切相关[69];而洪涝灾害也可能导致饮用水源被化学和微生物污染物污染,间接影响生殖健康[70],但是相关因素对生殖健康损伤的因果关系、剂量-反应关系、损伤机制等还亟需进行系统研究。个体层面,压力、焦虑、抑郁等心理因素也是不容忽视的生殖健康危险因素[71],除其本身可导致生殖损伤外,还需要特别关注相关因素可能协同或增强环境污染物的生殖发育毒性。微观层面,细胞衰老本身就是生殖危险因子,而环境有害因素会加速生殖细胞的衰老进程,如长期接触聚苯乙烯微塑料会引发睾丸过早衰老[72],长期暴露于$PM_{2.5}$环境中会显著加速女性的卵巢衰老[73]。此外,由于人类实际是长期地、低剂量地暴露于多种有害因素,这些因素的联合作用可能远超任何单一组分的毒性,即便各组分暴露剂量均低于“安全”阈值,也可能导致不良健康后果[74]。因此,根据人群流行病学数据,解析真实世界暴露水平,再通过体内、体外毒理学研究,构建针对真实环境水平化学混合物暴露的健康及跨代效应综合研究框架,才能全面、真实地理解低剂量混合物暴露对生殖发育的潜在影响,也将是未来研究的重点和热点。总之,鉴别并解析新的潜在生殖危险因素及其量效关系,是有效应对快速变化的自然和社会环境所带来的生殖健康新威胁的关键途径之一。

3.2 生殖损伤机制解析

生殖损伤的主要机制包括氧化应激、细胞凋亡、性激素紊乱、遗传与表观遗传调控异常等,尤其是表观遗传调控机制已成为持续的研究热点,且在实践中显示出良好的应用价值;如女性卵泡液中的特定miRNAs已成为评估卵母细胞质量、诊断多囊卵巢综合征(polycystic ovary syndrome, PCOS)和预测体外受精结局的有力工具[75];对于男性,精子和精浆中的miRNAs表达异常与精子质量差等多种类型的不育症有关[76]。父系环境暴露可通过DNA甲基化、组蛋白修饰和RNA甲基化等多种表观遗传机制调节子代表型,增加后代患各种疾病的风险[77]。此外,一些改变的miRNA可能会通过受精作用进入卵母细胞,调控早期胚胎的基因表达,并将获得性性状传递给下一代[78]。近年来,一些新的生殖损伤机制被提出,如“肠道-性腺轴”的概念,肠道菌群可直接参与性激素相关酶的合成,参与性激素的肠肝循环来调节性激素水平,并影响HPG轴[79]。在女性中,肠道菌群失调与PCOS和子宫内膜异位症的联系最为密切。这些疾病的共同特点是炎症和激素失衡,而菌群失调恰恰是这二者的重要驱动因素[80]。这些新的生殖损伤机制研究,丰富对环境因素诱导生殖损伤的本质认识,表观遗传修饰和特征性肠道菌群也逐渐成为生殖损伤新的诊断及干预潜在生物标志物。

3.3 精准化个体生殖健康防预

精准公共卫生(precision public health, PPH)通过综合评估遗传学、生活方式与环境之间的交互作用,在人群层面改善疾病预防、诊断和治疗,实现“在正确的时间为正确的人群提供正确的干预措施”,而整合个体遗传易感性、表观遗传特征与环境暴露信息将推动生殖损伤的精准预防和靶向干预,推动“精准环境生殖健康”,进而实现生殖损伤风险的分层管理,这也将是未来的重点研究方向[81]。代谢组学、肠道微生物

组和环境暴露组揭示的生物标志物,可塑造影响个体健康的特征图谱[82],而开发并用于分析大规模基因-环境复杂互作模式和效应的分析工具可加速识别个体的易感性,这将促进个体化精准环境生殖健康的发展。新兴可穿戴传感器技术及产品的普及,为实现动态、个体化的健康监测与早期预警开辟新途径。利用可穿戴传感设备可对孕期母体的体温、活动水平等生理参数,胎儿健康相关指标以及青春期发育相关的生理节律进行连续、实时的个体化追踪[83]。

综上所述,如何有效通过控制环境有害因素提升生殖健康是当下公共卫生领域的重大挑战,随着生命科学的快速发展,动物替代模型、器官芯片、多组学技术、AI等为环境有害因素的检测、效应及机制研究提供新的手段,尤其是AI和计算模型的进一步发展和应用,有望为有害因素快速筛选、早期风险评估等提供科学依据,也为未来生殖健康风险的预防与干预提供新策略。

利益冲突 本文所有作者声明不存在利益冲突

参考文献:

[1] 中华人民共和国统计局.人口总量降幅收窄人口素质持续提升报告(2025)[EB/OL].[2025-01-17]. https://www.stats.gov.cn/xxgk/jd/sjjd2020/202501/t20250117_1958337.html.
National Bureau of Statistics of the People's Republic of China. Report on the narrowing decline in total population and sustained improvement in population quality (2025)[EB/OL]. [2025-01-17]. https://www.stats.gov.cn/xxgk/jd/sjjd2020/202501/t20250117_1958337.html.

[2] 国家统计局人口和就业统计司.中国人口和就业统计年鉴-2024[M].北京:中国统计出版社,2024.
Department of Population and Employment Statistics, National Bureau of Statistics. China statistical yearbook on population and employment-2024 [M]. Beijing: China Statistics Press, 2024.

[3] FENG S T, LU X F, OUYANG K G, *et al*. Environmental occurrence, bioaccumulation and human risks of emerging fluoroalkylether substances: insight into security of alternatives [J]. Sci Total Environ, 2024, 922: 171151. DOI: 10.1016/j.scitotenv.2024.171151.

[4] FAN Z C, HONG R Y, LI S H, *et al*. Embryonic exposure to GenX causes reproductive toxicity by disrupting the formation of the blood-testis barrier in mouse offspring[J]. Toxicology, 2025, 515: 154161. DOI: 10.1016/j.tox.2025.154161.

[5] DAI Y H, HE J L, HE F, *et al*. Exposure to environmentally relevant levels of GenX affects placental and offspring development in mice[J]. Environ Pollut, 2024, 363(Pt 2): 125294. DOI: 10.1016/j.envpol.2024.125294.

[6] ZANG X P, WANG Y Z, JIANG L, *et al*. Single-cell transcriptomics reveals the cellular dynamics of hexafluoropropylene oxide dimer acid in exerting mouse male reproductive toxicity[J]. J Anim Sci Biotechnol, 2025, 16(1): 42. DOI: 10.1186/s40104-025-01177-x.

[7] MARTÍNEZ M Á, SALAS-HUETOS A, FERNÁNDEZ DE LA PUENTE M, *et al*. Exploring the association between urinary bisphenol A, S, and F levels and semen quality parameters: findings from Led-Fertyl cross-sectional study [J]. Environ Res, 2024, 263(Pt 2): 120086. DOI: 10.1016/j.envres.2024.120086.

[8] LUO L, GAO C, FAN Y J, *et al*. Perinatal bisphenol exposure and small-for-gestational-age neonates: the evolving effect of replacements then and now[J]. Environ Sci Technol, 2025, 59(12): 5983-5993. DOI: 10.1021/acs.est.4c13266.

[9] XIONG Y, XU S Y, WANG Z W, *et al*. BPA-free? Exploring the reproductive toxicity of BPA substitutes BPS and BPF on endometrial decidualization [J]. Ecotoxicol Environ Saf, 2024, 287: 117275. DOI: 10.1016/j.ecoenv.2024.117275.

[10] 雷连曼,孙姝,陈晨,等.双酚S暴露致生殖系统损伤及其机制的研究进展[J].安徽医科大学学报,2025,60(1):180-185. DOI:10.19405/j.cnki.issn1000-1492.2025.01.026.
LEI L M, SUN S, CHEN C, *et al*. Research progress on reproductive system damage caused by bisphenol S exposure and its mechanism [J]. Acta Universitatis Medicinalis Anhui, 2025, 60(1): 180-185. DOI: 10.19405/j.cnki.issn1000-1492.2025.01.026.

[11] PETERS A E, FORD E A, ROMAN S D, *et al*. Impact of bisphenol A and its alternatives on oocyte health: a scoping review[J]. Hum Reprod Update, 2024, 30(6): 653-691. DOI: 10.1093/humupd/dmae025.

[12] CUI Y J, ZHOU R X, YIN Y H, *et al*. Occurrence of organophosphate esters in food and food contact materials and related human exposure risks[J]. J Agric Food Chem, 2025, 73(8): 4455-4465. DOI: 10.1021/acs.jafc.4c11439.

[13] LI Y P, LIU C, MUSTIELES V, *et al*. Organophosphate esters, sperm mitochondrial DNA copy number, and semen quality: a longitudinal study with repeated measurements [J]. Environ Sci Technol, 2025, 59(7): 3388-3400. DOI: 10.1021/acs.est.4c09573.

[14] SHAHIN S, MEDLEY E A, NAIDU M, *et al*. Exposure to organophosphate esters and maternal-child health [J]. Environ Res, 2024, 252(Pt 2): 118955. DOI: 10.1016/j.envres.2024.118955.

[15] LI Y, ZHAO M H, SHEN X M, *et al*. Adverse effects of aryl organophosphate esters on reproduction[J]. Environ Sci

Technol, 2025, 59(21): 10122-10135. DOI: 10.1021/acs.est.5c01992.

[16] ALEMU B K, WANG C C, LI L C, *et al*. Effect of preconception antibiotics exposure on female reproductive health and pregnancy outcomes: a systematic review and meta-analysis[J]. EClinicalMedicine, 2024, 78: 102935. DOI: 10.1016/j.eclinm.2024.102935.

[17] FORTMANN I, WELP A, HOFFMANN N, *et al*. Perinatal antibiotic exposure and respiratory outcomes in children born preterm[J]. JAMA Netw Open, 2025, 8(5): e259647. DOI: 10.1001/jamanetworkopen.2025.9647.

[18] XU B T, PU M J, JIANG K L, *et al*. Maternal or paternal antibiotics? Intergenerational transmission and reproductive toxicity in zebrafish[J]. Environ Sci Technol, 2024, 58(2): 1287-1298. DOI: 10.1021/acs.est.3c06090.

[19] HOU L R, FU Y H, ZHAO C, *et al*. The research progress on the impact of antibiotics on the male reproductive system[J]. Environ Int, 2024, 187: 108670. DOI: 10.1016/j.envint.2024.108670.

[20] THOMAS S P, DENIZER E, ZUFFA S, *et al*. Transfer of antibiotics and their metabolites in human milk: implications for infant health and microbiota[J]. Pharmacotherapy, 2023, 43(5): 442-451. DOI: 10.1002/phar.2732.

[21] HE Y C, YIN R C. The reproductive and transgenerational toxicity of microplastics and nanoplastics: a threat to mammalian fertility in both sexes[J]. J Appl Toxicol, 2024, 44(1): 66-85. DOI: 10.1002/jat.4510.

[22] LU T Y, ZHENG W, HU F L, *et al*. Disruption of zebrafish sex differentiation by emerging contaminants hexafluoropropylene oxides at environmental concentrations *via* antagonizing androgen receptor pathways[J]. Environ Int, 2024, 190: 108868. DOI: 10.1016/j. envint. 2024. 108868.

[23] BALALI H, MORABBI A, KARIMIAN M. Concerning influences of micro/nano plastics on female reproductive health: focusing on cellular and molecular pathways from animal models to human studies[J]. Reprod Biol Endocrinol, 2024, 22(1): 141. DOI: 10.1186/s12958-024-01314-7.

[24] 吴静, 刘聪, 谢青贞. 微塑料暴露对雌性及其子代健康的影响[J]. 国际生殖健康/计划生育杂志, 2024, 43(2): 155-158. DOI:10.12280/gjszjk.20230418.
WU J, LIU C, XIE Q Z. Effects of microplastic exposure on the health of females and their offspring[J]. J Int Reprod Health/Fam Plann, 2024, 43(2): 155-158. DOI: 10.12280/gjszjk.20230418.

[25] 黄燕, 黄媛媛, 卓彦希, 等. 微纳米塑料暴露对生殖健康影响的研究进展[J]. 环境与职业医学, 2025, 42(4): 490-496. DOI:10.11836/JEOM24367.
HUANG Y, HUANG Y Y, ZHUO Y X, *et al*. Research progress on the impact of micro- and nano-plastic exposure on reproductive health[J]. J Environ Occup Med, 2025, 42(4): 490-496. DOI: 10.11836/JEOM24367.

[26] LI S W, MA Y, YE S Z, *et al*. Endogenous hydrogen sulfide counteracts polystyrene nanoplastics-induced mitochondrial apoptosis and excessive autophagy *via* regulating Nrf2 and PGC-1α signaling pathway in mouse spermatocyte-derived GC-2spd(ts) cells[J]. Food Chem Toxicol, 2022, 164: 113071. DOI: 10.1016/j.fct.2022.113071.

[27] FU X F, LIU L, HAN H, *et al*. Integrated fecal microbiome and metabolome analysis explore the link between polystyrene nanoplastics exposure and male reproductive toxicity in mice[J]. Environ Toxicol, 2023, 38(6): 1277-1291. DOI: 10.1002/tox.23763.

[28] TALAPKO J, TALAPKO D, KATALINIĆ D, *et al*. Health effects of ionizing radiation on the human body[J]. Medicina(Kaunas), 2024, 60(4): 653. DOI: 10.3390/medicina60040653.

[29] LI J, LIU J, ZHANG Y, *et al*. Effects of paternal ionizing radiation exposure on fertility and offspring's health[J]. Reprod Med Biol, 2024, 23(1): e12567. DOI: 10.1002/rmb2.12567.

[30] YIN J, YE Y, GAO Y, *et al*. Low-dose ionizing radiation and male reproductive immunity: elucidating subtle modulations and long-term health implications[J]. Int J Mol Sci, 2025, 26(5): 2269. DOI: 10.3390/ijms26052269.

[31] ROBALO CORDEIRO M, ROQUE R, LARANJEIRO B, *et al*. Menstrual blood stem cells-derived exosomes as promising therapeutic tools in premature ovarian insufficiency induced by gonadotoxic systemic anticancer treatment[J]. Int J Mol Sci, 2024, 25(15): 8468. DOI: 10.3390/ijms25158468.

[32] YOUSEFI B, JADIDI M, NABIZADEH Z, *et al*. Impairment of oogenesis and folliculogenesis in neonatal rats after maternal exposure to mobile phones[J]. Reprod Sci, 2025. DOI: 10.1007/s43032-025-01880-0.

[33] 薛一哲, 张兆文, 郭玲, 等. 5G手机辐射对小鼠精子质量和性激素水平的影响[J]. 辐射研究与辐射工艺学报, 2023, 41(1): 52-61. DOI: 10.11889/j. 1000-3436.2022-0062.
XUE Y Z, ZHANG Z W, GUO L, *et al*. Effects of 5G mobile phone radiation on sperm quality and sex hormone levels in mice[J]. J Radiat Res Radiat Process, 2023, 41(1): 52-61. DOI: 10.11889/j.1000-3436.2022-0062.

[34] CORDELLI E, ARDOINO L, BENASSI B, *et al*. Effects of

radiofrequency electromagnetic field (RF-EMF) exposure on male fertility: a systematic review of experimental studies on non-human mammals and human sperm *in vitro* [J]. Environ Int, 2024, 185: 108509. DOI: 10.1016/j.envint.2024.108509.

[35] WANG C, YU Q W, CHU T, *et al*. Relationship of environmental exposure temperature and temperature extremes on sperm DNA fragmentation index in men with different BMI values and the indirect effect of DNA fragmentation index on semen parameters [J]. Sci Total Environ, 2024, 916: 170292. DOI: 10.1016/j.scitotenv.2024.170292.

[36] 艾庆燕, 张珂珂, 孟欣瑶, 等. 热应激引起男性生殖系统损伤的机制及治疗研究进展[J]. 延安大学学报(医学科学版), 2025, 23(2): 90-94. DOI: 10.19893/j.cnki.ydyxb.2024-0264.
AI Q Y, ZHANG K K, MENG X Y, *et al*. Research progress on the mechanism and treatment of male reproductive system damage caused by heat stress [J]. J Yan'an Univ (Med Sci Ed), 2025, 23(2): 90-94. DOI: 10.19893/j.cnki.ydyxb.2024-0264.

[37] ZHANG X Z, FAN Z Y, WANG Q L, *et al*. Association between ambient temperature and semen quality among sperm donation volunteers in South China[J]. Environ Int, 2023, 173: 107809. DOI: 10.1016/j.envint.2023.107809.

[38] REKHA S, NALINI S J, BHUVANA S, *et al*. Heat stress and adverse pregnancy outcome: Prospective cohort study [J]. BJOG, 2024, 131(5): 612-622. DOI: 10.1111/1471-0528.17680.

[39] COWELL W, ARD N, HERRERA T, *et al*. Ambient temperature, heat stress and fetal growth: a review of placenta-mediated mechanisms [J]. Mol Cell Endocrinol, 2023, 576: 112000. DOI: 10.1016/j.mce.2023.112000.

[40] SØRENSEN M, POULSEN A H, NØHR B, *et al*. Long term exposure to road traffic noise and air pollution and risk of infertility in men and women: nationwide Danish cohort study[J]. Br Med J, 2024, 386: e080664. DOI: 10.1136/bmj-2024-080664.

[41] 李迎庆, 刘畅, 张中豪, 等. 军用密闭舱室噪声及CO联合染毒致大鼠生殖损伤效应[J]. 陆军军医大学学报, 2023, 45(9): 911-919. DOI: 10.16016/j.2097-0927.202212004.
LI Y Q, LIU C, ZHANG Z H, *et al*. Combined exposure to noise and CO induces adverse male reproductive effects in rats[J]. J Army Med Univ, 2023, 45(9): 911-919. DOI: 10.16016/j.2097-0927.202212004.

[42] SØRENSEN M, PERSHAGEN G, THACHER J D, *et al*. Health position paper and redox perspectives—disease burden by transportation noise[J]. Redox Biol, 2024, 69: 102995. DOI: 10.1016/j.redox.2023.102995.

[43] DE JONG R W, DAVIS G S, CHELF C J, *et al*. Continuous white noise exposure during sleep and childhood development: a scoping review[J]. Sleep Med, 2024, 119: 88-94. DOI: 10.1016/j.sleep.2024.04.006.

[44] LIN Y X, CHEN Y C, LIN Y, *et al*. Association between sleep quality and ovarian reserve in women of reproductive age: a cross-sectional study [J]. Fertil Steril, 2025, 123(3): 520-528. DOI: 10.1016/j.fertnstert.2024.09.018.

[45] CAVALHAS-ALMEIDA C, CRISTO M I, CAVADAS C, *et al*. Sleep and male (In)fertility: a comprehensive overview[J]. Sleep Med Rev, 2025, 81: 102080. DOI: 10.1016/j.smrv.2025.102080.

[46] 庹银凤, 王宝, 王清仪, 等. 昼夜节律紊乱与胚胎着床失败关系的研究进展[J]. 中国现代医学杂志, 2024, 34(15): 58-64. DOI: 10.3969/j.issn.1005-8982.2024.15.009.
TUO Y F, WANG B, WANG Q Y, *et al*. Research progress on the relationship between circadian rhythm disorders and embryo implantation failure[J]. Chin J Mod Med, 2024, 34(15): 58-64. DOI: 10.3969/j.issn.1005-8982.2024.15.009.

[47] GUO Y, ZHOU G Z, FENG Y, *et al*. The association between male viral infections and infertility: a systematic review and meta-analysis [J]. Rev Med Virol, 2024, 34(6): e70002. DOI: 10.1002/rmv.70002.

[48] KOTB A A, EL-MOKHTAR M A, SAYED I M. Effect of hepatitis E virus on the male reproductive system: a review of current evidence[J]. Viruses, 2025, 17(1): 66. DOI: 10.3390/v17010066.

[49] OKADA K, KIN C, YAMASHITA Y, *et al*. Possible mechanisms of spermatogenic dysfunction induced by viral infections: insights from COVID-19[J]. Reprod Med Biol, 2025, 24(1): e12625. DOI: 10.1002/rmb2.12625.

[50] LIU X, DONG S X, DING Y, *et al*. Hepatitis B virus impacts embryonic development and methylation of maternal genes in assisted reproductive technology patients [J]. J Assist Reprod Genet, 2025, 42(3): 809-815. DOI: 10.1007/s10815-024-03359-4.

[51] NOBREGA G M, MCCOLL E R, ANTOLINI-TAVARES A, *et al*. Placentas from SARS-CoV-2 infection during pregnancy exhibit foci of oxidative stress and DNA damage [J]. Am J Reprod Immunol, 2025, 93(1): e70034. DOI: 10.1111/aji.70034.

[52] HUANG R F, XIA H, MENG T, *et al*. Construction of human pluripotent stem cell-derived testicular organoids and their use as humanized testis models for evaluating the effects of semaglutide [J]. Theranostics, 2025, 15(6): 2597-2623. DOI: 10.7150/thno.104523.

[53] ZHANG T Y, ZHANG M T, ZHANG S C, *et al*. Research advances in the construction of stem cell-derived ovarian organoids[J]. Stem Cell Res Ther, 2024, 15(1): 505. DOI: 10.1186/s13287-024-04122-3.

[54] TRUONG N, ZAHRA A, LINTAO R C V, *et al*. Modeling reproductive and pregnancy-associated tissues using organ-on-chip platforms: challenges, limitations, and the high throughput data frontier[J]. Front Bioeng Biotechnol, 2025, 13: 1568389. DOI: 10.3389/fbioe.2025.1568389.

[55] MICHAELIS P, KLÜVER N, AULHORN S, *et al*. Leveraging zebrafish embryo phenotypic observations to advance data-driven analyses in toxicology[J]. Environ Sci Technol, 2025, 59(9): 4304-4317. DOI: 10.1021/acs.est.4c11757.

[56] HUANG Y S, LIU T, HUANG Q, *et al*. From organ-on-a-chip to human-on-a-chip: a review of research progress and latest applications[J]. ACS Sens, 2024, 9(7): 3466-3488. DOI: 10.1021/acssensors.4c00004.

[57] 李雅文, 王丹丹, 王芙蓉, 等. 基于蛋白质组学和代谢组学分析初步探讨苯并(k)荧蒽致小鼠生殖损伤的作用机制[J]. 陆军军医大学学报, 2024, 46(13): 1523-1534. DOI: 10.16016/j.2097-0927.202310083.
LI Y W, WANG D D, WANG F R, *et al*. Mechanism of benzo (k) fluoranthene induced reproductive damage in mice based on proteomics and metabolomics analysis[J]. J Army Med Univ, 2024, 46(13): 1523-1534. DOI: 10.16016/j.2097-0927.202310083.

[58] GUIMBAUD J B, SISKOS A P, SAKHI A K, *et al*. Machine learning-based health environmental-clinical risk scores in European children[J]. Commun Med (Lond), 2024, 4(1): 98. DOI: 10.1038/s43856-024-00513-y.

[59] BRENNAN KEARNS P, VAN DEN DRIES M A, JULVEZ J, *et al*. Association of exposure to mixture of chemicals during pregnancy with cognitive abilities and fine motor function of children[J]. Environ Int, 2024, 185: 108490. DOI: 10.1016/j.envint.2024.108490.

[60] MAITRE L, BUSTAMANTE M, HERNÁNDEZ-FERRER C, *et al*. Multi-omics signatures of the human early life exposome[J]. Nat Commun, 2022, 13(1): 7024. DOI: 10.1038/s41467-022-34422-2.

[61] YEŞILBOSTAN S, AKKURT M Y, ÖZKAVUKÇU S, *et al*. Genome editing in mouse spermatogonial stem cell lines targeting the Tex15 gene using CRISPR/Cas9[J]. Front Vet Sci, 2025, 12: 1599598. DOI: 10.3389/fvets.2025.1599598.

[62] BEKAERT B, BOEL A, DE WITTE L, *et al*. Retained chromosomal integrity following CRISPR-Cas9-based mutational correction in human embryos[J]. Mol Ther, 2023, 31(8): 2326-2341. DOI: 10.1016/j.ymthe.2023.06.013.

[63] YE R, MAO Y M, FEI Y R, *et al*. Targeting ferroptosis for the treatment of female reproductive system disorders[J]. J Mol Med (Berl), 2025, 103(4): 381-402. DOI: 10.1007/s00109-025-02528-x.

[64] LIU H D, ZHANG X, ZHANG M T, *et al*. Mesenchymal stem cell derived exosomes repair uterine injury by targeting transforming growth factor-β signaling[J]. ACS Nano, 2024, 18(4): 3509-3519. DOI: 10.1021/acsnano.3c10884.

[65] JAYLET T, COUSTILLET T, JORNOD F, *et al*. AOP-helpFinder 2.0: integration of an event-event searches module[J]. Environ Int, 2023, 177: 108017. DOI: 10.1016/j.envint.2023.108017.

[66] XIN L, LIU S S, SHI W J, *et al*. Knowledge-based machine learning for predicting and understanding the androgen receptor (AR)-mediated reproductive toxicity in zebrafish[J]. Environ Int, 2024, 191: 108995. DOI: 10.1016/j.envint.2024.108995.

[67] LEI M, ZHU Z Y, WEI C L, *et al*. Prenatal silicon dioxide nanoparticles exposure reduces female offspring fertility without affecting males[J]. Adv Sci (Weinh), 2025, 12(3): e2410353. DOI: 10.1002/advs.202410353.

[68] TANG C, ZHANG Y, ZHANG F C, *et al*. Evaluating the effects of neburon exposure on ovarian folliculogenesis using zebrafish and mouse granulosa cell line[J]. Environ Health Perspect, 2025. DOI: 10.1289/EHP15372.

[69] PAPADIOCHOU A, DIAMANTI A, METALLINOU D, *et al*. Impact of climate change on reproductive health and pregnancy outcomes: a systematic review[J]. Cureus, 2024, 16(8): e68221. DOI: 10.7759/cureus.68221.

[70] Safajou F, Nahidi F, Ahmadi F. Reproductive health challenges during a flood: A qualitative study[J]. Nurs Open, 2024, 11(1): e2044. DOI: 10.1002/nop2.2044.

[71] 杨彬伟, 孙磊, 凌曦, 等. 慢性心理应激对大鼠睾丸细胞老化的影响及糖皮质激素受体的作用研究[J]. 陆军军医大学学报, 2024, 46(24): 2698-2706. DOI: 10.16016/j.2097-0927.202406014.
YANG B W, SUN L, LING X, *et al*. Effects of chronic psychological stress on testicular cell senescence in rats and role of glucocorticoid receptor in the process[J]. J Amry Med Univ, 2024, 46(24): 2698-2706. DOI: 10.16016/j.2097-0927.202406014.

[72] WU D Y, ZHANG M, BAO T T, *et al*. Long-term exposure to polystyrene microplastics triggers premature testicular aging[J]. Part Fibre Toxicol, 2023, 20(1): 35. DOI: 10.1186/s12989-023-00546-6.

[73] CAO Z F, WU X Y, LIU H Y, *et al*. Associations of long-term exposure to fine particulate matter and its components with ovarian aging: evidence from a cross-sectional study in China[J]. J Hazard Mater, 2025, 494: 138589. DOI: 10.1016/j.jhazmat.2025.138589.

[74] 程千慧, 李赛男, 王琳琳. "真实世界暴露"的生殖发育毒理学综合研究策略: 从人群流行病学到体内和体外实验[J]. 生物医学转化, 2025, 6(1): 78-86. DOI:10.12287/j.issn.2096-8965.20250112.
CHENG Q H, LI S N, WANG L L. Integrated research strategies for reproductive and developmental toxicology of real-world exposure: Integrating population epidemiology with *in vivo* and *in vitro* experiments[J]. Biomed Transform, 2025, 6(1): 78-86. DOI: 10.12287/j. issn. 2096-8965. 20250112.

[75] VOROS C, ATHANASIOU D, MAVROGIANNI D, *et al*. Exosomal communication between cumulus-oocyte complexes and granulosa cells: a new molecular axis for oocyte competence in human-assisted reproduction[J]. Int J Mol Sci, 2025, 26(11): 5363. DOI: 10.3390/ijms 26115363.

[76] SHI Z Y, YU M, GUO T C, *et al*. microRNAs in spermatogenesis dysfunction and male infertility: clinical phenotypes, mechanisms and potential diagnostic biomarkers[J]. Front Endocrinol (Lausanne), 2024, 15: 1293368. DOI: 10.3389/fendo.2024.1293368.

[77] LIAO H, LU D, REISINGER S N, *et al*. Epigenetic effects of paternal environmental exposures and experiences on offspring phenotypes[J]. Trends Genet, 2025: S0168-9525(25)00107-6. DOI: 10.1016/j.tig.2025.04.015.

[78] KOROLENKO A A, NOLL S E, SKINNER M K. Epigenetic inheritance and transgenerational environmental justice[J]. Yale J Biol Med, 2023, 96(2): 241-250. DOI: 10.59249/FKWS5176.

[79] LV S Y, HUANG J R, LUO Y D, *et al*. Gut microbiota is involved in male reproductive function: a review[J]. Front Microbiol, 2024, 15: 1371667. DOI: 10.3389/fmicb.2024. 1371667.

[80] MOUSTAKLI E, STAVROS S, KATOPODIS P, *et al*. Gut microbiome dysbiosis and its impact on reproductive health: mechanisms and clinical applications [J]. Metabolites, 2025, 15(6): 390. DOI: 10.3390/metabo15060390.

[81] ROBERTS M C, HOLT K E, DEL FIOL G, *et al*. Precision public health in the era of genomics and big data[J]. Nat Med, 2024, 30(7): 1865-1873. DOI: 10.1038/s41591-024-03098-0.

[82] VO D K, TRINH K T L. Emerging biomarkers in metabolomics: advancements in precision health and disease diagnosis[J]. Int J Mol Sci, 2024, 25(23): 13190. DOI: 10.3390/ijms252313190.

[83] KEELER BRUCE L, GONZÁLEZ D, DASGUPTA S, *et al*. Biometrics of complete human pregnancy recorded by wearable devices[J]. NPJ Digit Med, 2024, 7(1): 207. DOI: 10.1038/s41746-024-01183-9.

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