中国科学: 生命科学 2024 年 第 54 卷 第 1 期: 136 ~ 146
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS
评 述 生殖健康专辑

绝经年龄影响因素研究进展

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收稿日期: 2023-08-30; 接受日期: 2023-10-15; 网络版发表日期: 2024-01-12
国家重点研发计划(批准号: 2022YFC2703800, 2022YFC2703000)资助

摘要 绝经是卵巢储备耗竭的表现. 绝经年龄提前提示了女性生殖寿命缩短, 生育机会降低, 影响出生人口数量; 同时伴随性激素水平的改变, 增加心血管疾病、骨质疏松、神经退行性变及肿瘤等疾病的发生风险, 严重影响女性身心健康和生活质量. 如何延缓卵巢衰老, 进而保持和提高生育力已成为生殖医学研究的热点问题. 全面认识绝经年龄的影响因素, 对于实现女性生育力保护, 尤其是对早绝经高风险女性的早期干预和综合管理具有重要意义. 本文将系统综述遗传、营养代谢、环境暴露等绝经年龄相关因素, 为女性生殖健康管理提供科学依据.

关键词 绝经年龄, 遗传, 代谢性疾病, 医源性因素, 环境污染物

卵巢储备是女性生殖寿命的决定性因素之一. 原始卵泡是卵巢储备的基本单位, 在胚胎期形成, 出生后在促性腺激素作用下启动激活和发育, 并随着年龄增长逐渐耗竭. 当原始卵泡数目低至1000个左右时, 卵泡难以激活或出现发育障碍, 雌孕激素不足以维持月经来潮, 便会发生绝经, 因此, 绝经是卵巢功能衰竭的重要标志[1]. 中国女性的平均绝经年龄为48~52岁, 约90%的女性在45~55岁之间绝经[2]. 40~45岁绝经被称为“早绝经”(early menopause, EM)[3], 40岁前绝经被称为“早发性卵巢功能不全”(premature ovarian insufficiency, POI)[4], 二者为常见的女性生殖衰老性疾病, 且发病率呈现逐渐上升趋势[5]. 绝经后的神经内分泌改变与心血管疾病、骨质疏松、神经退行性疾病、肿瘤等发病风险相关[6,7], 严重影响女性长期身心健康. 因此, 全面认识绝经年龄的影响因素, 将有助于实现绝经年龄预测和高风险人群的早筛、早诊、早治, 对于延缓生殖衰老、预防远期并发症、提高生活质量具有重要意义. 近年来, 先后有研究报道了遗传因素、宫内暴露及环境污染物等对卵巢功能及绝经年龄的影响(图1), 但诸多因素的影响效应仍存在争议. 本文将系统综述遗传、营养代谢、环境暴露等相关因素, 为女性生殖健康管理提供科学依据.

引用格式: 李玮琳, 郭婷, 秦莹莹. 绝经年龄影响因素研究进展. 中国科学: 生命科学, 2024, 54: 136–146
Li W L, Guo T, Qin Y Y. Research progress on factors influencing age at menopause (in Chinese). Sci Sin Vitae, 2024, 54: 136–146, doi: 10.1360/SSV-2023-0197

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https://engine.scichina.com/doi/10.1360/SSV-2023-0197

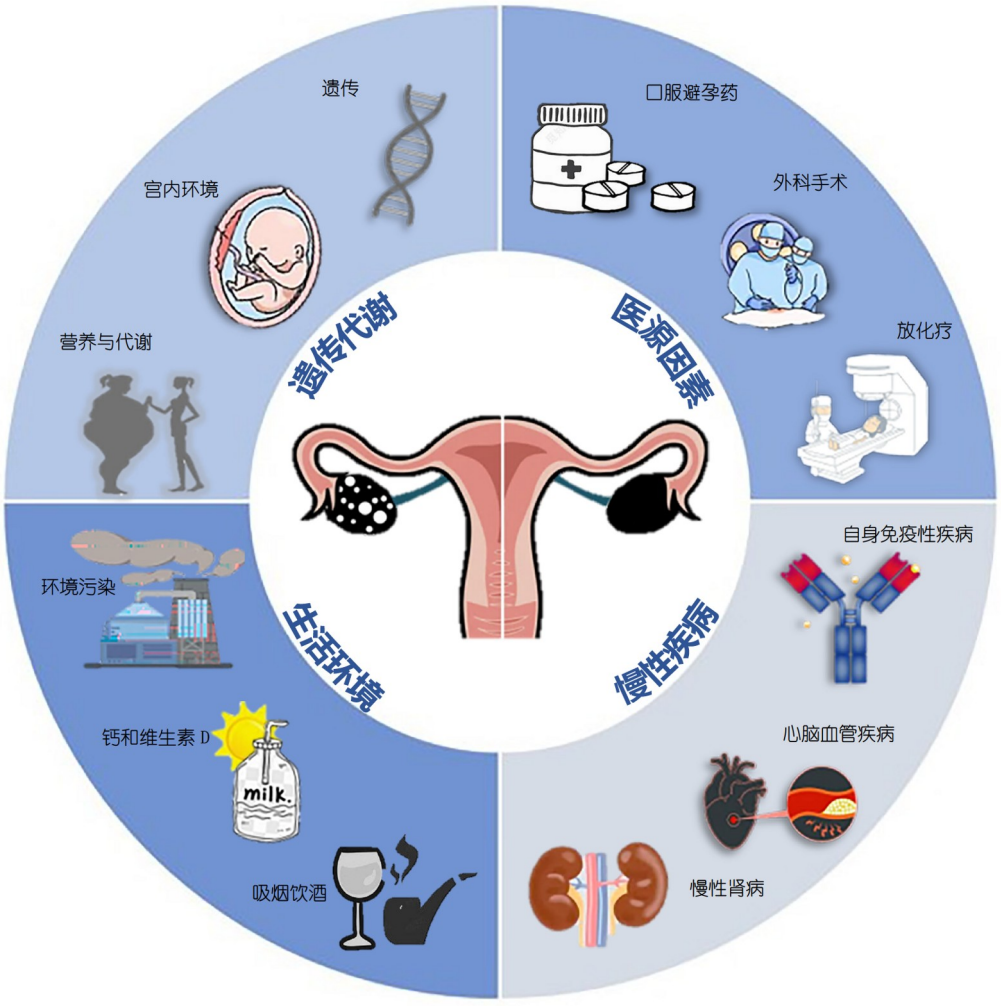


图 1　绝经年龄影响因素. 女性绝经年龄受到遗传代谢、医源性损伤、慢性疾病及不良生活环境暴露等因素的影响
Figure 1　The age of menopause is affected by genetic and metabolic disorders, iatrogenic factors, chronic diseases and environmental toxins

1　主要研究进展

1.1　遗传因素

随着生活水平的提高，女性的预期寿命已经从1850年的45岁左右提高至85岁，但绝经年龄仅从50岁延长至52岁[8,9]，提示营养状况改善和医疗卫生水平提高对绝经年龄的影响非常有限. 多数研究发现, 遗传因素是影响绝经年龄的主效因素[10]. 双生子及家系研究发现，绝经年龄在同卵双胎中的遗传度高达0.85~0.87[11]，在母女中的遗传度亦达0.44~0.52[12]，提示遗传能解释半数以上的绝经年龄差异. 随着遗传学研究方法的飞速发展，更多的证据支持遗传因素与自然绝经年龄(age at natural menopause, ANM)密切相关[13]. 一项纳入20万名女性的全基因组关联分析(genome-wide association study, GWAS)研究将ANM相关的遗传多态位点拓展到290个，并发现DNA损伤修复基因变异与绝经年龄提前相关；携带*BRCA2*和*CHEK2*基因突变的女性，其绝经年龄较非携带者分别提前1.54年和3.49年[8]. 同时，随着年龄增长，卵母细胞中BRCA2，RAD51等DNA损伤修复蛋白的表达量逐渐下降[8,14]；而携带*BRCA1*和*BRCA2*基因突变的女性，其抗苗勒管激素(anti-Müllerian hormone, AMH)随年龄下降的速度明显加快[8,15]，再次佐证了DNA损伤修复基因缺陷对卵巢功能的不利影响.

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POI表现为40岁之前出现卵巢功能减退及闭经, 是典型的病理性卵巢衰老疾病, GWAS研究证实了POI和早绝经(40~45岁绝经)具有相似的遗传易感位点[8,16]. 以往研究认为, 染色体异常和基因变异能解释20%~25% POI患者的病因[17]; 近期我国学者通过大规模POI全外显子组测序(whole exome sequencing, WES)分析, 绘制了POI遗传变异图谱, 发现23.5%的病因不明POI患者携带致病变异, 进一步提高了遗传因素在POI病因中的贡献度[18]. 目前已报道POI致病基因115个, 参与原始生殖细胞形成、减数分裂、卵泡发育、能量代谢及免疫调控等过程. POI患者的绝经年龄存在显著异质性, 与致病基因所在通路及突变类型有关, 例如, 减数分裂起始基因*STRA8*和*MEIOSIN*纯合突变可通过抑制减数分裂相关基因的表达引发减数分裂阻滞, 其突变携带者表现为原发性闭经或较早的继发性闭经[18]; 而减数分裂双链DNA断裂形成基因*PRDM9*和*ANKRD31*的杂合突变增加了卵母细胞对外源性损害的敏感性, 其突变携带者可表现为较晚的继发性闭经[19]. 此外, 原发性闭经患者中携带双基因或多基因突变的比例显著升高, 提示突变的累积效应可能引发卵巢功能减退加速. WES研究也发现, DNA损伤修复通路和减数分裂通路的基因变异在POI患者中显著富集, 再次强调了DNA损伤修复功能的完整性对卵巢储备的建立和维持不可或缺[18].

1.2 营养和代谢

无论是宫内营养缺乏还是出生后营养代谢失衡均会影响绝经年龄. 基础研究发现, 哺乳动物孕期营养缺乏可导致雌性子代生育力下降、促卵泡生成素(follicle stimulating hormone, FSH)水平升高、AMH水平下降及窦卵泡数减少, 提示宫内环境影响卵巢储备的建立和维持[20]. 人群观察性研究也发现, 妊娠期疾病或不良因素暴露, 如妊娠期贫血、高血糖、高血压及饮酒吸烟等, 可显著影响胎儿出生体重[21,22], 而新生儿的出生体重与女性绝经年龄显著相关[23]. 2010年一项英国出生队列研究发现出生体重与早绝经之间存在U型关联, 即与出生体重3.0~3.49 kg的女性相比, 极端出生体重(≤2.5或≥4.0 kg)女性的早绝经发生风险增加1倍[23]. 同时, 基于荷兰饥荒队列的研究也证实, 胎儿期暴露于严重饥荒的女性, 其绝经年龄明显提前[24], 进一步佐证了宫内营养代谢失衡可能是加速卵巢衰老、导致绝经年龄提前的原因之一.

成年后, 体重指数(body mass index, BMI)是反映机体营养和代谢状态的常用指标, 研究发现BMI与早绝经风险存在非线性关联[25]. 与BMI正常(18.5~24.9 kg/m^2)的女性相比, BMI偏低(<18.5 kg/m^2)女性的早绝经发生风险增加2倍[26]. 值得注意的是, 尽管有数据显示, 高BMI可能是绝经年龄的保护性因素[26], 但由于肥胖会增加高血压、糖尿病等代谢性疾病的患病风险, 因此不建议通过增重推迟绝经年龄, 而是通过积极运动及调整生活方式维持BMI在正常范围, 以降低早绝经风险[27].

1.3 月经史与婚育史

规律的月经依赖于周期性的卵泡发育, 月经情况在一定程度上是反映卵巢功能的"晴雨表". 队列研究发现, 11岁前的月经初潮与早绝经密切相关[28], 推测与原始卵泡过早激活引发的卵巢储备提前耗竭有关. 月经周期情况与绝经年龄的相关性目前尚存争议. 有研究发现, 月经规律但周期小于25天的女性面临更高的早绝经风险, 而月经周期大于40天的女性则风险相对较低[28], 推测前者可能由于排卵更为频繁, 卵巢储备耗竭过快, 进而引发绝经年龄提前. 此外, 对于月经不规律的女性, 如果从18~22岁开始出现月经不规则, 其发生早绝经的风险比月经规律者低50%[28]; 而25~35岁出现月经不规律的女性更易发生POI[29]. 这一差异可能与不同年龄伴发的排卵障碍疾病不同有关, 一般认为18~22岁的月经不规律可能与多囊卵巢综合征有关, 而25~35岁出现月经不规律可能与卵巢储备下降有关[28]. 多囊卵巢综合征女性由于相对优势的卵巢储备和稀发排卵, 卵巢功能维持时间更长. 因此, 月经周期情况对绝经年龄的影响需要结合年龄及卵巢储备指标进行综合评估.

由于妊娠期间排卵受到抑制, 生育力得以"保存", 因此妊娠史可能与绝经年龄存在相关性. 自然人群队列研究发现, 女性初次生育的年龄与自然绝经年龄之间无显著关联[28,30], 但分娩次数与绝经年龄呈正相关[31]. 与生育两次及以上的女性相比, 无分娩史者的早绝经发生风险增加1倍[32]. 这一现象与母乳喂养的观察结果一致, 即母乳喂养时长与绝经年龄呈正相关, 且哺乳期在半年以上的女性出现早绝经的风险最低[31]. 以上结果均佐证了妊娠期和哺乳期的排卵抑制

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会减缓卵巢储备的消耗.

值得注意的是, 不孕症和不良孕产史是绝经年龄提前的危险因素. 在一项纳入30余万名女性的观察性研究中, 合并不孕症、复发性流产和/或死产病史的女性, 其早绝经风险显著增加, 且这种关联在亚洲女性中尤为显著[33], 推测不良孕产相关的遗传缺陷或基础生殖疾病可能是卵巢衰老加速、绝经年龄提前的原因.

1.4　慢性疾病

(1) 糖尿病. 2021年的统计数据显示, 2型糖尿病在我国成年人中的患病率高达12.8%[34], 成为影响女性健康的主要代谢性疾病之一. 一项拉丁美洲的大型观察性研究发现, 45岁以下罹患2型糖尿病的女性出现早绝经的风险是非糖尿病女性的3倍; 对肥胖和高血压等混杂因素进行校正后, 糖尿病依然是绝经年龄提前的独立危险因素[35]. 目前1型糖尿病与绝经年龄的相关性尚存争议[36,37]. 有研究发现, 1型糖尿病患者出现初潮延迟、月经紊乱的比例高于非糖尿病患者[38]. 亦有研究观察到POI患者较正常人群罹患1型糖尿病的比例更高, 且并发1型糖尿病的POI患者出现闭经的年龄更早[29], 推测1型糖尿病可能与POI存在交叉的免疫致病机制[35,39]. 但由于各研究的样本量较小, 1型糖尿病与绝经年龄的相关性仍有待更多临床人群观察及机制研究的证据.

(2) 心脑血管疾病. 由于血管新生和老化与卵巢功能密切相关[40], 心脑血管疾病与绝经年龄也呈现显著关联[41]. 一项纳入15项观察性研究、覆盖30万名女性的巢式病例对照研究发现, POI或早绝经女性罹患心血管疾病(包括冠心病和卒中)的风险显著高于正常绝经(50~51岁)或晚绝经(52岁以上)人群[1,42]. 而另一项纳入17万名女性的病例对照研究则发现, 35岁前首次发生心血管疾病的女性, 其早绝经风险增加1倍, 但40岁后首次经历绝经前心血管疾病的女性并未增加相关风险[43]. 因此, 早发的心血管疾病与绝经年龄提前的关系更为密切.

(3) 慢性肾病. 根据全球肾脏预后组织公布的慢性肾病分期标准, 慢性肾病分为1~5期. 观察性研究发现, 慢性肾病5期患者的绝经年龄中位数为46~48岁, 平均提前了5年. 尿毒症引发的内环境紊乱、氧化应激和炎症反应等加速卵泡闭锁, 可能是导致慢性肾病5期患者绝经年龄提前的原因之一. 此外, 慢性肾病可导致催乳素、内啡肽和瘦素等激素水平升高, 进而抑制下丘脑-垂体-卵巢轴(hypothalamic-pituitary-ovarian axis, HPOA), 引发闭经. 这种病理性抑制状态可通过肾脏移植得以逆转, 患者多在术后6个月内恢复规律月经及排卵[44], 且近70%的年轻慢性肾病5期患者在肾脏移植后自然妊娠[45,46]. 因此, 慢性肾病患者的绝经风险需要综合考虑肾功能状态, 肾功能改善将有助于卵巢功能的维持.

(4) 自身免疫性疾病. 桥本甲状腺炎、系统性红斑狼疮等自身免疫性疾病好发于育龄期女性[47], 而这些自身免疫性疾病可导致系统性或器官局域性免疫紊乱, 如自身抗体分泌失调及免疫细胞亚群分化异常等[48], 进而损害卵巢功能. 回顾性研究发现, 罹患自身免疫性疾病的女性, POI的发病风险显著增加[29]. 4%~30%的POI患者伴发其他自身免疫性疾病[39], 包括内分泌腺相关疾病(如自身免疫性多腺体综合征、Addison病、甲状腺功能减退/亢进、甲状旁腺功能低下等)及非内分泌相关疾病(如特发性血小板减少性紫癜、系统性红斑狼疮、风湿性关节炎等)[49]. 其中, 桥本甲状腺炎是POI患者中发病率最高的自身免疫性疾病(14%~27%)[50], 其次为Addison病(10%~20%)[51,52]. 自身免疫性疾病患者体内存在多种自身抗体, 可与卵巢相关抗原结合, 产生细胞毒性作用, 进而加速卵泡耗竭. 常见的自身抗体包括抗类固醇生成细胞抗体(steroid-cell autoantibody, StCA)和抗肾上腺皮质抗体(anti-adrenocortical autoantibody, AAA), 其中StCA在伴发Addison病的POI患者中检出率为78%~100%[53]. 队列研究显示, 近40%的StCA阳性自身免疫性多腺体综合征患者在确诊后10~15年中发生POI[51,54,55]. 因此, 自身免疫性疾病是影响绝经年龄的重要因素, 但其引发卵巢功能减退的机制有待进一步阐明.

(5) 子宫内膜异位症. 子宫内膜异位症在育龄期女性中的发病率为6%~10%[56], 被认为是一种常见的慢性炎症性疾病[57]. 卵巢的子宫内膜异位囊肿可直接破坏周围正常的卵巢组织, 同时卵巢及盆腔异位病灶也可通过炎性介质释放及类固醇合成失调等影响卵巢局部微环境, 导致卵子数目和质量的下降[57]. 降低循环雌激素水平是减轻盆腔疼痛、延缓疾病进展的首选方案, 但部分患者会经历不同程度的更年期样症状[58]; 手术治疗虽然可清除病灶, 但可能会损伤卵巢皮质及盆腔环境, 进一步加速卵巢功能下降[57,59,60], 因此, 如

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何兼顾子宫内膜异位症的治疗效果和生育力保护一直是临床争论的热点. 对于严重的子宫内膜异位症合并不孕症的患者, 可考虑借助辅助生殖技术(assisted reproductive technology, ART)提高生育机会并进行生育力保存[56], 但多项ART回顾性研究发现, 子宫内膜异位症患者接受体外助孕过程中, 存在卵巢反应不良、卵母细胞成熟度和胚胎质量下降的风险[59,61]. 一项纳入10万名女性的队列研究, 在考虑了人种差异、孕产史、饮食行为习惯等因素后, 发现子宫内膜异位症与早绝经之间仍存在显著关联; 经腹腔镜证实的子宫内膜异位症患者, 其早绝经风险增加50%, 尤其是无分娩史、无口服避孕药服用史的女性, 该风险进一步增加[62]. 因此, 除了不孕不育, 子宫内膜异位症女性的早绝经风险同样值得临床关注.

1.5 医源性因素

(1) 口服避孕药. 口服避孕药(oral contraceptive, OC)能够抑制排卵, 减缓卵泡消耗. 有研究发现, 服用OC女性的绝经年龄相对延迟, 且这种相关性在35岁以上人群中更为显著[30]. 但由于不同研究中OC药物成分和用药时间存在差异, OC与绝经年龄的相关性仍然存在争议[29,63].

(2) 盆腔手术. 由于卵巢或盆腔手术可能对卵巢皮质及周围血供造成不可逆的损伤, 因此盆腔手术一直被视为卵巢功能下降和绝经年龄提前的危险因素[64]. 有观察性研究发现, 单侧卵巢切除术可导致绝经年龄提前7年[65]; 有输卵管结扎术史的女性, 其早绝经风险增加17%[63]. 因此, 卵巢或盆腔手术前应充分告知相关风险, 术中术者尽量减少卵巢损伤, 术后加强随访, 以便及早预防绝经年龄提前所造成的不良影响.

(3) 放化疗. 卵巢是对辐射最敏感的女性生殖器官, 腹腔或盆腔放疗可导致卵巢血管损伤及皮质纤维化, 引起卵泡闭锁和卵巢储备下降. 在接受放疗的女性肿瘤患者中, 早绝经风险随着卵巢周围辐射剂量的增加而升高[65]. 当盆腔辐射剂量大于20 Gy时, 超过70%幸存者发生急性卵巢功能衰竭[66,67]. 另外, 盆腔放疗还可直接损伤子宫肌层及内膜, 导致子宫源性闭经[68]; 颅脑或全身放疗可损伤下丘脑神经元及垂体细胞, 导致促性腺激素合成不足, 引发中枢性闭经[69].

化疗对女性生殖系统的影响更为广泛, 一方面可通过卵巢局部的血管损伤和炎症反应加速卵泡激活及闭锁; 另一方面可通过抑制HPO轴影响卵泡募集及发育. 化疗药物不仅可以直接作用于卵母细胞, 引发DNA损伤, 诱导卵母细胞凋亡; 其中的重金属和有机溶剂还可引发卵泡膜细胞及颗粒细胞功能受损, 导致卵母细胞数量和质量下降[70]. 与单纯放疗相比, 化疗引发的早绝经风险增加了12倍[71]. 育龄期女性在化疗后出现闭经称为化疗相关性闭经(chemotherapy-related amenorrhea, CRA), 其发生风险与化疗药物的种类、用药方案及患者年龄密切相关[72]. 在妊娠滋养细胞肿瘤和霍奇金淋巴瘤患者中, 接受联合化疗方案的患者较单药化疗患者的平均绝经年龄提前2年[73]. 在40岁接受化疗的女性肿瘤患者中, CRA发生率为13%; 而在45岁女性中的CRA发生率则高达36%[71,74,75]. 值得注意的是, 在化疗前使用长效促性腺激素释放激素类似物(gonadotrophin releasing hormone analogue, GnRHa)的双阴性乳腺癌患者, 化疗后出现绝经的风险显著降低[76], 提示化疗前的垂体抑制可通过抑制原始卵泡激活, 减轻药物对卵巢储备的损害.

1.6 生活环境暴露

(1) 吸烟. 吸烟是较早引起关注的卵巢功能影响因素之一. 烟草中的尼古丁和假木香碱可抑制颗粒细胞的芳香化酶活性[77], 抑制雌激素合成; 同时尼古丁的代谢产物可替宁会促进雌二醇代谢为二羟基雌酮[78], 并增加肾上腺来源的雄激素水平[79], 进一步拮抗雌激素作用, 最终影响卵泡发育及卵巢的内分泌功能. 大量研究发现, 吸烟与自然绝经年龄之间存在显著的剂量依赖性关系, 即吸烟时间越长, 频率越高, 绝经年龄越早[30]. 其中, 吸烟持续时间是最强的关联因素[80]. 一项纳入1万名女性的横断面研究发现, 吸烟者较非吸烟者发生早绝经的风险增加30%; 而烟龄30年以上女性的早绝经发生风险增加87%[81]. 值得注意的是, 在有吸烟史的女性中, 肺功能良好者的绝经年龄相对较晚[82], 提示吸烟对卵巢功能的影响存在一定的个体差异, 需联合肺功能评估等进行综合分析.

(2) 饮酒. 大量研究提示, 饮酒与绝经年龄存在相关性[83,84]. 一项纳入22项研究、随访超过10万名女性的Meta分析显示, 低度(0~8 g/d)和中度饮酒(16 g/d)可推迟绝经年龄, 这可能与酒精改善卵巢周围血供、提高外周血雌激素水平有关[83]. 但目前尚不清楚该相关性是否受到酒精饮品类型或饮品中其

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他成分的影响[85].

(3) 维生素D和钙. 有研究发现, 饮食中的维生素D和钙摄入量与绝经年龄呈正相关. 膳食维生素D摄入量较低的女性(中位数=148 IU/d)相较摄入量较高的女性(中位数=528 IU/d)有更高的早绝经风险[86], 这可能与维生素D具有促进抗苗勒管激素分泌、改善颗粒细胞功能有关. 从摄入来源分析, 乳制品来源的维生素D和钙与绝经年龄的关联更为密切[86]. 由于乳制品能够提供丰富的类固醇激素合成底物, 其对卵巢功能的保护作用可能不仅依赖于维生素D的补充. 有意思的是, 通过药物摄入的维生素D剂量与绝经年龄无关[86]; 而一项纳入10万名女性的前瞻性队列研究发现, 成年后的紫外线照射量与绝经年龄成正相关[87], 这提示通过膳食补充和户外活动, 而非合成药物, 所补充的维生素D对卵巢功能的保护作用可能更为有效.

1.7　环境污染物

随着科技的高速发展, 许多新兴材料进入了日常生活, 同时重工业、制造业以及化工医疗等也产生了众多新型环境污染物, 并通过呼吸、饮食以及皮肤接触等方式影响着人体健康. 近年来, 这些环境污染物与生殖疾病的关系受到越来越多的关注, 尤其是铅污染、二噁英和多氟烷基化合物对卵巢衰老的影响最为突出.

(1) 铅暴露. 基础研究发现, 卵巢颗粒细胞暴露于高浓度铅中会加速凋亡, 导致卵泡闭锁和卵巢萎缩[88]. 在非人灵长类动物中的研究发现, 铅可结合促性腺激素释放激素, 抑制垂体促性腺激素的分泌[89~91], 通过HPO轴影响月经周期[89]. 以往研究因检测铅浓度的人体部位不同, 导致铅暴露与绝经年龄的关系仍存争议, 如有研究报道, 胫骨的铅水平与绝经年龄呈正相关; 而髌骨的铅水平或外周血铅水平与绝经年龄之间无显著关联[89]. 因此, 不同检测部位反应的铅暴露水平与绝经年龄的相关性还有待进一步明确.

(2) 二噁英. 二噁英是具有高毒性和持久性的环境污染物, 也是一级致癌物, 其中2,3,7,8-四氯苯并二噁英(2,3,7,8-tetrachlorobenzo-p-dioxin, TCDD)被认为是毒性最强的化合物[92,93]. 由于TCDD与芳基烃受体具有高亲和力, 介导多种类固醇受体的表达, 长期暴露可影响类固醇代谢和转运[92], 降低雌雄生育力, 并存在跨代遗传效应[93]. 动物研究表明, 孕期和哺乳期的TCDD暴露对胚胎及新生儿的卵巢储备存在负面影响[93,94]. 而成年雌鼠的长期低剂量暴露可增加子宫内膜异位症的发病风险, 后者亦与卵巢功能下降有关[95]. 在人类女性中的观察性研究也发现, 绝经年龄与血清TCDD浓度呈正相关[96], 但是TCDD对卵巢功能影响的剂量效应仍需大规模临床研究加以证实.

(3) 多氟烷基化合物. 多氟烷基化合物(perfluorochemicals, PFCs)是一类普遍应用于工业和纺织业的有机物, 近年来由于PFCs频繁从人体和水源中被检出, 引起了生物和环境安全领域的关注. PFCs主要通过呼吸道和消化道进入人体[97], 其中全氟辛酸、全氟壬酸和全氟六苯磺酸酯可与低密度脂蛋白结合, 影响胆固醇代谢[98]; 而全氟羧酸可与核激素受体及盐皮质激素受体结合, 干扰内分泌环境[99]. 回顾性研究发现, 血液中全氟辛酸、全氟化钠和全氟化氢化合物水平较高的女性, 其早绝经发生风险分别增加36%, 47%和70%[100], 但不同化合物与绝经年龄的剂量关系及其机制尚有待论证.

2　总结与展望

女性绝经年龄受到多种因素的影响. 家族史、月经史、生育史、慢性疾病及不良环境暴露等均会不同程度影响卵巢储备的建立和维持, 进而影响绝经年龄, 对上述信息的系统性回顾和综合分析, 将有助于早绝经高风险人群的早诊早治, 如孕期保持良好的营养代谢状态并减少不良环境暴露, 将有助于女性胎儿的卵巢储备建立; 对于有早绝经家族史的女性, 通过相关遗传学检测, 明确引发卵巢功能异常的遗传因素, 并给予及时的遗传咨询和生育指导; 对于体重过轻、初潮年龄较早或月经异常的女性, 需警惕早绝经的发生, 并结合生化指标综合评估卵巢功能, 适时进行生育干预; 对于患有自身免疫性疾病、早发性心脑血管疾病及慢性肾病等疾患的女性, 积极治疗原发疾病将有助于卵巢功能的维持; 考虑到吸烟及环境污染物对卵巢功能的不利影响, 戒烟、保持健康的饮食和生活方式对延缓卵巢衰老具有积极作用. 不可否认的是, 目前人们对绝经年龄影响因素的认知仍存在局限性, 如1型糖尿病、口服避孕药、多氟烷基化合物等对卵巢功能的长期影响和具体机制, 有待严谨的临床观察和基础研究的证实.

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Research progress on factors influencing age at menopause

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Menopause is a manifestation of ovarian reserve depletion. Early onset of menopause indicates a shorter reproductive lifespan for women, reduces fertility opportunities, and affects the overall population size. In addition, it is associated with changes in hormone levels and increased risks of cardiovascular diseases, osteoporosis, neurodegenerative disorders, and tumors, which seriously impact the physical and mental health as well as the quality of life of women. Delaying ovarian aging and preserving ovarian reserve have become hot topics in the studies of reproductive medicine. A comprehensive understanding of the factors influencing age at menopause is of great significance for early intervention and management of female infertility, especially for those with high-risk of early menopause. In this paper, we will systematically review the factors related to menopausal age, including genetics, metabolic diseases, iatrogenic factors and environmental exposures, aiming to provide scientific basis for the management of female reproductive health.

age at menopause, genetics, metabolic diseases, iatrogenic factors, environmental pollutants

doi: 10.1360/SSV-2023-0197

https://engine.scichina.com/doi/10.1360/SSV-2023-0197