

DOI:10.12405/j.issn.2097-1486.2026.01.004

环境内分泌干扰物暴露与流产风险相关研究进展

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摘要: 流产是一种常见的妊娠并发症, 其发生受遗传、内分泌、环境及生活方式等多重因素的复杂影响。其中, 环境内分泌干扰物的普遍暴露, 引起了人们对女性生殖健康风险的深切关注, 特别是其与流产之间可能存在的关联是相关领域研究的热点问题。为此, 本综述梳理了主要环境内分泌干扰物增加流产风险的流行病学证据和潜在毒理机制。结果表明, 此类化学物质可通过干扰激素受体信号、影响子宫容受性建立、诱导氧化应激与细胞损伤、破坏胎盘功能以及引发表观遗传改变等多种途径, 导致胚胎植入失败, 并对妊娠维持产生持续不利影响。总体而言, 本综述为理解环境内分泌干扰物对妊娠结局的潜在不良影响提供了系统参考, 深化了相关风险认知, 并指出了未来可能的研究思路。

关键词: 流产; 环境内分泌干扰物; 子宫损伤

中图分类号: Q89

文献标志码: A

文章编号: 2097-1486(2026)01-0022-15

Research progress on the association between exposure to environmental endocrine-disrupting chemicals and the risk of pregnancy loss

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Abstract: Pregnancy loss is a common pregnancy complication influenced by a complex interplay of genetics, endocrine, environment, lifestyle, etc. Among these factors, the widespread exposure to environmental endocrine-disrupting chemicals (EEDs) has aroused deep concern for the potential risks to female reproductive health, the possible association between EEDs and pregnancy loss becoming a research focus in this field. Accordingly, this review systematically summarizes epidemiological evidence and potential toxicological mechanisms through which major EEDs may increase the risk of pregnancy loss. Findings indicate that these chemicals can contribute to embryo implantation failure and exert sustained adverse effects on pregnancy maintenance via multiple pathways, including interference with hormone receptor signaling, disruption of uterine receptivity establishment, induction of oxidative stress and cellular damage, impairment of placental function, and triggering of epigenetic alterations. In summary, this review provides a systematic reference for understanding the potential adverse effects of EEDs on pregnancy outcomes, deepens the understanding of associated risks, and suggests future research approach.

Keywords: pregnancy loss; environmental endocrine-disrupting chemicals; uterine injury

0 引言

常见的不良妊娠结局包括流产和早产^[1]。根据

欧洲人类生殖和胚胎学学会的定义, 流产指妊娠 24 周前发生的自然流产, 其在多个国家的发生率约占临床确认妊娠的 15% 至 20%^[2]。反复流产通常定义

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基金项目: 国家自然科学基金(22476120)

收稿日期: 2025-11-07; 修回日期: 2025-12-15

为连续两次及以上在妊娠20周前发生的妊娠丢失^[3],是一种严重的妊娠并发症,且在全球范围内呈现逐渐增加的趋势^[4]。流产的病因复杂,涵盖遗传异常、感染、免疫和植入障碍、子宫和内分泌异常以及生活方式因素等多个方面^[5]。随着研究的深入,环境污染物对流产等生殖健康结局的潜在影响越来越受到关注^[6-7]。

环境内分泌干扰物(environmental endocrine-disrupting chemicals, EEDs)是指环境中天然存在或人为引入,能够模拟或干扰天然激素生理功能,进而对生物体内分泌、神经、免疫和生殖系统造成可逆或不可逆影响的一类化合物。这类物质包括多种环境污染物——如双酚类化合物(bisphenols, BPs)^[8]、邻苯二甲酸盐(phthalate esters, PAEs)^[9]、全氟烷基和多氟烷基物质(per- and polyfluoroalkyl substances, PFAS)^[10]和有机氯农药^[11]等。这类化合物广泛用于多个工业领域,并可能通过食品包装迁移、农药残留和工业品降解等途径进入日常生活环境^[12]。皮肤和吸入是人体暴露于EEDs的主要途径,其相关的健康风险包括肿瘤、神经与生殖系统病变等多个方面^[13-15]。在真实环境中,女性常同时暴露于多种EEDs,可能共同导致生殖健康风险上升^[16]。值得注意的是,EEDs能够穿过胎盘屏障进入胎儿循环,从而引发一系列不良妊娠结局,如流产、早产、小于胎龄儿以及低出生体重等^[17]。

近年来,越来越多的证据将EEDs与流产风险联系起来。例如,双酚A(bisphenol A, BPA)可能通过干扰下丘脑-垂体-卵巢轴调控及诱发表观遗传修饰变化参与流产发生^[18];而全氟辛烷磺酸(perfluorooctane sulfonate, PFOS)具有长达3—8年的生物半衰期,其在甲状腺结合能力和胎盘转移效率方面均显著高于代谢较快的同类物,提示其潜在的流产相关毒性风险^[19-20]。此外,邻苯二甲酸二(2-乙基己基)酯(di(2-ethylhexyl) phthalate, DEHP)作为内分泌干扰物进入血液,会直接损害下丘脑和卵巢的功能,导致下丘脑-垂体-卵巢轴相关激素的无序分泌,并通过转移现有常驻肠道相关微生物群的组成和功能以间接增强下丘脑-垂体-卵巢轴稳态的损害,从而导致怀孕率下降^[21]。

当前,随着多个国家对部分传统EEDs实施管控,其结构类似物作为替代品被广泛应用于日常消费品和工业材料中。然而,这些新型EEDs对女性生殖健康,尤其是流产风险的潜在影响,尚未得到系统评估,其作用机制与关键靶点亦未完全明确。因

此,本综述旨在系统梳理主要EEDs(包括BPs、PAEs、PFASs和有机氯农药等)与流产风险的关联性研究,整合流行病学与实验证据,总结可能的生物学机制,并对未来研究方向提出展望,为深入理解EEDs的生殖毒性及其风险防控提供科学依据。

1 搜索策略

我们在PubMed(<https://www.ncbi.nlm.nih.gov/pubmed>)和Google Scholar(<https://scholar.google.com/>)中进行了文献搜索,并于2025年9月2日访问,对2015年至2025年发表的专注于环境内分泌干扰物和流产之间关系的研究使用以下关键词进行了搜索:环境内分泌干扰物、双酚、邻苯二甲酸盐、全氟烷基和多氟烷基物质、有机磷阻燃剂、多环芳烃、有机氯农药、抗生素和流产。此外,我们筛去了评论文章,以完善相关信息。

2 双酚类化学物

BPs,特别是BPA,常见于聚碳酸酯塑料和环氧树脂的制造中。这些材料被广泛应用于食品包装容器、婴儿奶瓶、牙科密封材料以及食品罐内衬等日常消费产品,从而增加了人群尤其是婴幼儿的暴露风险^[22]。人体暴露于BPs的主要途径是通过消化道摄入,例如从包装材料中迁移至食品或饮料中的BPA单体会随饮食进入人体;此外,皮肤接触和吸入途径也可能在特定职业环境中发生暴露^[23]。BPA是最早发现的合成雌激素之一^[24],通过与雌激素受体,特别是雌激素受体 α 的相互作用来扰动雌激素作用。这些雌激素效应可能导致雌激素敏感组织的细胞变化,引起正常的激素功能紊乱,生殖系统和内分泌系统损伤^[25]。BPA已被多项研究证实具有细胞毒性、生殖毒性和内分泌干扰潜力,受到多个国家和地区严格限制,并逐渐从部分商品中淘汰。在监管与公众意识的推动下,双酚S与双酚F等BPA替代品得以被大规模开发与应用,在环境及胎盘、脐带血等生物样本中的检出也日益频繁^[26-27]。然而,鉴于此类化学物与BPA在结构上的高度相似性,理论上它们可能带来与BPA相当或更为复杂风险的可能性,因此仍需审慎看待这些替代品的安全性。

2.1 流产风险

BPA及其类似物与不良妊娠结局尤其是流产风险之间的关联已引起广泛关注。研究表明,BPA暴露与较高的早产率、子痫前期及反复流产风险呈正相关。例如,Lathi RB等人指出,母体血清共轭

BPA水平与怀孕前三个月流产有显著相关性。与共轭BPA水平处于最低四分位数组的女性相比,水平处于最高四分位数组的患者总体流产风险增加了83%。该关联在非整倍体流产和整倍体流产中均得到证实,其^①相对风险分别为1.97和3.33^[28],这一结果在中国的一项研究中亦得到印证^[29]。此外,一项大型病例对照研究进一步证实,尿液中的BPA及其类似物浓度与不明原因复发性流产风险显著相关。当这些物质作为混合物共同暴露时,其浓度每增加一个对数单位,流产风险相应上升25%。在单一物质分析中,BPA及其替代物双酚AP的危害性并列最高,浓度每增加一个对数单位均会使风险增加12%;双酚AF、双酚B和双酚P则分别使风险增加9%、6%和4%。此外,该关联在30岁及以上女性中往往更为显著^[30]。还有研究指出,不仅较高剂量双酚F(5 μg/kg体重)与怀孕妇女自发流产相关,而且即使低剂量双酚F(1 μg/kg体重)仍能引起流产,只是发生率相对较低^[31]。然而,并非所有研究结论一致,一项研究指出几乎没有证据表明双酚A与卵泡期长度或早期流产风险增加有关^[32]。此外,来自中国的小型病例对照研究表明,30例不明原因复发性流产病例和30例对照组之间BPA水平没有显著差异^[33]。现有研究结论的不一致可能源于多方面原因。样本量较小及统计效力不足,尤其是在罕见结局的研究中,限制了检出真实关联的能力;研究设计上存在异质性,包括人群特征、暴露评估方法与结局定义的不同,也影响了结果间的可比性。此外,各研究对生活习惯、环境共暴露等混杂因素的控制程度不一,可能导致偏倚;而BPA在体内代谢快、单次测量难以反映长期暴露,同样会增加暴露错分的风险。人群暴露水平、遗传背景及地域差异等因素,亦可能在不同研究中导致效应估计的分歧。尽管如此,大量基础研究为BPs的生殖毒性提供了坚实的生物学合理性。人类与动物数据均提示双酚暴露会降低女性的生育能力^[34-36]。同时体外和体内证据表明,BPA及其多种类似物会干扰卵泡发育、减数分裂进程、细胞形态与纺锤体完整性等卵母细胞发育的关键环节^[37-39]。这些过程的破坏会导致卵母细胞质量下降,从而增加早期妊娠丢失的风险。因此,在肯定BPs对女性妊娠结局构成潜在威胁的同时,系统阐明其内在的生物学作用机制,是精准评估其健康风险并制定有效干预策略的迫切需求。

2.2 潜在机制

近年研究表明,流产妇女血清中双酚A(BPA)水平显著升高,提示BPA可能在流产发生机制中扮演重要角色。其作用主要涉及氧化应激、免疫失衡、子宫内膜结构与功能损伤,以及胚胎植入障碍等多个层面。

首先,BPA被确定为人类子宫内膜细胞的氧化应激诱导剂。在人类胚胎干细胞中,BPA通过雌激素受体α依赖的方式激活ERK/AKT/NF-κB信号通路,进而引发氧化应激,这一机制可能与生殖功能障碍密切相关^[40]。此外,BPA可以通过氧化应激诱导胚胎毒性,其特点是活性氧过度积累,激活促凋亡和铁凋亡相关途径,破坏细胞骨架和线粒体功能,以及内细胞团与外胚层细胞谱系分化受损,最终降低了植入潜力^[41]。临床研究进一步发现,反复自然流产患者尿液中BPA浓度与氧化应激标志物8-异前列腺素和促炎细胞因子干扰素γ水平呈正相关^[42]。此外,BPA暴露与血清还原型辅酶Ⅱ氧化酶1水平呈正相关,推测高浓度BPA可增强还原型辅酶Ⅱ氧化酶复合体活性,并通过活性氧/中性粒细胞胞外诱捕网(Neutrophil Extracellular Traps, NETs)通路促进流产发生,尤其在NETs形成相关的“NET阳性群体”中BPA浓度最高,支持BPA可能诱导NETs形成的假设。体外实验同样显示,BPA处理可显著提升健康女性中性粒细胞中还原型辅酶Ⅱ氧化酶活性及NETs释放能力^[43-44]。

其次,BPA干扰免疫平衡,影响母胎耐受。在同种异体妊娠模型中,BPA和四溴双酚A的暴露增加了胚胎吸收率,并降低了母体调节性T细胞的数量。其机制可能是通过下调吡啶胺2,3-双加氧酶1的表达,干扰了吡啶胺2,3-双加氧酶1依赖的母体免疫耐受,最终导致流产^[45]。另一方面,BPA替代物双酚S虽与抗炎细胞因子白细胞介素10水平正相关,但其病理性升高会打破平衡,干扰胎盘发育,成为导致不良妊娠结局的核心机制之一^[46]。此外,BPA暴露与炎症蛋白单核细胞趋化蛋白-1水平之间也存在正相关,表明BPA的积累可能助长炎症微环境,进而参与流产的发病过程^[43-44]。

子宫内膜的结构与功能完整性对胚胎的成功植入和妊娠维持至关重要。研究表明,BPs能够损害这种完整性,干扰胚胎发育并增加流产风险。在我们先前的研究中,BPA的类似物(包括双酚B、双酚

① 相对风险:指与对照组相比的风险比值。例如,相对风险为1.97表示风险增加97%。

S和双酚AF)暴露可引起小鼠子宫内膜组织结构的损伤,具体表现为子宫收缩活动增强、上皮厚度减小以及腺体数量增多^[47-48]。这种形态学变化可能源于子宫基因表达谱的差异变化,并进一步干扰了子宫内的免疫稳态。在免疫方面,双酚B和双酚AF暴露可显著提高子宫组织内嗜酸性粒细胞及调节性T细胞的比例,引起免疫细胞组成失衡;而双酚S则主要激活与白细胞迁移和活化相关的免疫信号通路。这些异常的免疫应答可能共同破坏子宫局部免疫微环境,增加流产风险。此外,双酚AF暴露还表现出更强的内分泌干扰效应,它会干扰九种激素的水平,导致动情周期延长,并破坏细胞外基质稳态和体液免疫过程的平衡。其中,基质金属蛋白酶7和印度刺猬因子被识别为这一过程中的关键基因。可变剪接分析进一步表明,胶原蛋白I型 $\alpha 2$ 链发生内含子保留事件,导致蛋白质结构变异,可能与子宫功能异常密切相关^[49]。此外我们的研究还发现类固醇5 α 还原酶1(*Srd5a1*)可能是暴露于双酚B和双酚AF引起的子宫异常的关键信号。而双酚B暴露组的差异表达基因显著富集于血管发育与血流调节相关通路,提示双酚B还可能通过影响子宫血管系统的形成与功能来阻碍胚胎发育。这些结果提示,BPs暴露可通过扰乱子宫内细胞外基质结构与免疫平衡来增加流产风险。

作为妊娠建立的基础事件,胚胎植入的成功取决于精准的分子对话与处于容受态的子宫微环境;此环节一旦失衡,常成为妊娠早期流产的直接诱因。研究表明,子宫上皮中谷胱甘肽过氧化物酶4的缺失可通过影响内膜容受性而诱发流产^[50]。在环境因素中,BPA被证明会影响胚胎附着和植入过程相关的子宫受体表达^[51-52]。围产期BPA暴露可破坏子宫上皮紧密连接蛋白的组成与功能,改变细胞旁离子及液体转运,从而损害子宫内膜在成年期接受胚胎的能力^[53]。在分子层面,BPA暴露能显著下调子宫内膜雌激素受体 α 的表达,进而抑制其下游靶基因——整合素 $\beta 3$ 的表达^[54]。整合素 $\beta 3$ 作为重要的雌激素依赖性黏附分子,其在子宫内膜与胚胎囊表面的表达不足直接影响附着与植入过程,最终导致着床位点减少和植入失败^[55]。BPA可通过下调白血病抑制因子(LIF)基因与上调黏蛋白1(MUC1)基因的表达来破坏子宫容受性;同时,它还能扰乱瞬时受体电位香草素亚型5/6(TRPV5/6)等钙离子通道的正常功能。这两方面共同导致胚胎植入所必需的钙稳态和子宫-胚胎对话失衡,从而降低植入率^[56]。此外,双酚类化学物还对蜕膜化过程具有干扰作用。

低剂量BPA可通过上调新型的内质网应激受体Luman的表达,引发蜕膜基质细胞的脱落功能障碍及内质网应激,进而阻碍正常的蜕膜化进程^[57]。双酚S暴露也可能激活内质网应激相关蛋白质(X盒结合蛋白1剪接变体、激活转录因子4及肌醇需求酶1 α)表达,破坏子宫内膜基质细胞蜕膜化,从而导致植入失败^[58]。总之这些研究表明,BPA会通过多重分子机制破坏子宫-胚胎对话,参与植入失败及早期妊娠丢失的病理过程。

3 邻苯二甲酸盐类化学物

PAEs是一类人工合成的化学增塑剂,广泛用于塑料制品(如玩具、个人护理产品、医疗设备、食品包装和农用薄膜)的生产中,以增强其柔韧性、可加工性和延展性^[59]。PAEs在工业、农业生产和日常生活中普遍存在,可通过磨损、蒸发和浸出等途径持续释放,并迁移至生态系统和人体中^[60]。环境监测显示,无论是发达国家还是发展中国家,在水体、土壤、水生生物甚至人体样本中均频繁检出微量PAEs或其代谢物^[61-65]。多项流行病学研究表明,接触某些PAEs可能会导致女性生殖健康问题^[66]、神经发育障碍^[67]、心血管疾病^[68]、肥胖^[69]、哮喘^[70]、糖尿病以及胰岛素抵抗^[71]等多种不良健康结局。作为内分泌干扰物,PAEs可以干扰激素合成、分泌、结合和代谢过程,表现出抗雄激素和类似雌激素的活性。此外,它们还被认定具有致畸、致癌、致突变和生殖毒性等一系列有害效应。动物实验和人群的流行病学研究证据表明,PAEs暴露对人类生殖健康具有潜在影响^[21,72]。早在2002年,美国国家毒理学计划人类生殖风险评估中心就已详细报告多种PAEs的生殖与发育毒性(<http://cerhr.niehs.nih.gov>),美国环境保护局和欧盟将它们列为优先控制污染物^[73]。因此,系统阐明PAEs暴露与女性妊娠结局之间的关联尤为必要。

3.1 流产风险

日益增多的证据提示,PAEs暴露可能与女性流产风险增加存在关联。有研究显示在超过80%的流产女性尿液中检测到邻苯二甲酸单甲酯(Monomethyl Phthalate, MMP)、邻苯二甲酸单乙酯、邻苯二甲酸单丁酯(Monobutyl Phthalate, MBP)和邻苯二甲酸单苄酯四种邻苯二甲酸盐代谢物,其中MMP和MBP水平显著高于对照组,且逻辑回归模型提示MMP浓度每增加一个对数单位,稽留流产的风险便会增加49%^[74]。一项病例对照研究应

用随机森林模型也发现PAEs暴露与早期妊娠丢失相关,其中DEHP的代谢物邻苯二甲酸单(2-乙基-5-羟基己基)酯、邻苯二甲酸单(2-乙基己基)酯和邻苯二甲酸单(5-羧基-2-乙基戊基)酯在病例与对照组间差异显著^[75]。另有研究通过贝叶斯核机器回归指出,PAEs混合物整体上与流产风险呈正相关,且DEHP是联合效应的主要贡献成分^[76]。此外,尿液中DEHP的主要生物活性代谢物邻苯二甲酸单乙基己基酯(Monoethylhexyl phthalate, MEHP)水平较高也被报道与流产风险升高有关^[77]。根据Chiang和Zong等人的研究,女性长期接触高水平的PAEs(如邻苯二甲酸二乙酯(Diethyl phthalate, DEP)和DEHP)是导致不良妊娠结局(包括胚胎毒性、胎儿毒性及流产率升高)的危险因素^[78-79]。动物实验进一步佐证了其生殖毒性。暴露于DEP、DEHP、邻苯二甲酸二丁酯和邻苯二甲酸二异丁酯等特定PAEs,可导致胚胎存活率下降、早期胚胎停止发育并被吸收的情况增加、窝仔数及体重减少,并诱发大鼠流产率上升^[80]。然而,少数关于PAEs混合物累积暴露的研究报告了不一致甚至相反的结论。例如,Jukic等人发现,更高的DEHP代谢物水平,特别是单(2-乙基-5-氧代己基)邻苯二甲酸盐,与降低流产风险的趋势相关^[32]。Deng等人则报道,在接受辅助生殖的妇女中,尿PAEs水平与流产之间没有显著关联,即使排除了男性不育的参与者,DEHP代谢物仍然与体外受精/细胞质内精子注射结果没有显著或不一致的关联^[81]。然而,多数研究受限于样本量(通常不足150例),导致统计检验效能不足,加之不同研究结论存在分歧,所以关于何种PAEs或其代谢物是导致流产的主要致病物质,至今尚未达成共识。为解释这些关联背后的生物学过程,机制性研究逐渐成为探索PAEs生殖毒性的关键方向。

3.2 潜在机制

PAEs暴露对女性生殖过程具有广泛而多重的不利影响,涉及胚胎植入、早期胚胎发育及妊娠维持等多个关键生理环节。在母体层面,该类化合物可显著干扰子宫功能,尤其是容受性建立与蜕膜化进程。长期暴露于PAEs混合物会引发子宫内膜结构异常,包括内膜增厚、组织纤维化及局部僵硬,这些病理改变与子宫内转化生长因子 β 信号通路的异常激活密切相关,成为着床障碍、不孕及反复流产的重要诱因^[82]。在分子机制上,DEHP通过激活丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和核因子 κ B(nuclear factor kappa-B, NF- κ B)信号通

路,上调雌激素受体 α 、孕激素受体及E-钙黏蛋白的表达,从而损害子宫内膜的容受性。此外,DEHP暴露不仅导致胚胎植入数量减少,还会引起胚胎空间分布异常,两者均显著增加流产风险^[83]。最新的研究发现,DEHP及MEHP会严重干扰小鼠的子宫蜕膜化过程。体内实验表明,DEHP暴露能显著减小小鼠子宫蜕膜瘤的重量和面积,并降低多个关键时间点的蜕膜化标志物表达。体外实验进一步证实,MEHP通过扰乱子宫内膜基质细胞的细胞骨架重塑,从而抑制其蜕膜化。机制上,研究人员通过蛋白质组学发现,肌微管蛋白相关蛋白6(Mttr6)在DEHP/MEHP暴露后表达上调;而降低Mttr6的表达则能有效缓解MEHP引起的蜕膜化缺陷。此外,分子对接分析揭示,MEHP可直接结合到Mttr6蛋白的ALA-131活性位点上。这些结果共同表明,DEHP/MEHP很可能通过直接靶向Mttr6并使其上调,进而破坏细胞骨架重塑,最终导致蜕膜化功能障碍^[84]。另一方面,邻苯二甲酸二异壬酯暴露则通过下调血管内皮生长因子A(Vegfa)和血管生成素2(Angpt2)等关键血管生成因子的表达,影响早期胎盘血管网络的形成^[85]。值得注意的是,Vegfa及其受体以及Angpt2的表达水平下降在临床流产病例中已得到多次验证^[86-87],提示该类化合物在人类生殖中可能具有类似的毒性路径。

在胚胎层面,PAEs类似物邻苯二甲酸丁基苄酯(Benzyl butyl phthalate, BBP)暴露可直接影响早期胚胎发育,显著降低其抵达关键发育阶段的比率^[88]。机制研究表明,BBP可引起转录组与代谢组的广泛紊乱,尤其干扰线粒体能量代谢与蛋白质翻译过程,并伴随内质网和高尔基体等细胞器的超微结构损伤。进一步实验显示,BBP可能通过作用于线粒体复合物I亚基A11,破坏电子传递链功能,诱发氧化应激与细胞凋亡。体外模型也证实,PAEs暴露会损害胚胎发育过程中的细胞间黏附结构与核完整性,从而削弱胚胎存活潜力,增加早期流产风险^[89]。此外,高浓度的MEHP暴露会损害胚胎发育,降低胚胎囊的形成百分比及其孵化能力,还可能通过增加Tet3的表达来改变甲基化过程^[90]。综上所述,PAEs通过对母体子宫微环境与胚胎自身发育的双重干扰,形成多途径、多阶段的生殖毒性效应,最终威胁妊娠成功与胚胎健康。

4 全氟烷基和多氟烷基类化学物

PFAS及其衍生物是一类具有高度环境持久性

的有机污染物。其独特的表面活性与化学稳定性使其在汽车、纺织、炊具、包装、农业和化妆品等多个工业与消费领域中得到广泛应用^[91]。随着PFAS的广泛使用与持续排放,该类污染物已在全球范围内的环境介质及人体样本中被普遍检出^[92-94]。一般人群通过饮食摄入、非饮食摄入、吸入和皮肤吸收等多种暴露途径接触PFAS^[95]。由于PFAS与血清白蛋白具有高度亲和力,其在进入人体后易于在血浆中蓄积^[96]。部分PFAS在人体内的清除半衰期较长,例如PFOS异构体的平均半衰期为4.0到7.5年^[97],而氯化多氟烷基醚磺酸作为目前已知在人体中生物持久性最强的PFAS之一,其半衰期可达15.3年^[98]。流行病学研究表明,PFAS暴露可对多个器官系统造成不良影响,包括肝脏^[99]、肾脏^[100]、甲状腺^[101]、神经系统^[102]、免疫系统^[103]和生殖系统^[104]等。在妊娠结局方面,研究发现血清全氟辛酸(Pentadecafluorooctanoic acid, PFOA)和全氟己烷磺酸(Perfluorohexane sulfonic acid, PFHxS)浓度较高的孕妇早产的概率增加^[105]。此外,部分母体负荷的PFAS可透过胎盘屏障,导致胎儿直接暴露^[106]。总之,现有证据提示PFAS对生殖健康存在潜在危害,然而其与流产风险的具体关联仍需进一步阐明。

4.1 流产风险

现有的研究对PFAS暴露与流产风险之间的关联进行了广泛探讨。Liew等人在一项病例对照研究中发现,母体暴露于高水平的PFOA、全氟庚烷磺酸以及PFAS混合污染物与流产风险上升有关,且在已生育女性中这一关联更为明显^[107]。类似地,Jensen等人研究也表明,妊娠期间全氟壬酸和全氟癸酸暴露水平处于最高三分位数组的女性,其流产风险显著高于处于最低三分位数组的群体^[108]。一项在中国西北地区开展的前瞻性队列研究,经全环境关联分析发现,全氟戊烷磺酸、PFHxS、PFOA、PFOS和全氟壬酸这五种PFAS均与流产概率增加显著相关^[109]。此外,有病例对照研究探讨了PFAS暴露与稽留流产之间的关系,结果显示怀孕前三个月PFOA暴露与妊娠早期后半段发生零星流产有关,PFOS暴露水平从第25百分位上升至第75百分位时,流产风险增加约50%,且呈现单调剂量-反应关联^[110]。另一方面,部分研究未观察到PFAS与流产之间的显著关联。例如,一项在中国北京和烟台开展的队列研究指出,在当前的平均暴露水平下,多数PFAS与早期流产之间并无显著关联^[111]。另一项针对接受体外受精女性的研究也显示,PFAS水

平与胚胎植入、临床妊娠或活产结局均无显著相关性^[112]。研究结论之间的差异可能源于多方面因素:包括研究设计与人群(如一般人群与辅助生殖群体)的异质性、暴露评估多局限于女性单次测量且未纳入男性伴侣暴露、对混杂因素(如生活方式、共暴露污染物及妊娠早期易感性差异)的控制不一致、部分研究样本量较小导致统计效力不足,以及不同人群的暴露水平与PFAS化合物谱存在差异。除了传统PFAS,其替代物的生殖毒性也受到关注。Chu等人报告指出,母体血清中PFAS替代物如6:2氯代多氟醚基磺酸(6:2 Cl-PFESA)和8:2氯代多氟醚基磺酸的浓度与不良分娩结果相关,其浓度每增加一个自然对数单位(ln-ng/mL),新生儿出生体重将分别降低54.44克和21.15克,这表明其对胎儿生长有潜在影响,可能导致流产^[113]。此外,暴露于6:2 Cl-PFESA和六氟环氧丙烷二聚体酸也与不明原因反复自然流产风险上升显著相关,这种关联在30岁以上女性中表现得更为突出^[114]。现有证据提示部分PFAS及其替代物可能在特定条件下增加流产风险,但不同研究之间存在不一致的发现。这种关联背后的生物学机制亟待深入阐明,以合理解释流行病学观察到的复杂现象。

4.2 潜在机制

现有流行病学与实验研究逐步揭示,妊娠期尤其是早期胚胎发育阶段暴露于PFOS,可能通过干扰子宫内膜容受性、诱导线粒体功能障碍、破坏细胞凋亡平衡以及影响胚胎有丝分裂等多个层面,显著增加不良妊娠结局的风险,其毒性机制复杂且具有多靶点作用特征。在组织病理层面,PFOS暴露可引发子宫组织一系列显著的形态学改变,包括子宫相对重量下降、局部出血、剥落和间质细胞间隙狭窄,部分细胞表现出不同程度的核凝结、核粉碎、细胞质不均匀和空泡变性等病理改变,提示其具有胚胎毒性^[115-116],可能会导致怀孕早期的流产或胎儿吸收。从分子机制角度进一步分析,PFOS表现出对子宫内膜关键基因的广泛干扰。PFOS可能通过表观遗传调控,如组蛋白乙酰化修饰等,抑制类固醇生成急性调节蛋白(*StAR*) mRNA表达,干扰卵巢雌二醇的生物合成^[117],而雌二醇水平降低可能导致流产风险增加。在生理浓度下,PFOS对参与植入过程和子宫内膜增殖的孕酮靶基因具有拮抗作用,这为流行病学研究中观察到的PFOS暴露与妊娠期延长、流产风险升高及生育力下降之间的关联提供了实验依据^[118]。

PFOS的毒性效应远非仅限于基因表达与信号转导,其对细胞能量代谢与内稳态的瓦解,直接削弱了滋养层功能并危及胚胎发育。研究显示,PFOS可引起滋养层细胞线粒体结构异常,包括膜电位崩溃、活性氧过度积累及线粒体肿胀,最终导致ATP合成受阻和能量代谢危机^[119]。在胚胎发育过程中,此类功能障碍不仅影响滋养细胞的迁移、侵袭与血管生成能力,还可促使蜕膜中M1型巨噬细胞极化,进而导致反复妊娠丢失^[120-121]。PFOA暴露会导致同源框A10、整合素 $\beta 3$ 及叉头框蛋白O1等重要功能因子在转录与翻译水平上的表达出现抑制,进一步削弱子宫内膜的受体反应能力与胚胎对接的分子基础^[122]。利用单细胞RNA测序技术,研究人员进一步揭示PFOS可特异性干扰子宫内膜中血管生成素样信号通路,该通路对上皮-基质细胞通讯至关重要,其失调被认为是导致胚胎植入失败的关键环节之一^[123]。值得注意的是,PFOS的发育毒性具有持续性与累积性。动物实验表明,妊娠期暴露于PFOS会导致胚胎流失和胎儿生长迟缓^[124]。其潜在机制包括上调Fas受体或配体的表达,介导子宫细胞过度凋亡,以及诱发母体对胚胎的免疫排斥。同时,PFOS可能通过降低B淋巴细胞瘤-2基因(*Bcl-2*)、增加*Bcl-2*相关X蛋白(*Bax*)表达,打破*Bcl-2*/*Bax*平衡,进一步加剧细胞凋亡,引起胚胎损伤或丢失^[116]。在细胞分裂调控层面,PFOS会干扰早期胚胎有丝分裂过程中纺锤体的正常组装,引起染色体排列错误与非整倍体发生^[119]。PFOS暴露会异常增加 α -微管蛋白的乙酰化水平^[125],而该修饰与纺锤体微管动力学密切相关,这为理解其导致胚胎发育停滞提供了新的视角。综上所述,PFOS通过干扰子宫内膜功能、诱导线粒体损伤、破坏细胞凋亡平衡以及影响胚胎有丝分裂等多个层面,共同参与早期妊娠失败的发生与发展。

5 其他

除上述主要化学物类别外,其他EEDs也显示出与不良妊娠结局的潜在关联。例如,有机磷阻燃剂广泛用作增塑剂,常见于纺织品、电子产品、家具泡沫及橡胶制品中^[126]。该类化合物可干扰机体内源性激素的调节功能,导致人类与动物生育能力异常^[127]。研究发现,尿液中较高浓度的二(1-氯-2-丙基)磷酸酯与胎儿染色体异常及自然流产风险升高相关^[128]。多环芳烃是另一类具有致癌性、生殖毒性与发育毒性的EEDs^[129]。Li等对80名接受体外受

精一胚胎移植的女性(包括40例早期流产与40例正常活产)的尿液样本进行分析,发现尿液中2/3-羟基菲水平与早期流产呈正相关^[130]。在环境污染物中,有机氯农药对女性妊娠结局的影响亦受到广泛关注。多项研究表明,女性产前农药暴露与自发流产之间存在显著关联^[131]。在复发性流产患者血清中, α -HCH、 β -HCH、2,4-DDE、4,4-DDE等单体农药及其总和浓度(如 $\Sigma 3\text{HCH}$ 、 $\Sigma 2\text{DDE}$ 、 $\Sigma 2\text{DDT}$ 与 $\Sigma 7\text{OCIP}$)均显著高于对照组。其潜在机制可能涉及有机氯农药通过降低胎盘组织中组蛋白H3第9位赖氨酸乙酰化(*H3K9ac*)的表达,影响胎盘正常发育与母胎免疫耐受,从而促进流产发生^[132]。此外,环境中残留的抗生素(如磺胺类、青霉素、阿莫西林与四环素等)亦具备内分泌干扰特性。一项嵌套病例对照研究指出,妊娠早期使用大环内酯类(红霉素除外)、喹诺酮类、四环素类、磺胺类及甲硝唑与自然流产风险增加有关^[133]。近期研究进一步发现,孕前抗生素暴露可使自然流产风险升高34%,其机制可能与扰乱母体肠道菌群平衡,干扰雌激素代谢及妊娠相关激素的生物合成,从而损害母体生育能力有关^[134]。综上所述,尽管针对这些EEDs的研究相对有限,但现有证据仍提示其在环境中的广泛存在及其与流产风险的潜在关联不容忽视。未来研究应将其纳入更全面的环境健康风险评估体系,以更完整地揭示环境污染物对女性生殖健康的综合影响。

6 总结与展望

环境中存在的内分泌干扰物对女性妊娠结局影响机制十分复杂。本综述综合现有研究发现,多数流行病学证据支持EEDs暴露与流产风险之间的关联,体内外实验进一步从分子层面揭示了其作用机制。这些污染物可通过破坏生殖器官结构与功能,干扰胚胎植入、胎盘发育等关键生理过程,最终导致妊娠丢失。其毒性作用主要经由干扰激素调节、诱导氧化应激、影响基因转录及表观遗传调控等多重生物学途径实现。尽管现有研究取得了重要进展,但该领域仍面临诸多挑战。首先,流行病学研究结果存在不一致性,这种异质性可能源于暴露评估方法的差异、混杂因素控制不足、研究人群特征不同以及样本量有限等因素。其次,现有研究主要集中在少数传统EEDs(如BPA、DEHP、PFOA和PFOS)上,而对日益增多的新型替代物(如双酚S、双酚F和氯化多氟烷基醚磺酸等)的生殖毒性了解有限。再者,大多数研究关注单一化合物的效应,而现实中

人体同时暴露于多种EEDs的混合物,其联合毒性效应亟待阐明。

据此,未来研究建议重点关注以下方向:在混合暴露评估方面,需从单一化合物评估转向复合暴露研究,采用贝叶斯核机器回归、加权分位数和回归等先进统计模型,解析化学混合物对流产风险的联合效应,并建立更符合真实暴露场景的体外测试系统。在机制研究层面,运用类器官、共培养系统和单细胞多组学技术,深入探讨EEDs对母胎界面细胞通讯、免疫微环境重编程和代谢网络的影响,特别关注其通过调控非编码RNA、DNA甲基化和组蛋白修饰等表观遗传机制参与流产发生的具体路径。同时,需要加强易感人群识别研究,深入探索遗传背景、表观遗传特征和生理状态对个体易感性的影响,并开展生命早期暴露的队列研究,阐明发育源性生殖疾病的发病机制。此外,随着传统EEDs逐步被替代,应建立系统的新化合物生殖毒性筛查平台,整合高通量筛选、计算毒理学和体外测试方法,在新化合物投入市场前全面评估其潜在风险。

总之,EEDs与流产风险关联的研究正处于从现象描述向机制阐明、从单一化合物评估向复杂混合物研究转型的关键时期。通过跨学科合作、新技术应用和研究范式创新,我们将能更全面地理解EEDs的生殖毒性,为制定有效的预防策略和保障女性妊娠结局提供科学基础。

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