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·综　述·

妊娠期全氟及多氟烷基化合物暴露对子代生长发育影响的研究进展

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【摘要】 妊娠期全氟及多氟烷基化合物(PFASs)暴露可能对处于生命早期敏感阶段的胎儿构成危害,影响宫内乃至出生后的生长发育。文章对国内外相关研究进行综述,总结不同国家和地区孕妇 PFASs 的暴露水平,探讨孕期 PFASs 暴露对子代生长发育的影响及潜在的生物学机制,以期为后续开展相关队列研究及制定保护性措施提供依据。

【关键词】 妊娠;氟;多氟化合物;生长和发育

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Research progress on the influence of prenatal exposure to per- and polyfluoroalkyl substances and offspring physical growth

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【Abstract】 Exposure to per- and polyfuloroalkyl substances(PFASs) during pregnancy may pose hazards to fetuses at the sensitive early stage of life, impacting intrauterine and postnatal growth and development. By reviewing existing domestic and international studies, the article summarizes the internal exposure levels of PFASs in pregnant women from different countries and regions, and clarifies the impact of prenatal PFASs exposure on the growth and development of offspring and potential biological mechanisms, so as to provide a basis for subsequent cohort studies and the formulation of protective policies.

【Keywords】 Pregnancy; Fluorine; Polyfluoro compound; Growth and development

根据健康和疾病发育起源学说(development origins of heath and disease, DOHaD),子代健康的环境风险因素可追溯至母亲妊娠期间的宫内暴露。生命早期不良宫内因素的暴露将会导致胎儿及新生儿的适应性改变,进而影响儿童期乃至成年期慢性非传染性疾病的发生发展[1]。全氟及多氟烷基化合物(per- and polyfluoroalkyl substances, PFASs)等环境污染物的宫内暴露所引起的近远期危害逐渐受到重视。本文将基于现有研究证据进行综述,总结不同国家和地区孕妇 PFASs 的体内暴露水平及孕期 PFASs 暴露与子代生长发育的关联,阐述 PFASs 对子代生长发育产生不良影响的潜在机制,为后续研究及制定针对性干预措施提供依据。

1　PFASs 的暴露情况

1.1　PFASs 的结构和主要暴露途径　PFASs 是一类人造有机物,目前工业合成种类已超过 4 000 种,广泛应用于纺织品、不粘炊具、地板抛光剂等领域[2]。其基本结构特征为脂肪族碳链中的氢原子被氟原子完全或部分取代[3]。按官能团可分为全氟羧酸和全氟磺酸两大类[4],具有≥7 个全氟烷基的全氟羧酸或具有≥6 个全氟烷基的全氟磺酸被定义为长链 PFASs。C-F 化学键的强键能使其具有耐热性、化学稳定性和难降解性,可在环境和生物体内长期蓄积[3]。

人类可以通过多种途径暴露,包括摄入受污染的饮用水和海产品、吸入空气及接触含有 PFASs 的包装材料和炊具涂层等[4]。当前,全氟辛烷磺酸(perfluorooctane sulfonate, PFOS)和全氟辛酸(perfluorooctanoic acid, PFOA)在环境中载量最高且人体暴露最为普遍,多个国家已对其实施了限制措施[5];然而,由于其具有较长的半衰期和高度稳定性,在人体中仍能被广泛检出。随着 PFOS 和 PFOA 的逐步淘汰,多种新型替代品如前体物质、短链 PFASs、官能团取代物等不断涌现[6]。

1.2　不同地区人群孕期 PFASs 的暴露水平　监测 PFASs 的体内暴露水平可为评估其健康风险提供依

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据,血液是能够较全面反映其内部暴露水平的生物基质[7]。孕妇作为一类尤为关键的易感人群,血液中已广泛检测出 PFASs 的存在。研究发现,不同国家和地区 PFASs 暴露水平差异较大,且物质种类构成也有所区别[8-13],PFOS、PFOA、全氟壬酸(perfluorononanoic acid, PFNA)、全氟己烷磺酸(perfluorohexanesulfonic acid, PFHxS)是现有研究主要关注的物质。在 2009 年 PFOS 被列入《斯德哥尔摩公约》之前,丹麦、挪威、美国等国家的孕妇群体中已检测出较高浓度的 PFOS 和 PFOA[14-16]。长期监测研究显示,美国、瑞典、澳大利亚人群 PFOS 和 PFOA 暴露水平在过去 20 年呈明显下降趋势[7]。

随着生产重心的转移,中国已成为全球 PFOS 和 PFOA 主要生产国[17]。目前我国孕妇体内 PFASs 暴露浓度较高,尤其是在上海和武汉地区,PFOS、PFOA、PFNA 和 PFHxS 等的中位浓度高于广西和北京地区,同时也高于美国、西班牙、巴西、瑞典、日本等国家[8-12,18-21]。值得注意的是,近年来研究发现我国孕妇体内多种替代物检出率较高[11,18,20],包括全氟庚酸(perfluoroheptanoic acid, PFHpA)、全氟丁烷磺酸(perfluoroheptanoic acid, PFBS)和6∶2全氟聚醚磺酸(6∶2 chlorinated polyfluoroalkyl ether sulfonate, 6∶2 Cl-PFESA)。在武汉和北京地区,孕妇体内 6∶2 Cl-PFESA 检出率均超过 80%,研究者指出其已成为我国孕妇血清中第三大流行的 PFASs[22]。因此,对 PFASs 传统物质进行长期监测的同时,亟需加强对新兴替代物的暴露研究。

2 PFASs 对子代生长发育的影响

当前已有多项流行病学研究表明孕期 PFASs 暴露可能影响胎儿及婴幼儿的生长发育,但研究结论尚不一致。研究关注的胎儿生长发育指标主要包括新生儿身长、体重、头围、旁氏指数、低出生体重(low birth weight, LBW)、小于胎龄儿(small for gestational age, SGA)和早产等;出生后的指标不仅包含单一时点测量值,还涵盖生长轨迹、时点间变化量等动态指标。

2.1 孕期 PFASs 暴露对胎儿生长的影响 在评估孕期 PFASs 暴露对胎儿生长影响的流行病学研究中,出生体重是最常见的结局指标。美国[23]、丹麦[24]、西班牙和中国[25]等多个国家的队列已经对 PFOS 或 PFOA 与出生体重之间的关联进行探索,结论基本为存在负向关联或关联不具有统计学意义两类。系统综述表明 PFOA 与出生体重间存在负向关联的趋势;部分研究也发现 PFOS 与出生体重间的类似关联[26]。PFNA 作为另一种备受关注的新型污染物,在人体内暴露水平持续上升。荟萃分析结果表明,PFNA 暴露与出生体重呈负相关,这一结论在不同地区研究中一致性较高,同时 PFNA 的不良影响可能会大于 PFOS 或 PFOA[27]。随着长链 PFASs 的逐步淘汰,研究者开始聚焦于官能团取代物和短链 PFASs 暴露对出生体重的影响。2020 年,Chu 等[28]首次报道中国人群中 6∶2 Cl-PFESA 的孕期暴露能够引起子代出生体重下降;而在中国无锡地区的研究发现,全氟戊酸(perfluoropentanoic acid, PFPeA)和 PFBS 与出生体重的增加均有关[29]。另外,多项研究还发现,PFOS、PFOA 和其他长链 PFASs(PFHxS、PFNA 等)的孕期暴露与子代出生时较低的腹围[24]、旁氏指数[30]、头围[31]和身长[32]密切相关。

除分析数值变量,研究者还探索了孕期 PFASs 暴露与不良出生结局(早产、SGA 和 LBW)的关联,以明确这种不利影响是否已达到致病程度。荟萃分析结果表明,PFOS 暴露与早产风险存在较为一致的正向线性关联,而 PFOA 和 PFNA 与早产风险的关联则呈现出“N 型”非线性模式[33],提示不同暴露水平引起的健康风险有所差异。来自中国广州出生队列的研究指出,6∶2 Cl-PFESA 暴露会增加早产的发生风险,且存在明显的阈值效应[28]。对于 SGA 和 LBW,系统综述指出除 PFOS 和 PFDA 外,多数研究并未观察到其他 PFASs 物质暴露与这两个结局之间的关联[33-34]。

随着传统 PFOS 和 PFOA 逐步淘汰,评估其替代物的跨代健康风险日益紧迫。上述证据表明,短链 PFASs 和 6∶2 Cl-PFESA 可能对胎儿生长产生不利影响,但仍需在不同人群中进一步确定其对母婴健康的具体影响。另外,丹麦、挪威已基于全国代表性数据开展风险评估,而我国研究多依赖单一地区出生队列[14-15],迫切需要开展多中心研究以提升结果代表性和推广性。

2.2 母亲孕期 PFASs 暴露对婴幼儿生长发育的影响 妊娠期 PFASs 暴露与子代出生后生长发育之间的关联呈现分段趋势。PFASs 暴露可能引发宫内生长受限,导致暴露与婴幼儿早期生长指标呈负相关;而随后的代偿性生长机制可能促使子代体重持续增长,最终增加儿童中后期的超重肥胖风险[13,23,35-36]。

目前关于母亲孕期 PFASs 暴露与婴幼儿期生长发育关联的流行病学研究仍较有限,主要集中在欧美地区[23,35],在中国仅有上海和台湾地区的研究证据[13,36]。丹麦全国出生队列研究发现,母亲孕早期 PFOS 暴露与 12 月龄婴儿体重及体质量指数(body mass index, BMI)标准化评分呈负相关[35]。美国俄亥俄州出生队列也表明,PFOS 与 PFOA 暴露与婴幼儿 4 月龄至 2 岁期间 BMI 标准化评分之间存在负相关[23]。在中国台湾的研究也观察到 PFOS 暴露与 2 岁前体重标准化评分的负向关联[36];而上海地区的研究揭示了

PFHpA 和短链替代物 PFBS 的暴露对子代 1 岁前多种体格生长指标的不良影响[13]。以上证据支持 PFASs 对生长发育的负面影响在出生后 2 年内持续存在。

孕期 PFOS、PFOA 及多种短链替代物的暴露与子代 3 岁及以后肥胖风险的增加有关。瑞典研究发现，孕期 PFOA、PFNA 和 PFHxS 的高暴露会引起子代 3 岁较高的 BMI 标准差评分[37]。荟萃分析进一步证实了生命早期 PFOA 暴露与 5~18 岁儿童超重风险增加和 BMI 标准化评分增加之间的相关性[38]。其他研究还观察到，妊娠期 PFOS、PFNA、PFHxS、PFBS 等物质的暴露会增加儿童期的腰围身高比、腰围臀围比、皮褶厚度、体脂肪量和体脂百分比[39-42]，并且这种不良影响可持续至子代成年[43]。研究者还通过拟合生长轨迹等方法评估 PFASs 暴露对子代动态生长过程的影响。Gao 等[44] 在中国上海开展的研究发现，孕期 PFHxS 及 PFASs 混合物高暴露会增加子代 0~2 岁“始于低值并持续上升”轨迹模式的发生风险。西班牙的研究也同样支持 PFNA 暴露与类似生长轨迹模式之间的正向关联[45]。Tanner 等[46] 拟合子代 0~5.5 岁体重增长轨迹，发现高浓度 PFOA 暴露能够引起婴幼儿期体重增长持续时间变长及增长速率达峰时间的推迟。此外，英国[47] 和西班牙[48] 的研究均报告了 PFASs 暴露与婴幼儿期体重增长值之间的正相关关系。上述纵向研究的结果一致表明，传统 PFASs 及部分替代物的暴露可能会导致儿童期生长指标的持续增加。

3　PFASs 对子代生长发育影响的机制

PFASs 对子代生长发育的影响机制尚未完全明确，但现有证据指出其可能涉及的机制包括干扰内分泌稳态、改变表观遗传以及激活氧化应激。

3.1　*干扰内分泌稳态*　甲状腺激素参与多种生物过程，包括从宫内到婴儿期的能量代谢调节及神经生长发育。流行病学研究主要发现了孕期 PFASs 暴露与母亲血促甲状腺激素呈正相关、与母亲血甲状腺素（thyroxin 4，T4）呈负相关[49]，以及与子代脐带血中 T4 或三碘甲状腺原氨酸之间呈负相关[50]。动物实验表明，PFASs 可上调体内尿苷二磷酸葡萄糖转移酶及肝脏有机阴离子转运蛋白的表达，增强 T4 的肝脏代谢，导致其血浆水平下降[51]。在体外实验中，PFASs 能够与转甲状腺素蛋白竞争性结合，增加游离甲状腺激素水平[52]。鉴于甲状腺激素的重要生理功能，PFASs 对甲状腺的毒性作用可能是孕期暴露影响子代生长发育的中间环节。

PFASs 还可能通过干扰雌激素稳态影响子代生长发育，雌激素可以通过调节胎盘血管生成和血流平衡，影响胎儿的气体交换和营养供应，与胎儿生长发育紧密相关[53]。日本出生队列的结果表明，母体孕期血清中 PFOS 和 PFOA 与子代脐带血中雌二醇水平呈正相关[54]。我国河北唐山的研究发现，雌三醇在脐血 PFOS 和 PFOA 浓度与出生指标的关联之间起重要中介作用[55]。研究显示，PFOS 和 PFOA 等物质不仅可以直接激活雌激素受体，还可以增强雌激素受体的反应性，进而通过负反馈调节影响体内雌激素水平[56]。此外，PFOS 还可以通过抑制芳香化酶活性和诱导胎盘滋养层细胞凋亡等途径损害雌激素合成和分泌的过程[57]。分子通路间存在复杂的相互作用，仍需更多基础研究以阐明孕期 PFAS 物质暴露对母婴内分泌稳态的综合影响。

3.2　*引起表观遗传改变*　研究提示孕期 PFASs 暴露通过表观遗传修饰对子代生长发育产生深远影响。多项研究提供了孕期 PFASs 暴露与子代全基因组甲基化水平之间呈负相关的一致证据[58]，全基因组 DNA 甲基化水平降低与学龄儿童肥胖的发生密切相关，据此研究者推测其改变可能是 PFASs 产生发育毒性的重要机制。无论是在人群还是动物模型中，产前 PFASs 暴露均能够影响脐带血或胎盘组织中与胚胎发育、代谢调控及生长因子相关的关键基因的甲基化水平[59-60]，如胰岛素样生长因子 2（insulin-like growth factor 2，IGF2）、中胚层特异性转录本（mesoderm specific transcript，MEST）、胰岛素受体底物 4（insulin receptor substrate 4，IRS4）等基因。中介分析显示，产前 PFOA 暴露与婴儿出生时 BMI 的负相关关系中，约有 21%是由 *IGF2* 基因甲基化水平下降所介导[63]。虽然 PFASs 影响甲基化过程的具体机制尚未完全明确，但现有研究已发现 PFASs 可上调多种细胞系中 DNA 甲基转移酶的转录水平，加剧体内甲基化稳态失衡，后续研究还需进一步厘清孕期 PFASs 暴露从引发甲基化失衡到最终导致子代不良生长发育的完整分子通路。

3.3　*激活过氧化物酶体增殖物激活受体*　PFASs 能够与过氧化物酶体增殖物激活受体（peroxisome proliferator-activated receptors，PPAR）产生相互作用。PPAR 的 3 种亚型（α，β/δ 和 γ）均在脂质、激素和葡萄糖代谢的调控中发挥关键作用[61]。分子流行病学研究显示，PFASs 与子代脐带血中的胆固醇、总脂质和甘油三酯水平均呈正相关[62]。动物实验进一步揭示，孕期 PFASs 暴露能够影响 PPAR-α 和 PPAR-γ 表达的模式，干扰子代正常的细胞分化进程及糖脂代谢[63-64]。研究者用 PFOS 处理人胎盘绒毛癌克隆细胞系后发现，脂肪酸结合蛋白的 mRNA 表达水平显著上调，脂肪酸摄取能力明显增强[65]。综上所述，PPAR 信号介导的脂质稳态失调可能是 PFASs 干扰子代生长发育的一个关键途径。

4 小结与展望

PFASs 作为常见的环境污染物，在中国人群中检出率较高。国内外研究发现，妊娠期 PFASs 暴露量与子代出生时体重、身长、头围的下降存在关联，也会引起子代儿童期生长指标的持续增加，进而增加超重肥胖的发生风险。近年来多项研究已提示短链 PFASs 和6∶2 Cl-PFESA 对于子代生长发育的潜在危害。然而，现有研究结果尚不一致，需开展大样本前瞻性队列研究，利用多时点生长指标明确 PFASs 对子代动态生长的影响，厘清其作用机制，为制定防控策略提供科学依据。同时，应建立多层次防控体系，通过严格管控污染源、系统监测食品和饮用水污染物浓度、加强孕妇健康教育等措施，最大限度降低 PFASs 对母婴健康的潜在危害。

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