综述

孕期暴露邻苯二甲酸酯对胎盘功能的影响及其机制研究进展

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［摘要］邻苯二甲酸酯（phthalates，PAEs）在生活中广泛存在，是一类典型的环境内分泌干扰物（environmental endocrine disruptors，EEDs）。胎盘富含激素受体，使其对EEDs高度敏感。孕期暴露于PAEs，其代谢物可以透过胎盘，通过干扰激素受体影响胎盘功能。胎盘功能障碍将导致胎儿生长受限，甚至引起胎儿死亡。孕期PAEs暴露与胎盘功能异常相关的机制包括侵润/融合、氧化应激、细胞分化/凋亡、激素分泌和脂质积累等。该文总结了孕期PAEs暴露水平概况，综述PAEs对胎盘功能的影响及相关研究进展，并探讨当前研究可能存在的局限性，为未来深入研究PAEs影响胎盘功能的分子机制提供参考。

［关键词］邻苯二甲酸酯；环境内分泌干扰物；孕期暴露；胎盘功能障碍

［DOI］10.3969/j.issn.1674-8115.2021.09.020　［中图分类号］R12　［文献标志码］A

Progress in the influence of prenatal exposure to phthalates on placental function and its mechanism

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[Abstract] Phthalates (PAEs) are widespread in life and are a class of environmental endocrine disruptors (EEDs). The abundance of hormone receptors makes the placenta highly sensitive to EEDs. During pregnancy, women can be exposed to PAEs, and their metabolites can pass through the placenta and affect its function by interfering with hormone receptors.The dysfunction of placenta will result in fetal growth restriction or, if more severe, fetal death. Functional placental disruptions linked to phthalates exposures include invasion/migration, oxidative stress, cell differentiation/apoptosis, hormone secretion and lipid accumulation.In this paper, the exposure level of PAEs during pregnancy is summarized, the mechanism for the effect of phthalates on placenta is reviewed, and the possible limitations of these studies are discussed, aiming to provide insights for further studies on the potential molecular mechanism through which PAEs disrupt placental function.

[Key words] phthalate (PAE); environmental endocrine disruptor (EED); prenatal exposure; placental dysfunction

环境内分泌干扰物（environmental endocrine disruptors，EEDs）是一类可以干扰正常内分泌功能的化学物质。孕期EEDs暴露对孕妇、胎儿均会产生影响，导致妊娠并发症、低出生体质量等不良结局[1-3]。邻苯二甲酸酯（phthalates，PAEs）是众多EEDs中备受关注的一种，产量大且日常生活中无处不在，导致人体内主要PAEs代谢物检出率常超过80%[4-5]，女性往往高于男性[6]。胎盘富含激素受体，对EEDs高度敏感[7]。因PAEs及其代谢物呈脂溶性，且胎盘的屏障作用有限，PAEs代谢物可以透过胎盘，通过干扰激素受体影响胎盘功能[8]。胎盘对于妊娠期胎儿生长发育至关重要，其功能障碍将导致胎儿生长受限，甚至引起胎儿死亡[9]。本文就孕期暴露PAEs对胎盘功能的影响及其机制做一综述。

1　孕期PAEs暴露水平

PAEs的结构中，有2个碳原子数相同或不同的烷基（R和R′）。根据烷基侧链碳原子数和化学特性不同，PAEs通常分为三大类[10]。一类是长链PAEs，碳原子≥C7，包括邻苯二甲酸二异癸酯（diisodecyl phthalate，DiDP）、邻苯二甲酸二异壬酯（diisononyl phthalate，DiNP）、邻苯二甲酸二（2-乙基己基）酯［di-2（ethylhexyl）-phthalate，DEHP］、邻苯二甲酸二正辛酯

[基金项目] 上海交通大学医工交叉基金（YG2019ZDA29）。
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[Funding Information] Medicine and Engineering Interdisciplinary Research Fund of Shanghai Jiao Tong University (YG2019ZDA29).
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[网络首发] https://kns.cnki.net/kcms/detail/31.2045.R.20210807.2321.004.html (2021-08-09 09:37:13)。

（di-n-octyl phthalate，DnOP）等，在工业中被作为增塑剂软化聚氯乙烯（polyvinyl chloride，PVC）材料，常见于食品包装、瓶装水、儿童玩具、医疗用品、地板和建筑材料等，其中产量最大的是DEHP。其余2类是中、短链PAEs，其中碳原子为C4~C6者包括邻苯二甲酸丁基苄基酯（benzylbutyl phthalate，BBzP）、邻苯二甲酸二异丁酯（diisobutyl phthalate，DiBP）、邻苯二甲酸二正丁酯（di-n-butyl phthalate，DnBP）等，碳原子≤C3者包括邻苯二甲酸二乙酯（diethyl phthalate，DEP）、邻苯二甲酸二甲酯（dimethyl phthalate，DMP）、邻苯二甲酸二环己酯（docyclohexyl phthalate，DCHP）等，主要用于油漆、油墨、黏合剂、溶剂、杀虫剂、化妆品、香水和药物等[11]。饮食是PAEs的重要接触途径，PAEs可以通过食品的生产、包装、储存和运输进入食品，还可以通过PVC等产品直接释放、迁移、浸出、蒸发和磨蚀等广泛存在于家庭环境中，孕妇可经摄入、吸入或经皮肤吸收暴露于该类化合物[12]。PAEs进入生物体内被代谢成生物活性更强、毒性更大的初级或次级代谢产物，主要随尿液排出体外[13]。短链PAEs进入生物体后，其中一个酯键迅速水解，转变为邻苯二甲酸单酯，即初级代谢物；中、长链PAEs水解为单酯后，还可以通过酶促氧化作用将邻苯二甲酸单酯的烷基侧链转化为更亲水的氧化产物，即次级代谢物[14]。尽管血液等生物样本也可检测到PAEs代谢物，但因该类样本中均存在酯酶，能促进外源性PAEs水解，从而降低了分析结果的准确性。而人体尿液中不含酯酶，且尿液中的代谢物浓度远远高于血液（是其10~100倍）[15]，因此尿液中的PAEs初级及次级代谢物成为了评估PAEs暴露水平的最佳生物标志物，已广泛应用于孕期暴露评价。

目前，DEHP研究报道较多，是产量最大的一种PAEs化合物，在欧洲和中国分别约占PAEs总量的30%和80%，而DnBP是全球应用最广的PAEs化合物[14]。因此，孕妇尿液中DEHP 5种代谢物总量（sum of five DEHP metabolites，MDEHP）和邻苯二甲酸单正丁酯（mono-butyl phthalate，MnBP）最受关注。其中，MDEHP包括邻苯二甲酸（2-乙基己基）单酯［mono-（2-ethylhexyl）phthalate，MEHP］、邻苯二甲酸（2-乙基-5羟基己基）单酯［mono-(2-ethyl-5-hydroxyhexyl)phthalate，MEHHP］、邻苯二甲酸（2-乙基-5-氧己基）单酯［mono-(2-ethyl-5-oxohexyl)phthalate，MEOHP］、邻苯二甲酸（2-乙基-5-羧基戊基）单酯［mono-2-ethyl-5-carboxypentyl phthalate，MECPP］、邻苯二甲酸（2-羧基甲基己基）单酯［mono-2-carboxymethyl-hexylphthalate，MCMHP］。不同孕期尿液中均可检出PAEs代谢物，且主要代谢产物检出率接近100%。孕妇尿液中PAEs代谢物平均浓度在1~400 ng/mL之间。不同国家孕妇尿液中PAEs代谢物总浓度和高浓度代谢物种类均有差异。亚洲国家PAEs代谢物总浓度为74~85 ng/mL，低于欧美国家（63~534 ng/mL），且亚洲国家以中链PAEs代谢物MnBP平均浓度最高（20~47 ng/mL），而欧美国家以短链PAEs代谢物邻苯二甲酸单乙酯（monoethyl phthalate，MEP）平均浓度最高（25~386 ng/mL）。在中国孕妇尿液中，MDEHP和MnBP平均浓度分别在14~44 ng/mL和20~47 ng/mL之间。不同国家孕妇的不同孕期尿液中PAEs代谢物的浓度见表1[4-5,12,16-29]。

2 孕期PAEs暴露对胎盘功能的影响及其机制

胎盘是维持胎儿宫内生长发育的重要器官。在受精后4~5 d受精卵发育为囊胚，囊胚由位于内部的内细胞团和外部的滋养外胚层组成，日后滋养外胚层发育为胎盘，内细胞团发育为胎儿。滋养外胚层由称为细胞滋养层细胞（cytotrophoblast cells，CTBs）的干细胞组成。人类在妊娠第10日左右，早期CTBs开始沿着2条途径（侵润迁移途径和融合途径）分化[30]。侵润迁移途径中，CTBs分化为具有侵润能力的绒毛外滋养层细胞（extravilloustrophoblasts，EVTs）向母体子宫发生侵润，并通过重铸螺旋动脉（spiral artery，SA）增加母体血液对胎盘的灌注，从而为胎儿的正常发育提供足够的氧气和营养物质。融合途径中，胎盘绒毛CTBs中有一类具有增殖分化能力的细胞，在CTBs层上发生融合形成一个多核合胞体细胞，称为合胞滋养细胞（syncytiotrophoblasts，STBs）；通过持续增殖和融合，STBs排列在胎盘绒毛上，形成STBs层作为母亲直接接触胎儿血液的屏障。CTBs通过分化出更多STBs，更新现有的STBs层，使STBs层中部分老化的细胞代谢到母体血液循环中完成自身的新陈代谢，从而实现胎盘的发育和成熟[31-32]。EVTs侵润失调可引发胎盘增生、胎盘内分泌功能不足或穿透性胎盘等胎盘缺陷，进而导致流产和产后大出血[33]。CTBs融合失调会导致人类胎盘STBs数量和孕酮分泌减少，从而出现子痫前期和宫内生长受限（intrauterine growth restriction，IUGR）等症状[34]。然而，孕期暴露PAEs对胎盘功能影响的机制，研究尚不充分。孕期PAEs暴露与胎盘功能异常可能相关的机制包括侵润/融合、氧化应激、细胞分化/凋亡、激素分泌、脂质积累和胎盘转运等[30]。

表1　不同国家孕妇尿液中PAEs主要代谢物的浓度

Tab 1　Concentrations of major metabolites of PAEs in pregnant women urine collected from various countries

Country	Number	Gestational period	Metabolite of PAEs								Reference
			MMP	MEP	MnBP	MiBP	MBzP	MDEHP	MCOP	Unit	
China	3 103	≤14 weeks	11.99	11.99	47.27		0.08	13.9		μg·g^{-1};median	［16］
China	210	≤12 weeks		8.30	19.72	11.59		40.09		ng·mL^{-1};GM	［12］
China	210	13–27weeks		6.09	27.77	10.69		43.93		ng·mL^{-1};GM	［12］
China	210	28–40 weeks		4.42	24.67	9.73		35.13		ng·mL^{-1};GM	［12］
Japan	111	9–40weeks	5.7	7.75	46.6		3.57	18.5		ng·mL^{-1};median	［17］
America	446	20–28 weeks	1.6	41.1	9.4	7.1	5.5	75.5	20.5	μg·g^{-1};GM	［18］
America	378	18–22 weeks	1.92	47.0	13.7	9.57	9.47	14.01		ng·mL^{-1};median	［19］
America	50	≤12 weeks，22–24 weeks	1.3	68.7	17.9	1.6	7.7	38.0		ng·mL^{-1};median	［20］
America	596	Progestation		40.8	10.4	6.5	2.7	47.0		ng·mL^{-1};median	［4］
America	132	6，21 and 35 weeks		37.7	10.2	6.3	2.5	36.1		ng·mL^{-1};median	［4］
America	380	18–22 weeks，24–32 weeks	2.2	46.7	16.3	10.8	11.9	92.8/(nmol·L^{-1})		ng·mL^{-1};median	［21］
America	168	≤13 weeks		30.37	6.04	3.46	2.98	65.58	15.40	ng·mL^{-1};GM	［22］
America	168	14–27 weeks		28.14	5.36	4.03	2.94	64.43	12.19	ng·mL^{-1};GM	［22］
America	168	≥28 weeks		28.14	6.98	5.34	3.31	69.91/(nmol·L^{-1})	13.32	ng·mL^{-1};GM	［22］
America	753	≤13 weeks		28.4	6.36	3.97	3.31	71.7/(nmol·L^{-1})	14.5	ng·mL^{-1};GM	［23］
Canada	2 000	<13 weeks	ND	28.00	12.00		5.20	18.1		ng·mL^{-1};median	［24］
Canada	370	≤13 weeks	ND	25.00	12.00		5.40	57.50/(nmol·L^{-1})		ng·mL^{-1};median	［25］
Netherlands	100	≥20 weeks	ND	222.0	62.2	57.1	11.7	76.9		μg·g^{-1};median	［26］
Norway	116	13–27 weeks		55.0	25.0	20.0	11.0	66.0		ng·mL^{-1};median	［27］
Spain	391	≤12 weeks		246.0	27.1	28.4	10.6	87.8		μg·g^{-1};median	［28］
Spain	391	28–40 weeks		386.0	28.1	29.8	10.0	80.0		μg·g^{-1};median	［28］
France	473	23–29 weeks		94.0	43.4	39.4	18.2	330.0/(nmol·L^{-1})	3.86	ng·mL^{-1};median	［5］
Greece	239	10–13 weeks		132.6	33.2	38.7	7.0	47.6		μg·g^{-1};median	［29］

Note: MMP—mono-methyl phthalate; MiBP—mono-isobutyl phthalate; MBzP—mono-benzyl phthalate; MCOP—mono carboxyisooctyl phthalate; ND—not detected; GM—geometric mean.

2.1　侵润/融合

因PAEs呈脂溶性，且胎盘的屏障作用有限，其代谢物可以透过胎盘，可能对侵润和融合过程产生影响，从而干扰胎盘功能［8］。Grindler等［3］研究表明，孕妇早期暴露于PAEs，尿液中代谢物的浓度与胎盘组织中表皮生长因子受体（epidermal growth factor receptor，EGFR）的表达和甲基化呈负相关。鉴于EGFR在胎盘组织中最为丰富且在胎盘发育中起重要作用［35］，应关注这些表观遗传修饰改变对胎盘病理学的影响。流行病学研究发现，DEHP代谢物总量在IUGR孕妇尿液中浓度较高［36］，且与胎盘滋养层分化基因低表达和各种与胎盘未知功能有关的长链非编码RNA低表达相关［37-38］。早产儿相较于正常胎龄儿，胎盘迷路微血管密度明显降低［39］。在动物实验研究中，CD-1小鼠妊娠期暴露于DEHP抑制了胎盘发育，组织病理学观察发现胎盘迷路层减少，该层类似于人类的合胞体，包含了与人类STBs功能相似的海绵滋养细胞［40］。有研究观察ICR小鼠不同妊娠期暴露于DEHP对胎盘发育的影响，结果显示妊娠中期暴露的小鼠胎盘迷路层细胞增殖率显著下降，血窦面积明显减小且胎盘重量明显减轻［41］。研究［42-43］表明，MEHP暴露能抑制EVTs侵润的重要蛋白——基质金属蛋白酶-9（matrix metalloproteinase-9，MMP-9）的活性，增加EVTs侵润的负调节因子——组织抑制因子基质金属蛋白酶-1（tissue inhibitor matrix metalloproteinase-1，TIMP-1）的表达，并通过激活过氧化物酶体增殖物激活受体（peroxisome proliferators-activated receptor γ，PPARγ）相关基因表达，最终抑制人绒毛膜滋养层细胞（human trophoblast 8，HTR-8/SVneo）和来源于大鼠胎盘的滋养细胞HRP-1的侵袭。

2.2　氧化应激

氧化应激涉及多种妊娠并发症，包括先兆子痫、早产和妊娠糖尿病，过量的活性氧（reactive oxygen species，ROS）和氧化应激可导致胎盘发育异常［44］。研

究[45]发现，孕妇尿液中PAEs代谢物浓度与尿液中氧化应激的生物标志物8-异前列腺素$F_{2\alpha}$（8-iso-prostaglandin $F_{2\alpha}$，8-iso-$PGF_{2\alpha}$）水平呈正相关。体外研究[46]表明，MEHP可导致人滋养细胞HTR-8/SVneo中ROS产物增加和DNA氧化损伤，并引起氧化还原敏感基因表达差异。多个研究发现，MEHP可能通过在滋养细胞中激活丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）信号通路，增强细胞内氧化应激的敏感性，导致线粒体功能障碍和细胞凋亡，最终抑制细胞增殖[47-48]；而与miR-17-5p、miR-155-5p、miR-126-3p相关的*PI3K/AKT*、*PTEN*、*NRF2*基因则介导了氧化应激反应信号通路[49]。

2.3 细胞分化/凋亡

PPARγ信号通路是胎盘发育重要的信号调节通路之一。在滋养细胞中表达的PPARγ通过调控滋养细胞分化相关基因，对胎盘的基本发育和功能发挥重要作用，包括诱导胎盘血管形成、血管重构、脂肪酸运输和炎症等[47,50-51]。Ahbab等[50]研究发现，大鼠孕期暴露于DCHP后，滋养层的退化、减少和不规则的血管形成可能与胎盘PPARγ表达减少有关；而大鼠孕期暴露于DEHP后，在大鼠胎盘母胎交界区和迷路层中PPARα和PPARγ的mRNA和蛋白表达量呈剂量依赖性升高，提示PPAR可能参与了DEHP对大鼠胎盘的调控[51]。体外研究[47]发现，MEHP作为PPARγ激活的高亲和性配体，对PPARγ转录活性具有“U”形剂量反应效应，同时还可对MAPK通路产生影响，共同干扰人CTBs分化。

小鼠孕期暴露于DEHP，与胎盘细胞凋亡有关的4个关键基因*Bax*、caspase-3、caspase-8和*Bcl-2*均受到影响，DEHP通过活化caspase-3和caspase-8，上调Bax、下调Bcl-2的mRNA和蛋白水平，诱导胎盘凋亡[40]。对取自正常分娩孕妇胎盘组织的绒毛细胞滋养层细胞体外研究[47]发现，MEHP可以提升caspase-3的活性。MEHP处理人滋养细胞HTR-8/SVneo导致*MiR-16*表达升高，并与抗凋亡基因*BCL-2*互补结合，诱导细胞死亡[49]。

2.4 激素分泌

人绒毛膜促性腺激素（human chorionic gonadotropin，hCG）是孕期最重要的激素。在妊娠初期，hCG的产生和分泌是诱导卵巢黄体合成孕酮的必要条件，导致子宫肌层松弛[47]。在妊娠的前3个月，hCG参与了CTBs和血管生成的融合和侵润过程[52]。hCG还可通过旁分泌和自分泌的方式触发妊娠期EVTs的分化和更替[47]。Adibi等[37]研究发现，孕妇尿液中PAEs代谢物浓度与*hCG*基因靶点低表达显著相关，提示PAEs代谢物可能通过影响hCG的异常分泌来干扰滋养细胞分化。在不同性别来源的人CTBs中，不同浓度MEHP暴露均能减少hCGβ的释放，说明暴露于MEHP会抑制滋养细胞的激素功能[47]。

胎盘促肾上腺皮质激素释放激素（corticotropin-releasing hormone，CRH）和环氧合酶-2（cyclooxygenase-2，COX-2）是分娩的关键介质，受非典型的核因子κB（nuclear factor-κB，NF-κB）信号通路调控[53]。在原代培养的人滋养细胞中，MEHP可能通过NF-κB信号通路提升RelB/p52异源二聚体的核转运能力，从而以剂量效应的方式增加了*CRH*和*COX-2*的mRNA和蛋白质丰度，进而提前诱导产前基因的活性，导致早产[53]。

2.5 脂质积累

在妊娠期间维持必需脂肪酸（essential fatty acid，EFA）稳态对胎儿发育至关重要。许多EFA稳态蛋白受PPAR调控[51]。大鼠动物实验研究发现，DEHP及其代谢产物MEHP可能通过PPAR的反式激活影响EFA稳态，并对其转运体和酶产生下游影响[51]。经高浓度MEHP处理的人绒毛细胞滋养层细胞中的PPARγ活性增加，而经同步处理的胎盘绒毛中发现脂滴积聚。这些实验证明，MEHP能越过胎盘屏障影响胎盘所有细胞类型（合胞体滋养层、绒毛细胞滋养层、间充质细胞）的脂质含量[47]。MEHP暴露后，来源于大鼠胎盘的滋养细胞株HRP-1中甘油糖脂和磷脂的显著积累[43]，以及来源于人类胎盘的滋养细胞株JEG-3中脂质代谢的改变[54]，都提示了PAEs孕期暴露可能导致胎盘脂质失衡。

2.6 胎盘转运

胎盘的关键作用之一是将母体的营养物质输送给胎儿，同时将胎儿产生的代谢废物运回到母体以排出体外。人类胎盘转运过程是复杂的，以一种协调的方式维持胎儿快速生长。胎盘转运过程受到干扰与异常的胎儿生长有关，有可能引发妊娠糖尿病（gestational diabetes mellitus，GDM）和胎儿生长受限（fetal growth restriction，FGR）等常见的妊娠病理状况[55]。相对分子质量<600的物质能够通过被动扩散的方式穿过胎盘屏障[56]。PAEs最大相对分子质量不超过500，其进入胎盘后对转运功能的影响报道较少。Bailey-Hytholt等[57]通过构建类似胎盘滋养层细胞膜的脂质双层结构，发现DEHP能与膜脂质相互作用，被吸附并嵌入双层膜中，从而影响母胎界面的转运特性。

3　总结与展望

孕妇作为特殊的易感人群广泛暴露于PAEs。PAEs代谢物可以透过胎盘并通过多种路径影响其功能，从而对母体和胎儿产生影响。当前，孕期暴露于PAEs对胎盘功能影响的流行病学证据仍需进一步补充。胎盘与胎儿出生体质量之比（placental-to-birth weight ratio，PFR）可作为反映胎盘功能的综合指标之一，PFR低提示胎盘活性和营养素转移能力强[5]。然而孕期PAEs暴露对胎盘功能综合影响的流行病研究鲜有报道，这种影响有无性别差异尚需进一步研究。PPARγ的调控在胎盘发育过程中起重要作用，但PAEs对其基因表达的影响尚未完全阐明，应进一步探索PAEs通过PPARγ通路对胎盘产生影响的分子机制。此外，在体内、体外胎盘毒理学实验中发现，其染毒剂量通常较高（超过了估计的人群每日摄入量，有些甚至超过3个数量级[58]）；应加强开展在环境暴露剂量下，PAEs暴露对胎盘病理、生理功能影响的研究。而且，目前多数研究基于DEHP及其代谢产物，其他种类PAEs的研究报道较少，尤其是近年来的新型替代品DiNP。应进一步关注其他PAEs及其代谢产物对胎盘功能的影响，开展混合效应机制研究。

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［收稿日期］ 2020-07-16 ［本文编辑］ 吴 洋