专栏：环境与女性生殖健康（Ⅱ）
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镉对胚胎/胎儿发育的损害作用及其机制

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摘要：

镉对生态环境和人群健康的危害受到广泛关注。以往研究主要关注成年期镉暴露对肝脏、肾脏、肺脏、大脑和睾丸等脏器的损害作用，但对子代及其远期损害作用的研究甚少。近年来，孕期母体环境镉暴露与胚胎/胎儿发育损伤的关联研究已成为当前重要的公共卫生问题，镉的发育毒性作用及其机制已有大量研究报道。众多研究资料显示，孕期母体镉暴露能够引起胚胎/胎儿死亡、胎儿畸形和胎儿生长受限等。此外，出生前镉暴露还可以引起子代智力低下、情感障碍、心血管疾病、雄性生殖障碍等慢性疾病高发。镉引起胚胎/胎儿发育损伤的机制主要包括母源性机制、胎盘机制和胎儿损伤机制等。因此，本文着重综述了镉对胚胎/胎儿发育的损害作用及其机制的研究进展。

关键词：镉；胚胎发育；胎儿发育；胎盘

Adverse effects of cadmium on embryonic and fetal development and its mechanism *ZHU Hua-long, XIONG Yong-wei, WANG Hua* (*Department of Health Toxicology, Key Laboratory of Environmental Toxicology of Anhui Higher Education Institutes, School of Public Health, Anhui Medical University, Hefei, Anhui* 230032*, China*)

Abstract:

The adverse effects of cadmium on ecosystem and human health have attracted worldwide attention. Previous studies have focused mainly on the toxic effects of cadmium exposure in adulthood on liver, kidney, lung, brain, and testis; however, there are few studies on progeny and its long-term effects. Recently, the association between maternal cadmium exposure during pregnancy and embryonic/fetal dysplasia has become a hot topic in public health as a lot of studies have reported cadmium-induced developmental toxicity and its mechanism. Other studies have shown that maternal cadmium exposure during pregnancy can cause fetal death, fetal malformation, and fetal growth restriction. In addition, prenatal cadmium exposure can lead to lower IQ, mood disorders, cardiovascular diseases, male reproductive impairments, and other chronic diseases. The mechanisms of cadmium causing embryonic/fetal development injury mainly include maternal mechanism, placental mechanism, and fetal injury mechanism. Therefore, the adverse effects of cadmium on embryonic and fetal development and its mechanism were summarized in this review.

Keywords: cadmium; embryonic development; fetal development; placenta

重金属镉（cadmium，Cd）广泛存在于铅锌矿、有色金属冶炼、电镀以及使用镉化合物制成的原料或触媒等。工业生产中含镉的废水、废气和废渣大量排放，农业活动中含镉的化肥、农药和杀虫剂广泛使用，引起水、大气和土壤污染。普通人群主要通过长期进食镉污染的大米、饮水，或吸入香烟烟雾等暴露于低浓度的镉，而作业工人可通过职业暴露短期接触较高水平的镉。镉在人体内的半衰期长达10~30年，体内蓄积的镉对骨骼、肝脏、肾脏、睾丸、胎盘、肺脏和大脑等组织产生损害作用[1]。孕期母体镉暴露可以引起胚胎死亡、胎儿畸形、胎儿生长受限等发育毒性，其中胎儿生长受限还可能增加成年期慢性疾病发生风险[2-4]。本文拟综述镉对胚胎/胎儿发育损害作用及其机制的研究进展。

1 镉引起胚胎与胎儿发育损害

1.1 胚胎/胎儿死亡和胎儿畸形

动物实验研究表明，镉暴露可引起胚胎/胎儿死亡和胎儿畸形。胎牛（奶

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牛和水牛）死亡组的母牛血浆、胎盘、胎牛血浆和羊水中的镉含量均明显高于正常出生组[5]；受孕第5天和第9天CFLP小鼠经腹腔注射2.5 mg/kg氯化镉分别引起4.2%和18.0%的胎鼠死亡[6]；受孕第12天和第18天Wistar大鼠经皮下注射50 μmol/kg氯化镉分别引起11.7%和82.2%的胎鼠死亡[7]。上述动物实验结果提示孕期母体暴露于一定剂量的镉可以引起胚胎/胎儿死亡，但尚未检索到胚胎和胎儿死亡相关的人群调查资料。

人群调查发现，先天性心脏锥干畸形的新生儿胎粪中镉浓度较健康新生儿明显升高（*n*=132），且孕妇高镉（发镉质量分数≥25.85 ng/g）暴露明显升高新生儿先天性心脏锥干畸形发生风险（2.81倍）和先天心脏畸形发生风险（1.96倍）（*n*=672）[8-9]。Swiss小鼠于受孕第7至第9天分别每日单次经皮下给予不同剂量氯化镉（1、2、4 mg/kg），于妊娠第18天（GD18）对所有胎鼠进行外观畸形评价，结果发现高剂量镉处理引起21.3%（17/80）露脑畸形、5.0%（4/80）小颌畸形、5.0%（4/80）突眼、10%（8/80）畸形脚和6.4%（5/80）多趾畸形，而中低剂量镉处理未引起露脑和突眼畸形[10]；不同品系的小鼠于GD8单次腹腔注射氯化镉（4或5 mg/kg）溶液，于GD18进行胎鼠畸形检查，结果显示，C57BL/6N胎鼠露脑畸形率为33.1%，CD-1小鼠胎鼠露脑和脑膜膨出畸形率达20%，而SWV胎鼠露脑畸形率为4.6%[11-12]；受孕第9天CD-1小鼠单次腹腔注射氯化镉（4.5 mg/kg）溶液，于GD18进行胎鼠畸形检查，结果显示，镉处理引起22.8%胎鼠前肢缺趾畸形和卷尾/短尾畸形[13]。上述结果提示，镉诱发的畸形类型主要与镉暴露的发育关键期有关，而畸形发生率高低可能与镉暴露剂量等有关。

1.2 对胎儿体格生长的影响

孕期母体镉暴露与胎儿生长受限的关联尚存在争议。最近几项小样本或横断面调查结果显示，母亲孕期血清镉（*n*=55、125）、全血镉（*n*=1 027、901和209）或尿液镉（*n*=1 616）水平与新生儿出生体重呈现负相关[14-16]。然而，也有两项研究发现，母亲孕期全血镉含量（*n*=1 565和44）与新生儿出生体重无关联[17-18]。但这些研究要么样本量太少、代表性较差，要么用尿液镉不能准确反映母亲孕期镉暴露的真实水平。一项基于人群较大型的出生队列研究发现，孕期母体高镉暴露明显增加小于胎龄儿发生风险（1.43倍）（*n*=3 254）[12]。Wang等建立的两种动物实验模型均发现，小鼠在整个孕期（GD0—GD17）经饮水暴露于低剂量镉（250 mg/L）引起胎鼠体重和身长明显下降，孕晚期（GD13—GD17）母鼠每日单次暴露于低剂量镉（0.5 mg/kg，腹腔注射）诱发胎鼠生长发育迟缓[19-20]。最新研究发现，脐血清镉浓度与新生儿出生体重呈现负相关[21]。上述研究结果提示，镉暴露可以引起胎儿生长受限。宫内生长受限儿（包括低出生体重儿）较正常出生体重儿成年后冠心病、高血压、肥胖、高血脂等慢性疾病的发生风险明显升高[22-25]。

1.3 远期健康影响

人群调查发现，出生前高镉暴露明显限制4岁女童身高生长[26]，增加5岁儿童智力低下[27]以及7~8岁儿童情感障碍的发生风险（相对危险度为1.53）[28]。一项韩国的多中心出生队列研究发现，孕早期母体血镉浓度与60月龄幼儿操作智商呈现负向关联，而与其认知智商无关联[29]。Ji等[20]研究发现，孕晚期连续5 d低剂量镉暴露（0.5 mg/kg，腹腔注射）引起胎鼠体重、身长和睾丸质量均明显下降，导致雄性仔鼠成年后血清和睾丸睾酮含量降低，并降低F2代平均每窝活胎数。最近研究发现，大鼠从妊娠第0至第20天暴露于30 mg/L氯化镉溶液，其仔鼠成年后（出生后60~70 d）发生左心室肥大、主动脉环内皮细胞反应性下降，这些远期影响可能与主动脉血红素加氧酶-1（heme oxygenase-1，HO-1）表达上调相关[30]。这些结果提示，孕期母体镉暴露可能是子代成年后部分慢性疾病高发的重要因素之一。

2 镉损害胚胎/胎儿发育的毒性作用机制

2.1 母源性机制

镉暴露致胚胎/胎儿发育损害可能的毒性作用机制，一方面可能通过诱发母体锌缺乏或皮质酮升高而间接损害胚胎/胎儿发育。孕妇吸烟可能通过降低母血浆锌含量而引起脐血红细胞锌含量下降，后者可能与低出生体重有关[31]；孕期镉暴露引起大鼠和小鼠肝脏金属硫蛋白表达明显上调，而肝脏金属硫蛋白结合大量锌，导致母鼠血清锌含量降低，这可能引起胎鼠缺锌和胎鼠生长受限[19, 32]。以上结果提示，母血锌含量降低可能是镉诱发胎儿发育异常的原因之一。连续35 d暴露于较高剂量氯化镉（100、300 mg/L）引起小鼠血浆皮质酮和醛固酮含量明显升高，而低剂量（30 mg/L）氯化镉处理对小鼠血浆皮质酮含量无影响[33]；早期研究已经发现，镉主要通过激活下丘脑-垂体-肾上腺轴而刺激肾上腺分泌大量皮质酮，最终释放入血[34]。在正常妊娠中，人类胎盘11β-羟类固

醇脱氢酶2（11β-HSD2）通过催化母体皮质醇转变为皮质酮，而啮齿类动物胎盘11β-HSD2催化皮质酮转变为11-脱氢皮质酮，继而保护胎儿免受过多母体糖皮质激素暴露[35]。体外研究发现，镉处理明显下调人胎盘绒毛膜癌滋养层细胞11β-HSD2蛋白质表达、mRNA表达和活性[36]。上述结果提示，镉暴露通过诱发母体营养素缺乏或内分泌紊乱而间接损害胚胎/胎儿发育。

另一方面，镉可能通过诱发母源性疾病间接损害胚胎/胎儿发育。人群调查发现，妊娠合并先兆子痫的妇女易分娩低出生体重儿和宫内生长受限儿等[37]；动物实验研究发现，从受孕第5至19天连续暴露于氯化镉（0.5 mg/kg，腹腔注射）引起母鼠高血压、蛋白尿、肾小球内皮增生和胎盘迷路层和蜕膜层病理改变等先兆子痫表型，伴有胎鼠体重和身长明显下降[38]。这些结果提示，镉引起胎儿生长受限可能与其诱发的先兆子痫有关。此外，环境镉暴露还与2型糖尿病有关。几项人群研究发现，孕妇尿镉含量与其空腹血糖水平呈正相关，且糖尿病孕妇镉含量显著高于正常对照组[39-41]；巢式病例-对照研究发现，孕妇妊娠糖尿病组新生儿胎粪镉含量明显高于正常妊娠组，且随着新生儿胎粪镉含量升高，其母亲妊娠糖尿病发生率升高[42]；动物实验证实，孕期镉暴露诱导大鼠胰岛β细胞坏死、变性和脱落，并引起大鼠血糖水平明显升高[43]；妊娠糖尿病模型小鼠（血糖大于250 mg/dL）其子代易发生神经管畸形、胎鼠生长发育迟缓或巨大儿[44-45]。这些结果提示，镉抑制胚胎/胎儿发育可能与先兆子痫或妊娠期糖尿病等母源性疾病有关。

2.2 胎盘机制

胎盘是联结母体与胎儿之间的枢纽，由绒毛膜和底蜕膜组成，具有物质转运、屏障功能和内分泌功能[46-48]，研究发现孕期母体镉暴露引起胎盘镉大量蓄积，胎盘极有可能是镉的毒作用靶器官。镉污染地区孕妇胎盘镉含量较无污染地区明显升高，且胎盘组织的镉引起胎盘细胞端粒缩短[49]。另一项人群研究发现，孕妇吸烟容易引起新生儿低出生体重，其胎盘镉含量明显高于非吸烟孕妇[50]。最近研究发现，母血镉浓度与胎盘镉浓度呈正相关，且镉通过上调金属硫蛋白表达引起胎盘镉蓄积[51-52]。早期动物实验结果发现，孕鼠镉暴露未引起全胚胎体内镉浓度升高[53-54]。Wang等[19]研究结果发现，小鼠孕期经腹腔注射较高剂量镉后，胎盘镉含量明显高。孕期母体镉暴露引起胎盘结构异常与功能障碍。孕鼠暴露氧化镉明显降低胎盘重量和胎鼠体重[54]。孕中期小鼠暴露于氯化镉（4.5 mg/kg，腹腔注射）引起胎盘组织血窦区面积减少、胎盘细胞增殖抑制、胎盘细胞凋亡加快[13, 19]。长期主动吸烟或被动吸烟的孕妇主要通过镉暴露引起胎盘滋养细胞基底膜变薄、绒毛间质胶原含量升高和迷路层血管形成障碍，以及11β-HSD2表达下调[55]；动物实验结果表明，孕鼠镉暴露下调胎盘锌转运体1和锌转运体2表达而干扰胎盘转运锌至胚胎体内[19]；孕鼠镉处理通过下调胎盘质子偶联叶酸转运体而干扰胎盘转运叶酸进入胚胎体内[12]。体外研究进一步发现，镉处理明显下调人胎盘滋养层细胞11β-HSD2、瘦素、P450胆固醇侧链裂解酶、胎盘催乳素等内分泌功能相关基因表达[32, 56-58]。上述结果提示，孕期母体镉暴露可能通过损害胎盘结构和部分功能而诱发胎儿生长受限。

进一步研究发现，整个孕期经饮水暴露于氯化镉（70 mg/L）引起大鼠胎盘脂质过氧化产物丙二醛和髓过氧化酶含量明显升高，而还原型谷胱甘肽含量以及超氧化物歧化酶和过氧化氢酶活性下降[59]；孕中期单次高剂量镉暴露（4.5 mg/kg，腹腔注射）引起小鼠胎盘谷胱甘肽含量明显下降，HO-1和3-硝基络氨酸蛋白表达明显上调，且自由基清除剂N-叔丁基-α-苯基硝酮明显抑制镉上调胎盘HO-1和3-硝基络氨酸蛋白表达，减弱镉耗竭的胎盘还原型谷胱甘肽[13]。此外，抗氧化剂N-乙酰半胱氨酸预处理通过抑制胎盘内质网应激反应和氧化应激而明显保护镉所致胎鼠生长受限[28]。上述结果提示，氧化应激和内质网应激可能在镉诱导胎盘结构与功能障碍中起重要作用。

2.3 胎儿损伤机制

早期人群研究报道，母体镉可以少量透过胎盘屏障，且脐血镉含量与新生儿出生体重大小呈现负相关[60]。最新研究发现，吸烟孕妇流产的胚胎组织中镉含量较非吸烟孕妇流产的胚胎组织中镉含量升高2倍[61]。动物实验结果表明，整个孕期经饮水暴露于氯化镉（70 mg/L）或孕中期单次暴露氯化镉（4.5 mg/kg，腹腔注射）均引起母鼠肝脏、胎盘、胎鼠肝脏镉含量升高[20, 59]。这些结果提示，镉可以少量透过胎盘屏障进入胚胎/胎儿体内。

体外研究发现，89 μmol/L乙酸镉处理明显抑制鸡胚胎外胚层细胞增殖，促进鸡胚胎体节和神经管细胞凋亡，继而导致鸡胚胎外观畸形[62]；50 μmol/L镉处理可能通过下调细胞增殖与分化调控因子MSX1和MSX2表达而引起鸡胚胎脐膨出[63]；体外全胚胎实验还发现，较高剂量镉暴露（1 mmol/L）明显诱导海胆细胞凋亡，伴有裂解型Caspase-3活性升高和裂解型死

亡底物（α-胞衬蛋白和A型核纤层蛋白）增多[64]。上述结果提示，镉可以通过直接抑制胚胎细胞增殖和促进胚胎细胞凋亡而诱导胚胎/胎儿发育异常。

3 总结与展望

如上所述，镉暴露引起胚胎/胎儿死亡、胎儿畸形、胎儿生长受限以及远期损害效应，主要与镉诱发的母源性损伤、胎盘损伤和对胚胎/胎儿的直接损伤机制有关（图1）。

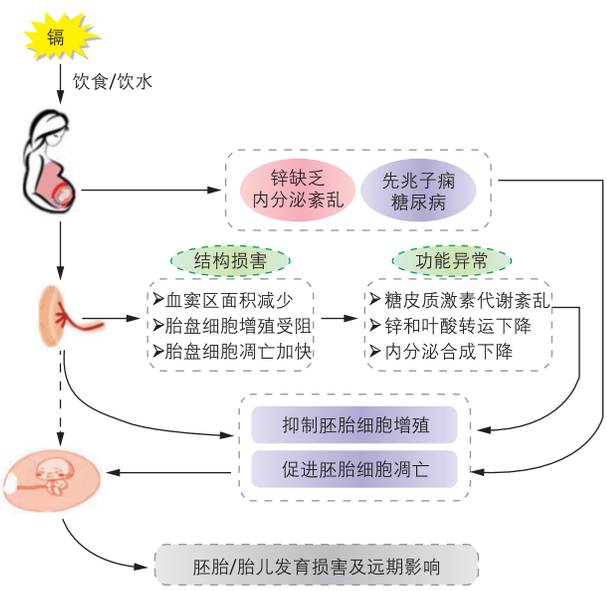

图1 镉损害胚胎/胎儿发育及其作用机制

结合发育毒理学研究进展，进一步阐明以上发育毒作用机制，需深入研究镉抑制胎盘血管发生与形成、诱导细胞自噬等胎盘机制，推进母体镉暴露对子代神经、呼吸、消化、免疫和生殖等系统发育损害的远期效应（包括传代效应）及其机制，拓宽镉与其他环境有害因素联合暴露对胚胎/胎儿发育的损害效应及其机制。这些有待更多人群流行病学和动物实验证据的支持。

参考文献

[1] BERNHOFT R A. Cadmium toxicity and treatment [J]. Scientific World Journal, 2013, 2013: 394652.

[2] THOMPSON J, BANNIGAN J. Cadmium: toxic effects on the reproductive system and the embryo [J]. Reprod Toxicol, 2008, 25 (3): 304-315.

[3] CHATZI L, IERODIAKONOU D, MARGETAKI K, et al. Associations of prenatal exposure to cadmium with child growth, obesity, and cardiometabolic traits [J]. Am J Epidemiol, 2018, 188 (1): 141-150.

[4] HUANG K, LI H, ZHANG B, et al. Prenatal cadmium exposure and preterm low birth weight in China [J]. J Expo Sci Environ Epidemiol, 2017, 27 (5): 491-496.

[5] KAUR S. Lead and cadmium in maternal blood, umbilical cord blood, amniotic fluid and placenta of cows and buffaloes after foetal death (abortion) and after normal parturition [J]. Sci Total Environ, 1989, 79 (3): 287-290.

[6] SELYPES A, LORENCZ R, BERENCSI G, et al. The effect of prednisolone on the foetotoxicity of cadmium in pregnant mice [J]. J Appl Toxicol, 1986, 6 (1): 47-48.

[7] SALTZMAN R A, MILLER R K, DI SANT'AGNESE P A. Cadmium exposure on day 12 of gestation in the Wistar rat: distribution, uteroplacental blood flow, and fetal viability [J]. Teratology, 1989, 39 (1): 19-30.

[8] KUNDAK A A, PEKTAS A, ZENCIROGLU A, et al. Do toxic metals and trace elements have a role in the pathogenesis of conotruncal heart malformations? [J]. Cardiol Young, 2017, 27 (2): 312-317.

[9] JIN X, TIAN X, LIU Z, et al. Maternal exposure to arsenic and cadmium and the risk of congenital heart defects in offspring [J]. Reprod Toxicol, 2016, 59: 109-116.

[10] PANIAGUA-CASTRO N, ESCALONA-CARDOSO G, CHAMORRO-CEVALLOS G. Glycine reduces cadmium-induced teratogenic damage in mice [J]. Reprod Toxicol, 2007, 23 (1): 92-97.

[11] ROBINSON J F, YU X, HONG S, et al. Cadmium-induced differential toxicogenomic response in resistant and sensitive mouse strains undergoing neurulation [J]. Toxicol Sci, 2009, 107 (1): 206-219.

[12] ZHANG G B, WANG H, HU J, et al. Cadmium-induced neural tube defects and fetal growth restriction: association with disturbance of placental folate transport [J]. Toxicol Appl Pharmacol, 2016, 306: 79-85.

[13] WANG Z, WANG H, XU Z M, et al. Cadmium-induced teratogenicity: association with ROS-mediated endoplasmic reticulum stress in placenta [J]. Toxicol Appl Pharmacol, 2012, 259 (2): 236-247.

[14] KIPPLER M, WAGATSUMA Y, RAHMAN A, et al. Environmental exposure to arsenic and cadmium during pregnancy and fetal size: a longitudinal study in rural Bangladesh [J]. Reprod Toxicol, 2012, 34 (4): 504-511.

[15] MENAI M, HEUDE B, SLAMA R, et al. Association between maternal blood cadmium during pregnancy and birth weight and the risk of fetal growth restriction: the EDEN mother-child cohort study [J]. Reprod Toxicol, 2012, 34 (4): 622-627.

[16] IKEH-TAWARI E P, ANETOR J I, CHARLES-DAVIES M A. Cadmium level in pregnancy, influence on neonatal birth

weight and possible amelioration by some essential trace elements [J]. Toxicol Int, 2013, 20 (1): 108-112.

[17] AL-SALEH I, SHINWARI N, MASHHOUR A, et al. Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in Saudi Arabian population [J]. Int J Hyg Environ Health, 2014, 217 (2-3): 205-218.

[18] ZHANG YL, ZHAO YC, WANG JX, et al. Effect of environmental exposure to cadmium on pregnancy outcome and fetal growth: a study on healthy pregnant women in China [J]. J Environ Sci Health A Tox Hazard Subst Environ Eng, 2004, 39 (9): 2507-2515.

[19] WANG H, WANG Y, BO QL, et al. Maternal cadmium exposure reduces placental zinc transport and induces fetal growth restriction in mice [J]. Reprod Toxicol, 2016, 63: 174-182.

[20] JI YL, WANG H, LIU P, et al. Effects of maternal cadmium exposure during late pregnant period on testicular steroidogenesis in male offspring [J]. Toxicol Lett, 2011, 205 (1): 69-78.

[21] SABRA S, MALMQVIST E, SABORIT A, et al. Heavy metals exposure levels and their correlation with different clinical forms of fetal growth restriction [J]. PLoS One, 2017, 12 (10): e0185645.

[22] VISENTIN S, GRUMOLATO F, NARDELLI GB, et al. Early origins of adult disease: low birth weight and vascular remodeling[J]. Atherosclerosis, 2014, 237 (2): 391-399.

[23] LONGO S, BOLLANI L, DECEMBRINO L, et al. Short-term and long-term sequelae in intrauterine growth retardation (IUGR) [J]. J Matern Fetal Neonatal Med, 2013, 26 (3): 222-225.

[24] SZOSTAK-WEGIEREK D, SZAMOTULSKA K. Fetal development and risk of cardiovascular diseases and diabetes type 2 in adult life[J]. Med WiekuRozwoj, 2011, 15 (3): 203-215.

[25] KERNS SL, GUEVARA-AGUIRRE J, ANDREW S, et al. A novel variant in CDKN1C is associated with intrauterine growth restriction, short stature, and early-adulthood-onset diabetes[J]. J Clin Endocrinol Metab, 2014, 99 (10): E2117-2122.

[26] SIOEN I, DEN HOND E, NELEN V, et al. Prenatal exposure to environmental contaminants and behavioural problems at age 7-8 years [J]. Environ Int, 2013, 59: 225-231.

[27] KIPPLER M, TOFAIL F, HAMADANI JD, et al. Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural bangladesh [J]. Environ Health Perspect, 2012, 120 (10): 1462-1468.

[28] GUO MY, WANG H, CHEN YH, et al. N-acetylcysteine alleviates cadmium-induced placental endoplasmic reticulum stress and fetal growth restriction in mice [J]. PLoS One, 2018, 13 (1): e0191667.

[29] JEONG KS, PARK H, HA E, et al. Performance IQ in children is associated with blood cadmium concentration in early pregnancy [J]. J Trace Elem Med Biol, 2015, 30: 107-111.

[30] RONCO AM, MONTENEGRO M, CASTILLO P, et al. Maternal exposure to cadmium during gestation perturbs the vascular system of the adult rat offspring [J]. Toxicol Appl Pharmacol, 2011, 251 (2): 137-145.

[31] KUHNERT BR, KUHNERT PM, LAZEBNIK N, et al. The effect of maternal smoking on the relationship between maternal and fetal zinc status and infant birth weight [J]. J Am Coll Nutr, 1988, 7 (4): 309-316.

[32] SCHEUHAMMER AM, ONOSAKA S, RODGERS K, et al. The interaction of zinc and cadmium in the synthesis of hepatic metallothionein in rats [J]. Toxicology, 1985, 36 (2/3): 101-108.

[33] LALL SB, DAN G. Role of corticosteroids in cadmium induced immunotoxicity [J]. Drug Chem Toxicol, 1999, 22 (2): 401-409.

[34] HIDALGO J, ARMARIO A. Effect of Cd administration on the pituitary-adrenal axis [J]. Toxicology, 1987, 45 (1): 113-116.

[35] STAUD F, MAZANCOVÁ K, MIKŠÍK I, et al. Corticosterone transfer and metabolism in the dually perfused rat placenta: effect of 11β-hydroxysteroid dehydrogenase type 2 [J]. Placenta, 2006, 27 (2/3): 171-180.

[36] YANG K, JULAN L, RUBIO F, et al. Cadmium reduces 11β-hydroxysteroid dehydrogenase type 2 activity and expression in human placental trophoblast cells [J]. Am J Physiol Endocrinol Metab, 2006, 290 (1): E135-E142.

[37] AABIDHA PM, CHERIAN AG, PAUL E, et al. Maternal and fetal outcome in pre-eclampsia in a secondary care hospital in South India [J]. J Family Med Prim Care, 2015, 4 (2): 257-260.

[38] WANG F, ZHANG Q, ZHANG X, et al. Preeclampsia induced by cadmium in rats is related to abnormal local glucocorticoid synthesis in placenta [J]. Reprod Biol Endocrinol, 2014, 12: 77.

[39] FENG W, CUI X, LIU B, et al. Association of urinary metal profiles with altered glucose levels and diabetes risk: a population-based study in China [J]. PLoS One, 2015, 10 (4): e0123742.

[40] ROMANO ME, ENQUOBAHRIE DA, SIMPSON CD, et al. A case-cohort study of cadmium body burden and gestational diabetes mellitus in american women [J]. Environ Health Perspect, 2015, 123 (10): 993-998.

[41] WALLIA A, ALLEN NB, BADON S, et al. Association between

urinary cadmium levels and prediabetes in the NHANES 2005-2010 population [J]. Int J Hyg Environ Health, 2014, 217 (8): 854-860.

[42] PENG S, LIU L, ZHANG X, et al. A nested case-control study indicating heavy metal residues in meconium associate with maternal gestational diabetes mellitus risk [J]. Environ Health, 2015, 14: 19.

[43] DEMIR H, KANTER M, COSKUN O, et al. Effect of black cumin (*Nigella sativa*) on heart rate, some hematological values, and pancreatic β-cell damage in cadmium-treated rats [J]. Biol Trace Elem Res, 2006, 110 (2): 151-162.

[44] FINE EL, HORAL M, CHANG TI, et al. Evidence that elevated glucose causes altered gene expression, apoptosis, and neural tube defects in a mouse model of diabetic pregnancy [J]. Diabetes, 1999, 48 (12): 2454-2462.

[45] ORNOY A. Prenatal origin of obesity and their complications: gestational diabetes, maternal overweight and the paradoxical effects of fetal growth restriction and macrosomia [J]. Reprod Toxicol, 2011, 32 (2): 205-212.

[46] LARQUÉ E, RUIZ-PALACIOS M, KOLETZKO B. Placental regulation of fetal nutrient supply [J]. CurrOpin Clin NutrMetab Care, 2013, 16 (3): 292-297.

[47] HSIAO EY, PATTERSON PH. Placental regulation ofmaternal-fetal interactions and brain development [J]. DevNeurobiol, 2012, 72 (10): 1317-1326.

[48] NEWBERN D, FREEMARK M. Placental hormones and thecontrol of maternal metabolism and fetal growth [J]. CurrOpin Endocrinol Diabetes Obes, 2011, 18 (6): 409-416.

[49] LIN S, HUO X, ZHANG Q, et al. Short placental telomere was associated with cadmium pollution in an electronic waste recycling Town in China [J]. PLoS One, 2013, 8 (4): e60815.

[50] RONCO AM, ARGUELLO G, MUÑOZ L, et al. Metals content in placentas from moderate cigarette consumers: correlation with newborn birth weight [J]. Biometals, 2005, 18 (3): 233-241.

[51] SAKAMOTO M, YASUTAKE A, DOMINGO JL, et al. Relationships between trace element concentrations in chorionic tissue of placenta and umbilical cord tissue: potential use as indicators for prenatal exposure [J]. Environ Int, 2013, 60: 106-111.

[52] KIPPLER M, HOQUE AM, RAQIB R, et al. Accumulation of cadmium in human placenta interacts with the transport of micronutrients to the fetus [J]. Toxicol Lett, 2010, 192 (2): 162-168.

[53] RONCO AM, URRUTIA M, MONTENEGRO M, et al. Cadmium exposure during pregnancy reduces birth weight and increases maternal and foetal glucocorticoids [J]. Toxicol Lett, 2009, 188 (3): 186-191.

[54] BLUM JL, XIONG JQ, HOFFMAN C, et al. Cadmium associated with inhaled cadmium oxide nanoparticles impacts fetal and neonatal development and growth [J]. Toxicol Sci, 2012, 126 (2): 478-486.

[55] JAUNIAUX E, BURTON GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit [J]. Early Hum Dev, 2007, 83 (11): 699-706.

[56] LEE CK, LEE JT, YU SJ, et al. Effects of cadmium on the expression of placental lactogens and Pit-1 genes in the rat placental trophoblast cells [J]. Mol Cell Endocrinol, 2009, 298 (1/2): 11-18.

[57] STASENKO S, BRADFORD EM, PIASEK M, et al. Metals in human placenta: focus on the effects of cadmium on steroid hormones and leptin [J]. J Appl Toxicol, 2010, 30 (3): 242-253.

[58] KAWAI M, SWAN KF, GREEN AE, et al. Placental endocrine disruption induced by cadmium: effects on P450 cholesterol side-chain cleavage and 3β-hydroxysteroid dehydrogenase enzymes in cultured human trophoblasts [J]. Biol Reprod, 2002, 67 (1): 178-183.

[59] ENLI Y, TURGUT S, OZTEKIN O, et al. Cadmium intoxication of pregnant rats and fetuses: interactions of copper supplementation [J]. Arch Med Res, 2010, 41 (1): 7-13.

[60] FRIAS-ESPERICUETA MG, CARDENAS-NAVA NG, MÁRQUEZ-FARÍAS JF, et al. Cadmium, copper, lead and zinc concentrations in female and embryonic pacific sharpnose shark (Rhizoprionodon longurio) tissues [J]. Bull Environ Contam Toxicol, 2014, 93 (5): 532-535.

[61] RZYMSKI P, NIEDZIELSKI P, PONIEDZIALEK B, et al. Identification of toxic metals in human embryonic tissues [J]. Arch Med Sci, 2018, 14 (2): 415-421.

[62] THOMPSON J, HIPWELL E, LOO HV, et al. Effects of cadmium on cell death and cell proliferation in chick embryos [J]. Reprod Toxicol, 2005, 20 (4): 539-548.

[63] DOI T, PURI P, BANNIGAN J, et al. Msx1 and Msx2 gene expression is downregulated in the cadmium-induced omphalocele in the chick model [J]. J Pediatr Surg, 2010, 45 (6): 1187-1191.

[64] AGNELLO M, FILOSTO S, SCUDIERO R, et al. Cadmium induces an apoptotic response in sea urchin embryos [J]. Cell Stress Chaperon, 2007, 12 (1): 44-50.

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