· 儿少卫生与妇幼保健 ·

妊娠期维生素 D 缺乏经 Wnt/β－catenin 信号通路抑制胎盘发育引发不良妊娠结局

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摘要：目的　探究母体孕前及妊娠期间维生素 D 缺乏（vitamin D deficiency，VDD）是否通过 Wnt/β－catenin 信号通路阻碍胎盘正常发育，进而引发不良妊娠结局。**方法**　将 4 w 龄雌性 SD 大鼠按体质量随机分为两组，对照组（Ctrl）饲喂大鼠标准饲料、维生素 D 缺乏组（VDD）饲喂维生素 D 缺乏饲料。饲料干预 8 w 后，眼眶取血，VDD 大鼠模型构建成功后进行雌雄合笼，于孕 18 天（GD18）时处死母鼠，并收集组织样本。**结果**　造模 8 w 时，与 Ctrl 组相比，VDD 组母鼠血清 25（OH）D 水平显著降低（$P<0.001$）；GD18 时，VDD 组胎盘 25（OH）D、1，25（OH）$_2$D、VDR 水平分别为（6.75 ± 1.40）ng/ml、（24.23 ± 8.31）ng/L、（74.46 ± 27.54）nmol/L，均显著低于 Ctrl 组的（16.76 ± 3.12）ng/ml、（36.19 ± 4.27）ng/L、（137.52 ± 26.25）nmol/L，（$P<0.01$）；GD18 时，VDD 组胎盘直径、重量、合体滋养层面积和胎儿重量均显著低于 Ctrl 组。与 Ctrl 组相比，VDD 组每窝活胎数、着床数减少，吸收胎数增加；与 Ctrl 组相比，VDD 组孕鼠胎盘组织中 β－catenin 蛋白磷酸化水平明显升高。**结论**　母体孕前及妊娠期 VDD 是导致胎盘发育不良的重要原因，进而可诱发不良妊娠结局，其机制可能涉及 Wnt/β－catnin 信号通路。

关键词：维生素 D；Wnt/β－catenin 信号通路；胎盘发育；妊娠结局

中图分类号：R151.41；R－33　　**文献标志码：**A　　**文章编号：**1003－8507（2025）08－1405－07

DOI：10.20043/j.cnki.MPM.202404321

Vitamin D deficiency in pregnancy inhibits placental development and induces adverse pregnancy outcome via Wnt/β－catenin signaling pathway

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Abstract: Objective　Toinvestigate whether maternal vitamin D deficiency（VDD）prevents normal placental development through the Wnt/β－catenin signalling pathway during preconception and pregnancy, which in turn triggers adverse pregnancy outcomes. **Methods**　Four－week－old female SD rats were randomly divided into two groups according to body mass, Ctrl group fed with standard rat chow and VDD group fed with vitamin D deficiency chow. After eight weeks of feed intervention and successful construction of the VDD rat model, blood was taken from the orbits, male and female were co－caged. The females were executed at 18 days of gestation（GD18）. Tissue samples were collectedfor later experiment. **Results**　At eight weeks of modelling, the serum 25（OH）D levels of female rats in VDD group were significantly lower compared with those of the Ctrl group（$P<0.001$）. At GD18, measured the placental 25（OH）D, 1,25（OH）$_2$D, and VDR levels, these indexes in the VDD group were（6.75 ± 1.40）ng/ml,（24.23 ± 8.31）ng/L,（74.46 ± 27.54）nmol/L, which were significantly lower than indexes in the Ctrl group:（16.76 ± 3.12）ng/ml,（36.19 ± 4.27）ng/L, and（137.52 ± 26.25）nmol/L（$P<0.01$）. Placenta diameter, weight, syncytial trophoblast area, and foetal weight were measured at GD18. There was a significant difference between the two groups. At GD18, compared with the Ctrl group, the number of implanted fetuses and live fetuses per litter decreased, but the number of absorbed fetuses increased in the VDD group. The level of β－catenin hosphorylation was significantly increase in the placental tissues of pregnant rats in the VDD group. **Conclusion**　Maternal vitamin D deficiency before and during pregnancy is an important cause of placental dysplasia, which in turn can induce adverse

基金项目：山西省回国留学人员科研资助项目（2022－114）；山西省基础研究计划项目（202203021211227）

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pregnancy outcomes, and the mechanism may involve the Wnt/β - catenin signalling pathway.

Keywords: Vitamin D; Wnt/β - catenin signaling pathway; Placental development; Pregnancy outcome

维生素 D 缺乏已成为全球性问题,患病率估计为如美国 24%、欧洲 40%、澳大利亚 20.1%、韩国 66.9%、中国 28.6% ~96.3%[1-2]。VD 存在肾外合成途径,其维生素 D 受体(Vitamin D receptor, VDR)也广泛存在于人源细胞中,以胎盘组织最为突出[3]。妊娠期间,孕妇维生素 D 需求生理性增加,VDD 在孕妇中更为常见,且可能增加胎盘功能障碍相关并发症的风险,如子痫前期(preeclampsia, PE)、妊娠期糖尿病(gestational diabetes mellitus, GDM)、宫内生长受限(intrauterine growth restriction, IUGR)等[4]。

Hippo 和 Wnt 信号通路与胎盘发育密切相关[5-6]。我们先前的研究证明,母鼠妊娠期 VDD 时,胎盘组织 Hippo 信号通路异常激活,进而引发胎盘炎症和发育障碍[7]。但 Hippo 信号通路上似乎并无 VDR 的结合位点,该通路仅受 VD 的间接调控[8]。研究发现,妊娠期间 Wnt/β - catnin 信号通路相关蛋白在胎盘中高表达,参与调节滋养层细胞的关键生理过程[9-10]。在结肠癌细胞中,维生素 D 和 VDR 复合物能直接与核 β - catenin 结合,抑制 Wnt/β - catenin 信号的异常激活,从而抑制癌细胞增殖和迁移[11]。显然,机体对胎盘发育和癌细胞增殖的要求相反,且研究发现 VD 在其他生理细胞类型中也可作为 Wnt/β - catenin 通路的共激活剂[10,12]。尽管如此,维生素 D 与 Wnt/β - catenin 信号通路在胎盘组织中的相互作用机制尚未明确。本研究旨在探讨 VDD 是否通过调控 Wnt/β - catnin 信号通路阻碍胎盘发育进而引发不良妊娠结局。

1 材料与方法

1.1 *动物* 本研究选用 4 w 龄雌性 SD 大鼠,体重 90 ~130 g,由斯贝福(北京)生物技术有限公司提供,许可证号:SCXK(京)2019 - 0010。

1.2 *材料与试剂* 大鼠 25(OH)D、1,25(OH)$_2$D 酶联免疫分析(enzyme linked immune sorbent assay, Elisa)试剂盒(MM - 70906R1、MM - 0704R1,酶免,中国江苏);WB Lysis Buffer(BMP2020,Abbkine,中国武汉)、Protein Quantification Kit (BCA Assay)(KTD3001, Abbkine, 中国武汉)、ECL 发光液(BMU102 - CN,Abbkine,中国武汉)、高速台式离心机(德国 Eppendorf - 5415 型)。

以下一抗用于 Western blotting 实验:兔抗鼠 β - catenin(#9562,CST,美国;1∶1 000)、兔抗鼠 Phospho - β - catenin(Ser33/37/Thr41)(#9561,CST,美国;1∶1 000)、兔抗鼠 β - actin(81115 - 1 - RR,Proteintech,中国武汉;1∶5 000)。二抗:辣根过氧化物酶标记羊抗兔 IgG 抗体

1.3 *动物干预方法* 参照 Wang 等人的 VDD 模型建立方法[13],按将 4 w 龄 SD 雌性大鼠体质量随机分为对照组(Ctrl 组,饲喂正常饲料,VD 含量 56.25 μg/kg)和维生素 D 缺乏组(VDD 组,饲喂 VD 缺乏饲料,VD 含量 0 μg/kg)(饲料标准参考 GB + 14924.3 - 2010 中实验动物配合饲料营养成分),每组 10 只。将所有大鼠在环境温度(23 ±2 ℃)和湿度(55 ±5%)条件下饲养,且均自由饮食、饮水,Ctrl 组置于自然光照下,VDD 组采用无紫外线的黄光,均维持 12 h 的明/暗循环。雌鼠饲料干预 8w 后,于 20:00 与健康的 12w 龄 SD 雄性大鼠合笼,次日 8:00 检查阴栓,有阴栓者视为交配成功,并定为妊娠 0d(GD0),所有孕鼠于 GD18 时麻醉后处死并采集标本。动物实验方案经山西医科大学动物实验伦理委员会批准,符合动物伦理要求(批准文号 SYDL2020005)

1.4 Elisa 大鼠在造模 8w 时进行眼眶取血,血液样本置于无菌无酶 EP 管中,静置 2h 后 3 000 r/min 离心 15 min,取上清;采集的胎盘组织在预冷的 PBS(组织重量(g):PBS 体积(mL) = 1∶9)中快速匀浆后,以 3 000 r/min 离心 20 min,收集上清液。根据 Elisa 试剂盒说明书测定 25(OH)D、1,25(OH)$_2$D、VDR 水平。

1.5 *苏木精 - 伊红染色* 胎盘石蜡切片经苏木素、伊红染色,显微镜下观察,分别采集细胞滋养层随机 5 个视野和胎盘组织全景视野的图像,采用 Image J 软件测量胎盘合体滋养层面积。

1.6 Western blotting 使用蛋白质提取试剂提取胎盘组织的蛋白质,BCA 法测定并调整蛋白浓度,在 SDS - PAGE 凝胶体系中电泳分离蛋白质,随后用湿转法将其转移到 PVDF 膜上,称取脱脂奶粉溶解于 TBST 溶液,配制成奶粉浓度 5% 的封闭液,室温封闭 PVDF 膜 2h,用 TBST 洗膜 3 次,再放入相应一抗稀释液中,置于摇床 4 ℃孵育过夜,次日吸除一抗,用 TBST 洗膜 3 次,放入二抗稀释液中(稀释比 1∶5 000),在摇床上室温孵育 1.5 h,用 TBST 洗膜 3 次,加入 ECL 发光液,显影仪显影。用 Image J 软件进行灰度分析。

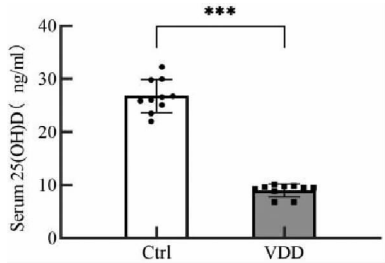
1.7 *统计分析* 使用 SPSS Statistics 25 和 Graphpad Prism 8.0.2 软件进行相关的统计描述与分析,t 检验作为计量资料的检验方法,用均数 ± 标准差($\bar{x} \pm s$)表

示；χ^2 检验作为计数资料的检验方法，用率（%）表示，检验水准 $\alpha = 0.05$。

2　结　果

2.1　母鼠孕前血清 25(OH)D 水平　与预期相同，维生素 D 缺乏饲料喂养 8 w 后，VDD 组母鼠血清 25(OH)D 浓度显著低于 Ctrl 组（9.01 ± 1.22 ng/ml vs 26.79 ± 3.10 ng/ml，$n = 10$，$P < 0.001$，图 1A）。

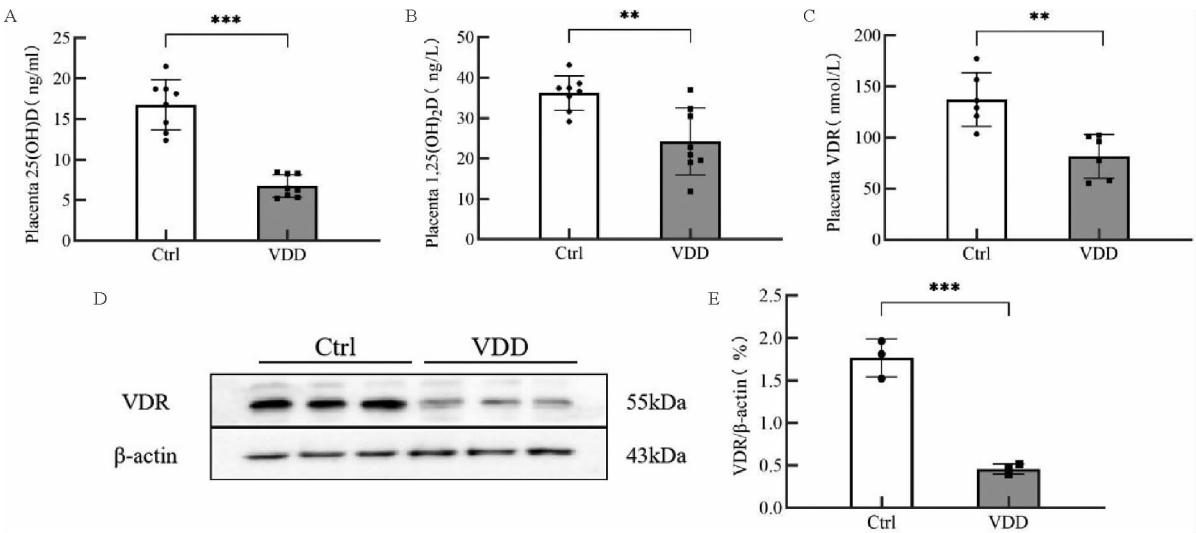
2.2　GD18 胎盘 25(OH)D、1,25$(OH)_2$D、VDR 水平　GD18 时，VDD 组胎盘 25(OH)D、1,25$(OH)_2$D、VDR 水平分别为（6.75 ± 1.40）ng/ml、（24.23 ± 8.31）ng/L、（74.46 ± 27.54）nmol/L 均显著低于 Ctrl 组（16.76 ± 3.12）ng/ml、（36.19 ± 4.27）ng/L、（137.52 ± 26.25）nmol/L（$n = 8$，$P < 0.001$，图 2A－C）。同样，Western Blotting 结果显示，VDD 组胎盘 VDR 蛋白表达量显著性低于 Ctrl 组（$P < 0.001$，图 2D－E）。



注：* * * $P < 0.001$ versus Ctrl group；$n = 10$。

图 1　两组孕前血清 25(OH)D 水平比较

Fig. 1　Comparison of preconception serum 25(OH)D level between two group



注：* * $P < 0.01$，* * * $P < 0.001$ versus Ctrl group；$n = 3$ or 6 or 8。

图 2　两组之间胎盘 25(OH)D（A）、1,25$(OH)_2$D（B）和 VDR（C－E）水平比较

Fig. 2　Comparison of placenta 25(OH)D (A), 1,25$(OH)_2$D (B) and VDR level (C－E) between two groups

2.3　妊娠期 VDD 损害胎盘、胚胎发育

2.3.1　胎盘　GD18 时，VDD 组胎盘直径、重量分别为（12.04 ± 0.71）mm、（0.32 ± 0.36）g，均显著低于 Ctrl 组的（13.13 ± 1.12）mm、（0.49 ± 0.53）g（$n = 8$，$P < 0.05$ 或 $P < 0.001$），图 3A－C）。

HE 染色观察胎盘病理学形态改变发现，GD18 时，VDD 组孕鼠的胎盘合体滋养层面积显著性小于 Ctrl 组（15.98 ± 0.28% vs 24.73 ± 0.62%）（$n = 8$，$P < 0.05$，图 3D），且 VDD 组胎盘组织中的细胞滋养层出现较大范围的细胞坏死、细胞空泡变性和血管紊乱（图 3E）。

2.3.2　胚胎　GD18 时，VDD 组胚胎重量显著低于 Ctrl 组（1.201 ± 0.17 g vs 1.608 ± 0.93 g）（$n = 8$，$P < 0.001$，图 4B），VDD 组胚胎顶臀长略低于 Ctrl 组但无显著性差异（23.41 ± 1.52 mm vs 24.51 ± 1.09 mm）（$n = 8$，$P > 0.05$，图 4A、C）。同时，VDD 组胚胎偶见脑部发育缺陷，表现为头部发育不完全，头骨未闭合（图 4D）。

2.4　妊娠期 VDD 诱导不良妊娠结局　GD18 时，与 Ctrl 组比较，VDD 组孕鼠孕期体重增长量显著降低（112.43 ± 17.44 g vs 60.95 ± 11.27 g）（$n = 10$，$P < 0.001$）；每窝活胎数显著减少（14.50 ± 2.93 vs 10.002.07）（$n = 8$，$P < 0.01$）；每窝着床数减少、吸收胎数增加（$n = 8$），但无统计学差异（表 1）。

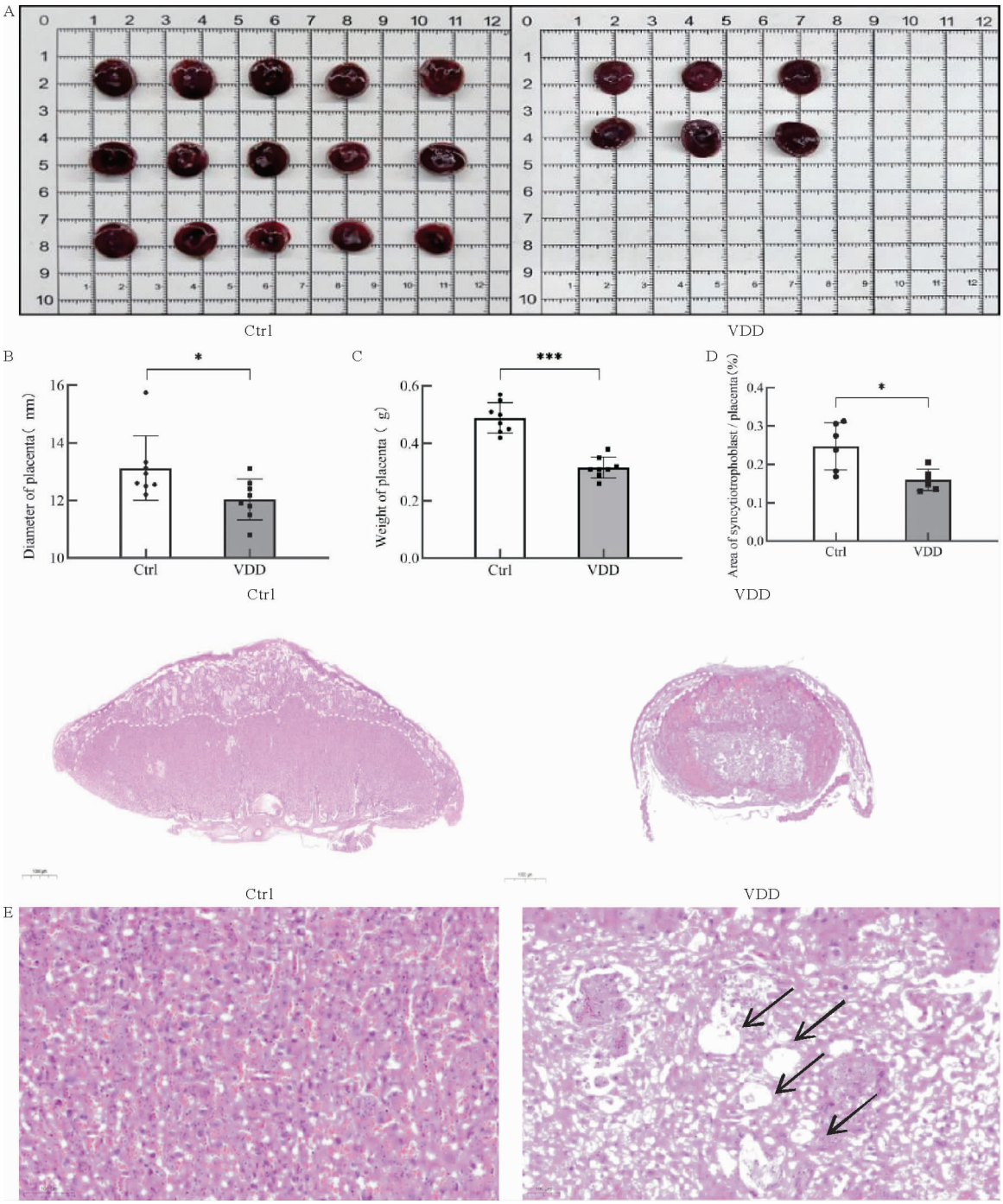


图 3 孕鼠 GD18 时胎盘发育 (1)胎盘;(B－D) 两组之间胎盘直径、重量、合体滋养层面积比较;(E)两组之间胎盘病理学改变比较。上图标尺 1 000 μm;下图标尺 100 μm;黑色箭头:空泡变性;白色虚线框:合体滋养层

Fig. 3 Placental development at GD18 of pregnant rats (A) Placenta; (B－D) Comparison of placenta diameter, weight and area of syncytiotrophoblastbetween two groups; (E) Comparison of histological structure and pathological changes of placenta between two groups. Scale bar in the figure top:1 000 μm; Scale bar in the figure below:100 μm; Black arrows: vacuolar degeneration; White dotted line box: yncytiotrophoblast

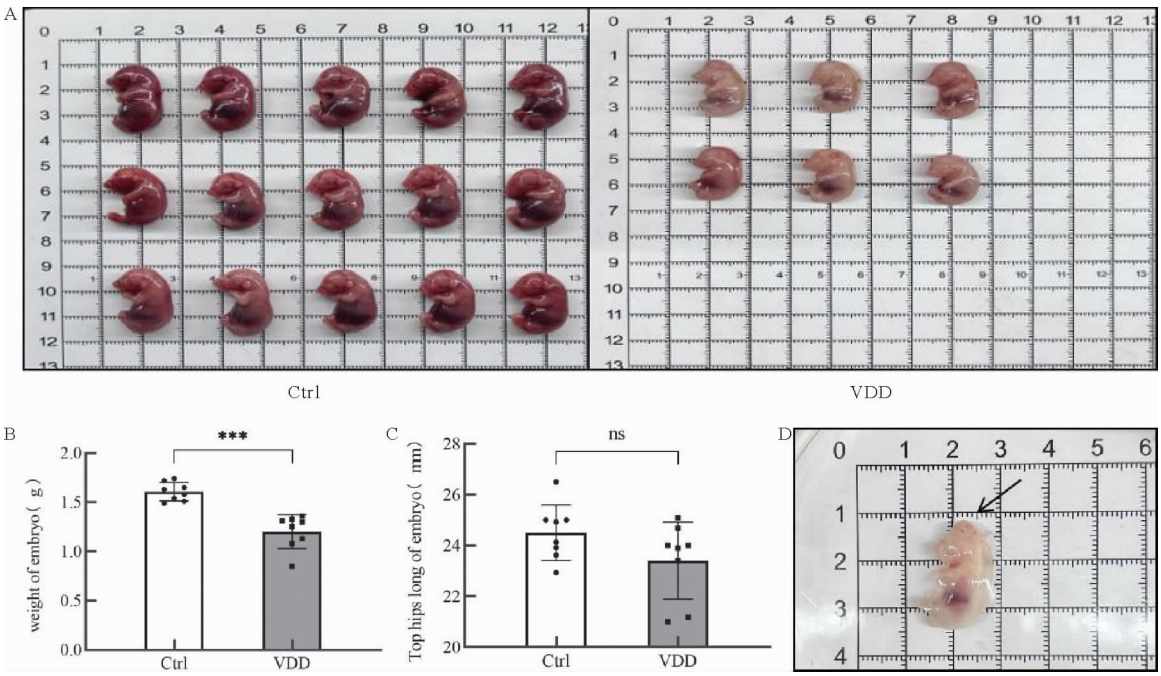
表 1 两组间妊娠结局比较($\bar{x} \pm s$, $n = 8$ or 10)

Table 1 Comparison of pregnancy outcomes between two groups ($\bar{x} \pm s$, $n = 8$ or 10)

Parameters	Ctrl	VDD
孕期体重增长量(g)	112.43 ± 17.44	60.95 ± 11.27[a]
妊娠大鼠数量(n)	10	10
每窝着床数(n)	14.50 ± 3.89	11.50 ± 1.41
每窝吸收胎数(n)	0.75 ± 0.89	1.50 ± 1.51
活胎数(n)	115	91
每窝活胎数(n)	14.50 ± 2.93	10.00 ± 2.07[b]

a $P < 0.0001$; b $P < 0.001$; versus Ctrl group, $n = 8$ or 10。

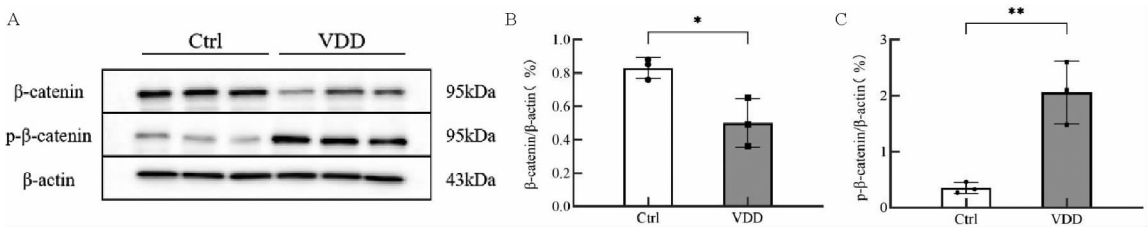
2.5　维生素 D 缺乏经 Wnt/β－catenin 信号通路抑制胎盘发育　β－catenin 是 Wnt 信号通路经典途径上的关键蛋白，对 GD18 孕鼠胎盘组织中 β－catenin 蛋白、p－β－catenin 蛋白的表达水平进行检测，Western blotting 结果显示，与 Ctrl 组相比，VDD 组孕鼠胎盘 β－catenin 蛋白表达水平下调（$P<0.05$），p－β－catenin 蛋白表达水平上调（$P<0.01$）（图 5A－C）。



注：$^{ns}P>0.05$，$**P<0.01$，$***P<0.001$ versus Ctrl group，$n=6$ or 8。

图 4　孕鼠 GD18 时胚胎发育　（A）胚胎；（B－C）两组之间胚胎重量和胎儿顶臀长比较；（D）头部发育不良的胚胎（黑色箭头）

Fig. 4　Placental and embryo development at GD18 of pregnant rats　（A）Embryo；（B－C）Comparison of embryo weight and top hips long between two groups；（D）Fetus withbrain dysplasia（black arrows）



注：$*P<0.05$，$**P<0.01$ versus Ctrl group。

图 5　两组间胎盘中 Wnt 通路相关蛋白的表达比较

Fig. 5　Comparison of Wnt pathway related proteins expression in placenta between two groups

3　讨　论

3.1　妊娠期 VDD 损害胎盘发育引发不良妊娠结局　常见的不良妊娠结局包括 PE、GDM、IUGR、新生儿低钙血症、骨骼脆性、自身免疫性疾病发生率增加等[3]，PE 和 IUGR 是与胎盘功能不全相关的妊娠特异性疾病[14]，其往往伴随着胎盘早衰和细胞的异常凋亡[15]，可见胎盘在维持胎儿发育中的重要作用不可忽视。事实上，在妊娠过程中，胎盘通过侵袭和重塑子宫血管系统介导了母胎间的营养和代谢物质交换，足月时，胎盘重量仅占子宫总质量的 10% ~20%，但其代谢所需能量占传递到子宫的氧气和葡萄糖总量的 40% ~60%[16]。据报道，作为胎母血管界面，胎盘发育受损时，其代谢将发生改变，会显著影响母体通过胎盘向胎儿输送的氧气和营养物质的效率，导致胎盘糖代谢和脂肪酸代谢紊乱，从而进一步诱发不良妊娠结局[17]。

大范围流行病学资料显示，妊娠期维生素 D 缺乏症是在全球范围内长期存在的公共卫生问题[3,18]，研究发现多种不良妊娠结局都与妊娠期间维生素 D 水

平相关[19],维生素 D 在孕妇体内影响着胎盘植入、血管生成、上皮－间质转化和免疫调节等[3],这些生理过程的异常都将影响胎盘正常发育及功能。母体 25(OH)D 透过胎盘屏障到达胎儿体内[3],是胎儿维生素 D 的主要来源,而且胎盘也可以合成 1,25(OH)$_2$D$_3$以供胎儿使用[20]。有研究发现妊娠期间 VDD 可导致小鼠胎儿 IUGR,VDD 饮食喂养的小鼠胎儿体质量和顶臀长均降低[21],这与本研究 VDD 模型大鼠妊娠结局结果一致。也有研究表明 VDD 引起的 IUGR 胎儿的胎盘重量降低、形态异常,包括胎盘梗死、胎盘绒毛表面积减少从而阻碍母胎之间的物质交换[22-24],这与本研究中 VDD 组胎盘重量和直径显著降低,胎盘合体滋养层面积显著减少,迷路层大面积细胞坏死、血细胞减少,严重阻碍胎盘的正常功能相对应。

3.2 VDD 经 Wnt/β－catenin 信号通路抑制胎盘发育引发不良妊娠结局 Wnt 是一类被脂肪酸修饰的分泌型蛋白,不同的信号蛋白与细胞膜上的卷曲蛋白(Frizzled,Frz)受体和辅助受体低密度脂蛋白受体相关蛋白(low－density lipoprotein related proteins, LRP)结合后激活细胞内的相应信号通路,所以 Wnt 信号通路分为经典和非经典途径,经典 Wnt 通路(即 Wnt/β－catnin 通路),在进化中高度保守,控制着细胞的增殖、分化与迁移,非经典 Wnt 通路(即 Wnt/JNK 通路、Wnt/Ca2＋通路)对细胞极性和迁移产生影响[25]。关于 Wnt/β－catnin 信号通路,目前研究主要集中其在癌细胞中的异常激活会增加癌细胞转移、浸润的风险[25],但 Wnt/β－catnin 信号通路在胚胎发育和成体组织稳态中的作用也不可小觑[26],然而,其与维生素 D 共调控胎盘细胞功能的具体机制目前尚不清楚。

在本研究中,β－catnin 蛋白的表达在 VDD 组胎盘中下调,p－β－catnin 蛋白表达水平上调。这提示,妊娠期 VDD 损害胎盘和胎儿发育,引发不良妊娠结局,可能与 Wnt/β－catnin 信号通路相关蛋白表达异常有关。

目前有[14]较少的研究关注维生素 D 通过调控 Wnt/β－catnin 信号通路影响胎盘发育,然而,人群妊娠期维生素 D 广泛缺乏从而引发多种不良妊娠结局的事实警示我们,须通过多种方式对孕前、孕期妇女体内维生素 D 水平进行干预,且当妊娠期 VDD 发生时,以 Wnt/β－catnin 信号通路为靶点来改善和预防不良妊娠结局将是公共卫生视角下有前景的领域。

利益冲突声明 本研究不存在任何利益冲突

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收稿日期:2024-04-18

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收稿日期:2024-11-19