生理学报 *Acta Physiologica Sinica*, December 25, 2021, 73(6): 991–998
DOI: 10.13294/j.aps.2021.0089 http://www.actaps.com.cn

综 述

母体应激影响胎儿发育的胎盘机制研究进展

华天桢[1,#]，高灵通[1,#]，张治宇[2]，赵厚铭[1]，高 路[1,3,4,*]

[1]海军军医大学基础医学院生理学教研室，上海 200433；[2]海军军医大学长征医院健康管理中心，上海 200003；[3]上海市胚胎源性疾病重点实验室，上海 200030；[4]上海市辅助生殖和生殖遗传重点实验室，上海 200000

摘 要：胎盘是维系母体与胎儿的唯一纽带，是母体维持正常妊娠进程和胎儿正常发育的基础。母体应激是多种因素导致的母体生理、心理变化，主要特征是升高的糖皮质激素影响下丘脑-垂体-靶腺轴，引发体内激素的分泌变化，并调节应激相关基因的表达，改变胎盘的重量、代谢、营养转运等，进而对胎儿发育造成影响。本文首先简介母体应激的表征及其对子代的影响，进而阐述应激状态下机体的相应变化，最后阐明研究已证实的母体应激影响胎儿发育的胎盘机制，并提出尚未得到深入研究的重要问题。研究母体应激对胎儿发育的影响及具体作用机制可为多种应激相关妊娠疾病的治疗提供理论基础。

关键词：母体应激；胎盘；胎儿发育；糖皮质激素；下丘脑-垂体-靶腺轴
中图分类号：R339.2；R335；R339.3

Placental mechanisms underlying the effects of maternal stress on the fetal development

HUA Tian-Zhen[1,#], GAO Ling-Tong[1,#], ZHANG Zhi-Yu[2], ZHAO Hou-Ming[1], GAO Lu[1,3,4,*]

[1]*Department of Physiology, College of Basic Medical Sciences, Naval Medical University, Shanghai 200433, China;* [2]*Department of Health Management, Changzheng Hospital, Naval Medical University, Shanghai 200003, China;* [3]*Shanghai Key Laboratory of Embryo Original Diseases, Shanghai 200030, China;* [4]*Shanghai Key Laboratory for Assisted Reproduction and Reproductive Genetics, Shanghai 200000, China*

Abstract: Placenta is the only link between the pregnant woman and fetus, and the basis for maintaining the normal pregnancy process and fetal development. Maternal stress is the maternal physiological and psychological changes caused by various factors, characterized by the increased level of glucocorticoid, which affects the hypothalamic-pituitary-target gland axis and regulates the expression of target genes. Maternal stress also changes the weight, metabolism and nutrient transportation of the placenta, which will substantially influence the development of fetus. This paper will firstly summarize the characteristics of maternal stress and its influence on offspring. Then, the changes in the body under maternal stress will be described. Finally, we will clarify the proven mechanisms underlying maternal stress and raise some important problems that have not been clarified in this area. The study of maternal stress on fetus and its underlying mechanisms will serve as theoretical basis for the diagnosis and treatment of the stress-related pregnant diseases and disorders.

Key words: maternal stress; placenta; fetal development; glucocorticoid; hypothalamic-pituitary-target gland axis

Received 2020-09-26 Accepted 2021-02-08

Research from the corresponding author's laboratory was supported by the National Key Research and Development Project (No. 2019YFC1005203); National Natural Science Foundation of China (No. 81771608 & 82120108011); Major Project of Shanghai Municipal Education Commission's Scientific Research and Innovation Plan (No. 2021-01-07-00-07-E00144); Outstanding Academic Leaders Program of Shanghai Municipal Science and Technology Commission (No. 18XD1405100); "Shuguang Program" supported by Shanghai Municipal Education Commission (No. 17SG36), and the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning.

[#]These authors contributed equally to this review.

[*]Corresponding author. Tel: +86-21-81870980; E-mail: roadgao@163.com

胎盘的形成是由囊胚外层滋养层细胞侵入子宫壁，逐渐分化为滋养层、蜕膜以及血管组织并建立起血液循环的过程 [1]。胎盘是联系母体与胎儿并发挥多种功能的器官 [2]。母体通过胎盘向胎儿提供营养与氧气，并接受废物，同时保护胎儿免受母体免疫系统攻击。胎盘分泌的激素、生长因子等对于胎儿发育和妊娠进程起到调节作用。胎盘的正常发育对妊娠的建立至关重要，其发育异常会导致胎儿的正常生长受阻，造成胎儿生长受限、流产、早产、死胎等 [3]。罹患胎儿宫内生长受限 (intrauterine growth restriction, IUGR) 的新生儿在幼龄时会表现出低体重和相对较低的智力和认知能力 [4, 5]。发育异常的胎盘还会向母体释放多种细胞因子，破坏孕妇多脏器正常功能，继发引起先兆子痫等妊娠综合征，其子代易发生营养不良、器官缺血缺氧等症状 [6]，受高血压等心血管疾病困扰的概率显著增加 [7,8]。

应激反应是机体受应激原刺激，引起神经、内分泌活动产生适应性变化的反应 [9]。母体应激是指母亲在妊娠期间受某些异常因素，如疾病、缺氧、营养不良、贫血等引起的情绪、心理和内分泌的适应性变化 [10]。母体应激反应引起的内分泌活动可导致胎盘中激素含量的变化，一方面可通过血液循环影响胎儿的发育；另一方面还可通过作用于胎盘发育的不同时期，影响滋养层细胞的分化，对胎盘的大小、代谢、免疫、营养转运等产生影响 [11]，进而导致胎儿发育的异常。由此可见，胎盘的结构和功能的变化在介导母体应激对胎儿发育的影响中发挥着至关重要的作用。本文将重点综述母体应激所致激素的变化影响胎儿发育和胎源性疾病的胎盘机制，并阐明现有研究存在的问题，为进一步的研究提供思路。

1 母体应激对子代多个系统产生影响

有研究表明，适度的母体应激对胎儿的妊娠结局有利：妊娠后期的内源性糖皮质激素 (glucocorticoid, GC) 增加可促进胎儿的神经发育和认知发展，促进胎儿器官成熟尤其是肺成熟，增加早产儿的存活率 [12]。但越来越多的研究表明，过度的母体应激给子代宫内发育和出生后带来许多不利因素，其主要对子代的神经系统、内分泌代谢系统、心血管系统和免疫系统造成影响。

1.1 神经系统

母体应激与子代神经系统结构和功能之间存在密切联系。经历母体应激暴露的子代会表现出更大的杏仁核体积和更小的前额叶皮层体积，进而引发前额叶皮层激活，引起子代的负面情绪 [13]。产前抑郁和创伤后应激障碍引起的母体应激通过改变大脑中多巴胺的作用回路 [14, 15]、谷氨酸和 γ- 氨基丁酸神经元的活性水平 [16]，导致子代出现焦虑情绪、情绪和认知障碍、注意缺陷多动障碍 (attention deficit hyperactivity disorder)、自闭症、霸凌倾向、精神分裂症等心理问题 [17, 18]。妊娠期间的应激可诱发子代成年后的代谢紊乱 [19]。

1.2 内分泌代谢系统

孕期应激影响联合高脂蔗糖饮食可导致子代血糖、胰岛素和瘦素水平的升高，增加子代罹患肥胖症和 2 型糖尿病的风险 [20]。营养不良或妊娠期选择性蛋白质剥夺导致的母体应激可提高母体血浆中的 GC 水平，引发胎盘氨基酸转运体表达的区域特异性改变，降低胎儿和胎盘重量，导致子代成年后发生代谢综合征的概率增加 [21]。

1.3 心血管系统

营养限制引起的母体应激使胎儿血管生成减少，导致外周阻力增加，进而引起主动脉增大并伴有血压升高。而吸烟引起的母体应激则导致母体胎盘绒毛组织内血管内皮生长因子 A 的含量上升，与先兆子痫的发生有关 [22]。本研究组前期研究显示，孕期 GC 暴露导致成年期子代雄性大鼠心脏缺血再灌注损伤后心功能显著下降，提示母体应激可对子代心脏功能造成长期影响 [23, 24]。

1.4 免疫系统

母体应激还可对子代的免疫系统造成影响。母体应激可抑制淋巴干细胞增殖，影响子代淋巴细胞的数量 [25]；引起辅助性 T 细胞 2 (helper T cell 2, Th2) 分泌的细胞因子白细胞介素 4 (interleukin 4, IL-4) 和 5 (IL-5) 升高，异常激活 Th2 免疫反应 [26]；降低单核细胞中高亲和力 IgE 受体启动子的甲基化水平 [27]，通过表观遗传调节破坏免疫稳态。

2 母体应激对子代发育影响的胎盘机制

研究表明，母体应激可通过调节胎盘对激素的屏障作用、生长因子传递系统、胎盘营养转运系统、胎盘血管形成、胎盘中细胞的增殖和凋亡以及母胎界面免疫反应等对子代产生影响 (图 1)。

2.1 影响胎儿GC暴露

研究表明，在妊娠期间，母体下丘脑 - 垂体 -

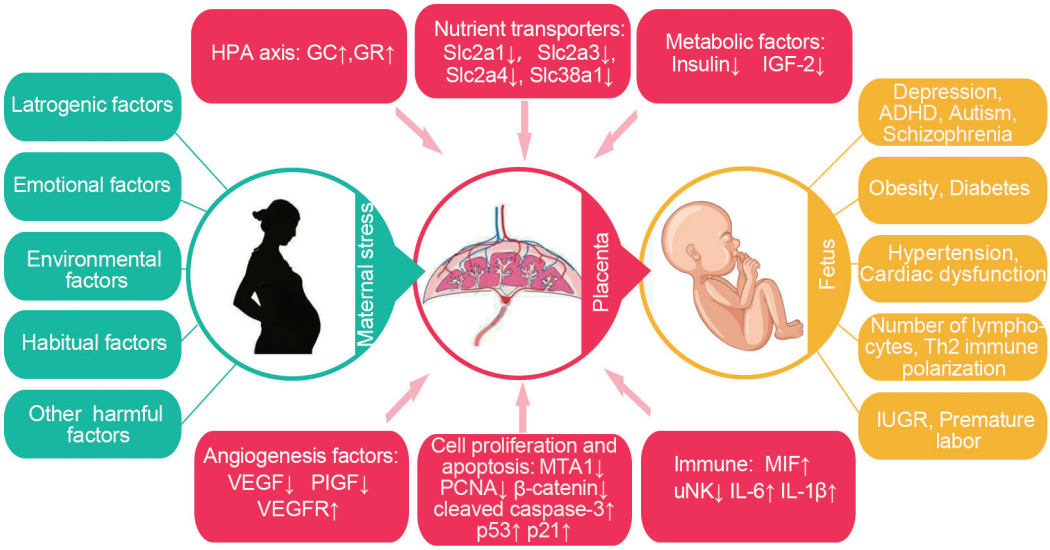

图 1. 母体应激影响胎儿发育的胎盘机制

Fig. 1. Placental mechanisms underlying the effects of maternal stress on the fetal development. Various factors of maternal stress can affect the development of fetus by regulating the placenta's hormone barrier, growth factor transport system, placental nutrient transport system, placental angiogenesis, placental cell proliferation and apoptosis, and the immune response at the maternal-fetal interface. HPA, hypothalamic-pituitary-adrenal; GC, glucocorticoid; GR, glucocorticoid receptor,; VEGF, vascular endothelial growth factor; PIGF, placental growth factor; VEGFR, vascular endothelial growth factor receptor; Slc, solute carrier; MTA1, metastasis tumor antigen 1; PCNA, proliferating cell nuclear antigen; IGF, insulin-like growth factor; MIF, macrophage migration inhibitory factor; uNK, uterus natural killer; IL, interlukin; ADHD, attention deficit hyperactivity disorder; Th2, helper T cell 2; IUGR, intrauterine growth restriction.

肾上腺 (hypothalamic-pituitary-adrenal, HPA) 轴的激活与母体应激直接相关 [28]。促肾上腺皮质激素释放激素 (corticotropin releasing hormone, CRH) 是应激反应中的关键调节因子，协调应激过程中内分泌、神经和行为反应 [29]。CRH 通常在人的血浆中检测不到，但在缺氧和感染导致的应激中，CRH 在核因子 κB 的激活下释放增加，通过胎盘作用于胎儿，会对胎儿发育中的脑细胞产生神经毒性 [30]。在妊娠过程中，胎盘会异位合成并释放大量 CRH 进入母胎循环。CRH 在母体应激时对胎盘组织中的葡萄糖转运体 (glucose transporter, GLUT) 调节出现紊乱，使得胎儿和胎盘的葡萄糖供应与组织的代谢需求不匹配，从而导致胎儿宫内生长迟缓和出生体重偏低，这一作用可能与母体应激引起的胎盘 CRH I 型受体 (CRH-R1) 表达下调有关 [31]。CRH-R1 参与应激时 HPA 轴反应的启动，并促进肾上腺促皮质激素 (adrenocorticotropic hormone, ACTH) 的释放，增加 GC 的分泌。GC 是人体 HPA 轴的最终产物 [32]，在应激反应中被释放，以调节各种重要功能，从而维持机体的稳态。研究显示，在母体应激中，母体内的 GC 水平升高，胎盘重量减小 [33]。妊娠时，胎儿肾上腺产生的 GC 含量较低，为了满足妊娠末期胎儿器官成熟的需要，胎儿需要通过胎盘从母体获得自体所需 40%~50% 的 GC [33]。胎盘将母体的大部分 GC 拒之门外，为胎儿的发育创造安全的环境。在正常妊娠过程中，母体供给胎儿的 GC 大约只有 15% 能通过胎盘 [34]，其余具有生物活性的 GC 在通过胎盘时被 11β- 羟基类固醇脱氢酶 2 型 (11β-hydroxysteroid dehydrogenase 2, 11β-HSD2) 转化为无活性的可的松或 11- 脱氢皮质酮。母体应激减少 11β-HSD2 的表达，对 GC 的屏障作用减弱，大量 GC 通过胎盘，使胎儿遭受过量 GC 暴露，影响胎儿的正常生长和发育 [35, 36]，同时通过印记效应，对子代成年后疾病的发生和发展造成影响。例如孕期镉暴露通过激活蛋白激酶 R 样内质网激酶 /p- 真核生物起始因子 2α 信号，下调 11β-HSD2 的蛋白表达，从而增加活性 GC 通过胎盘滋养层的量 [37]。同时，研究表明，母体产前应激还与胎盘中 GC 受体 NR3C1 (nuclear receptor subfamily 3 group C member 1) 基因表达增加有关 [38]。NR3C1 作为一种具有转录因子

和转录因子调节因子双重功能的核受体，可能作为11β-HSD2基因表达的上游调节因子，引起胎盘11β-HSD2基因表达下调[39]。因此，胎盘NR3C1与11β-HSD2之间的正反馈调节可能是胎盘GC敏感性和胎儿GC暴露增加的内在机制之一。

除此之外，在应激状态时，母体内的肾上腺素、去甲肾上腺素、血管紧张素水平也有一定程度的上升，但尚无明确证据证明这些激素可以通过胎盘对胎儿的发育产生影响[40]。

2.2 影响母体及胎儿的胰岛素水平

母体应激可降低母亲血液中的胰岛素水平，并通过减少胎儿胰腺中的胰岛数量降低胎儿的胰岛素水平，进而导致胎儿血糖浓度升高[41]。同时，母体应激的后代会出现胰岛素抵抗现象，发生代谢综合征、高胰岛素血症和2型糖尿病等疾病的概率显著增加[42]。这与母体应激时胎盘中肿瘤坏死因子、白细胞介素-6等促炎细胞因子增加，破坏胰岛素信号传导有关[42]。母体应激也导致大脑觉醒系统(蓝斑)和交感系统分泌儿茶酚胺类激素，而后者可通过血管加压素(vasopressin)使母体以昼夜节律和脉冲方式分泌皮质醇，透过胎盘屏障降低子代对胰岛素的敏感性，在子代胰岛素抵抗的进展中发挥促进作用[43]。母体应激对胎儿胰岛素样生长因子(insulin-like growth factor, IGF)系统的IGF-1和IGF-2以及其他几个与IGF结合蛋白相关的基因表观遗传有影响。IGF-2的表达主要受分布在IGF-2和与其相邻的差异甲基化区域调控。母体应激时，母体血液中IGF-2甲基化程度增加，通过胎盘交换的IGF-2减少，引起新生儿出生体重显著下降[44]。另外，应激反应诱导的葡萄糖和胰岛素的变化可促进胎盘的大小和重量发生适应性变化，胰岛素与GC或氧分子相互作用，影响胎盘生长，从而对胎儿的宫内发育和生长造成影响[45, 46]。

2.3 影响胎盘GLUT和氨基酸转运体

在孕期，胎儿的营养来自于母体，而胎盘是母体和胎儿营养物质发生交换的纽带。因此，胎盘中GLUT和氨基酸转运体的表达对胎儿的发育至关重要。许多应激相关基因调控胎盘滋养细胞中营养物质的转运和细胞的摄取，影响胎盘和胎儿的生长。Fowden等[47]研究显示，在营养不良应激时，胰岛素和GC抑制胎盘中IGF-2的产生，胎盘中IGF-2的降低下调GLUT (Slc2a1、Slc2a3、Slc2a4)和氨基酸转运体(Slc38a1)基因的表达，减少葡萄糖和氨基酸的转运，使得胎盘将营养物质转运给胎儿的能力下降，导致胎盘重量和胎儿体重下降[48]。Slc2a1表达下调现象在慢性应激和母体缺氧条件下也同样存在，因此Slc2a1可作为胎盘葡萄糖转运受损的标志[49]。Slc2a3和Slc2a4在母体应激状态下的表达降低可能与胎盘对母体和胎儿的血糖浓度增加的适应有关，从而避免B淋巴细胞数量和胎儿胰岛素浓度在葡萄糖诱导下发生大幅改变[50]。胎盘中氨基酸、葡萄糖等营养物质转运体和IGF-2等生长因子的减少，使得胎盘将营养物质转运给胎儿的能力下降，影响胎儿的能量供应，从而对胎儿的宫内发育和生长造成影响[31]。

2.4 影响胎盘血管形成

胎盘的血管形成对胎儿的生长发育至关重要，它的血流供给能够提供营养物质和氧气，是保证胎盘行使正常功能的基础。研究表明，胎盘、胎儿发育和胎盘血流量之间存在显著正相关性[51]。胎盘部位血管形成的主要影响因子包括血管内皮生长因子、成纤维细胞生长因子和血管生成素以及它们各自的受体。孕期地塞米松暴露可通过影响Akt/mTOR通路下调大鼠胎盘中血管内皮生长因子和胎盘生长因子的表达，并上调血管内皮生长因子受体2的表达，抑制胎盘血管的形成，导致宫内生长迟缓[52]。营养不良引起的母体应激可导致滋养层下基底膜和毛细血管基底板增厚，并伴有血管生成因子表达的改变，造成母体和胎儿胎盘交换距离增加[22, 53]。而在缺氧应激下，胎盘绒毛微血管结构表现为毛细血管直径增大和毛细血管间距离的增加，血管形态变得不规则，分支增多。这些均导致毛细血管表面积增加，增大了母胎血液的交换面积[54]。不难看出，胎盘血管重塑是对各种母体应激源的潜在适应性反应。

2.5 影响胎盘细胞的增殖和凋亡

母体妊娠时胎盘细胞凋亡或生理死亡增加常导致胎儿生长迟缓，提示胎盘细胞凋亡可能是控制胎儿-胎盘生长的关键因素[55]。研究显示，外源性GC和11β-HSD2抑制剂卡宾诺酮可明显刺激胎盘细胞凋亡[56]。GC的过度暴露可导致雄性子代小鼠胎盘中cleaved caspase-3蛋白表达增加55%、雌性子代小鼠胎盘中cleaved caspase-3蛋白表达增加250%以上，而BAX (BCL2-associated X protein)或BCL2 (B-cell lymphoma-2)蛋白表达在雄性或雌性子代小鼠胎盘中均无显著变化[57]；同时还有研究显示，GC的过度暴露导致大鼠胎盘中促进细胞增殖

相关基因 MTA1 (metastasis tumor antigen 1) 在基底区细胞核中表达下调、增殖细胞核抗原 (proliferating cell nuclear antigen, PCNA) 在基底区和迷宫区的表达下调、细胞周期相关基因 p53 和 p21 在胎盘迷路区表达增加，从而促进胎盘细胞的凋亡 [58, 59]。在正常妊娠中，11β-HSD2 的表达降低了胎盘活性内源性 GC 水平，从而限制了其对细胞凋亡的诱导。而卡宾诺酮抑制 11β-HSD2 活性，通过增加内源性 GC 在胎盘中的暴露刺激胎盘细胞凋亡并抑制胎儿生长 [60]。此外，孕期干扰素 (interferon, IFN) 暴露也会导致母胎界面细胞凋亡失调，从而引发流产。研究表明，妊娠大鼠体内注射 IFN 可促进胎盘界面的细胞 —— 主要是人绒毛滋养细胞和合胞滋养细胞的凋亡，其作用机制分为上调 IFN 调节因子 -1 (IRF-1) 表达和下调 Fas 配体 (Fas ligand, FasL) 表达两方面 [61]。IRF-1 在 Fas/CD95 介导的细胞凋亡中起关键促进作用。在细胞滋养细胞中，IFN 诱导 IRF-1，促进 caspase-3 的活性表达，导致细胞凋亡 [62]。IFN 可在妊娠各期降低 FasL 和 p53 mRNA 的表达水平，而 FasL 表达下调会导致胎盘免疫豁免特性的丧失 [63]。综上，激素、细胞因子过度暴露引发的母体应激可通过介导胎盘细胞的增殖与凋亡，影响妊娠过程和胎儿的宫内发育。

2.6 影响母胎界面免疫反应

母体应激可诱发母胎界面免疫反应改变，主要是导致巨噬细胞迁移抑制因子 (macrophage migration inhibitory factor, MIF) 的激活，进而引发下游的一系列细胞因子激活 [64]。妊娠期 MIF 在母体蜕膜和滋养层等部位的显著表达表明该因子在母胎界面中发挥免疫调节作用 [65]。MIF 具有特殊的促炎作用，可以影响巨噬细胞和淋巴细胞的功能，诱导多种促炎细胞因子 (肿瘤坏死因子 α、IFN-γ、IL-1β、IL-2、IL-6、IL-8、巨噬细胞炎症蛋白)、一氧化氮和前列腺素，同时拮抗 GC 对免疫应答的作用 [66, 67]。也有研究显示，MIF 通过下调蜕膜中的子宫自然杀伤细胞 (uterus natural killer, uNK) 活化受体，抑制其细胞活性 [68]。同时，研究显示，应激导致 MIF 在小鼠滋养层细胞高表达，还可通过促进滋养细胞巨细胞 (trophoblast giant cells) 分泌大量与催乳素 (prolactin) 密切相关的激素，如胎盘催乳素样蛋白 A (placenta prolactin-like protein A)，特异性作用于 uNK 细胞，降低其溶细胞活性，并调节着床部位 T 淋巴细胞的活性 [69]。此外，在妊娠早期的慢性可变应激暴露中，IL-6 和 IL-1β 在雄性子代胎盘中的含量显著高于雌性子代胎盘 [45]，这提示母体应激对免疫反应的影响具有一定的性别差异性，可能是导致性别倾向的妊娠并发症和疾病易感性的重要诱因。

母体应激可深刻影响胎儿发育的不同时期、不同方面。然而，胎儿在母体应激反应中受到的影响和具体机制仍未得到完全阐明；其发育过程与母体应激反应的联系尚不明了；相应干预措施亟待完善。而胎盘作为母体与子代相联系的纽带与屏障，其正常发育对妊娠结局、子代生长的重要性不言而喻。因此，母体应激影响胎儿发育的胎盘机制极其重要。母体应激反应是母体的全身性变化，母体应激时激素通过胎盘对胎儿发育的影响机制较为明了。但是现有的研究还未完全阐明母体应激时其他系统通过胎盘对胎儿产生的影响的具体机制，尤其是对母体应激时胎盘发育或功能异常的非基因组机制知之甚少。所以，深入开展此方向的研究，对因母体应激所致的胎盘发育异常进行早期干预治疗，有望显著降低胎儿的发育异常及出生缺陷，对改善母婴健康具有重大的理论价值和现实意义。

参考文献

1 Hemberger M, Hanna CW, Dean W. Mechanisms of early placental development in mouse and humans. Nat Rev Genet 2020; 21(1): 21–43.

2 Rubin R. Unraveling the mysteries of the human placenta. JAMA 2018; 320(24): 2511–2518.

3 Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol 2019; 15(5): 271–289.

4 Selvaratnam RJ, Wallace EM, Wolfe R, Anderson PJ, Davey MA. Association between iatrogenic delivery for suspected fetal growth restriction and childhood school outcomes. JAMA 2021; 326(2): 145–153.

5 Morsing E, Maršál K. Pre-eclampsia- an additional risk factor for cognitive impairment at school age after intrauterine growth restriction and very preterm birth. Early Hum Dev 2014; 90(2): 91–101.

6 Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Sheiner E. Long-term maternal atherosclerotic morbidity in women with pre-eclampsia. Heart 2015; 101(6): 441–446.

7 Jayet PY, Rimoldi SF, Stuber T, Salmòn CS, Hutter D, Rexhaj E, Thalmann S, Schwab M, Turini P, Sartori-Cucchia C, Nicod P, Villena M, Allemann Y, Scherrer U, Sartori C. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. Circulation 2010;

122(5): 488–494.
8 Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, Kylintireas I, Contractor H, Singhal A, Lucas A, Neubauer S, Kharbanda R, Alp N, Kelly B, Leeson P. Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? Hypertension 2010; 56(1): 159–165.
9 Challis JR. Endocrine disorders in pregnancy: stress responses in children after maternal glucocorticoids. Nat Rev Endocrinol 2012; 8(11): 621–630.
10 Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999; 286(5442): 1151–1158.
11 Ward IL, Weisz J. Maternal stress alters plasma testosterone in fetal males. Science 1980; 207(4428): 321–329.
12 Van den Bergh B, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, Hoyer D, Roseboom T, Räikkönen K, King S, Schwab M. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci Biobehav Rev 2020; 117: 26–64.
13 Jones CW, Esteves KC, Gray S, Clarke TN, Callerame K, Theall KP, Drury SS. The transgenerational transmission of maternal adverse childhood experiences (ACEs): Insights from placental aging and infant autonomic nervous system reactivity. Psychoneuroendocrinology 2019; 106: 21–27.
14 Romero G, Huth-Bocks A, Puro-Gallagher E, Riggs J. Maternal prenatal depression, PTSD, and problematic parenting: the mediating role of maternal perceptions of infant emotion. J Reprod Infant Psychol 2021; 39(2): 125–139.
15 Pastor V, Pallarés ME, Antonelli MC. Prenatal stress increases adult vulnerability to cocaine reward without affecting pubertal anxiety or novelty response. Behav Brain Res 2018; 339: 181–194.
16 Soliani F, Cabbia R, Kümpel VD, Batistela MF, Almeida AG, Yamauchi Junior L, Andrade T. Unpredictable chronic prenatal stress and manifestation of generalized anxiety and panic in rat's offspring. Prog Neuropsychopharmacol Biol Psychiatry 2018; 85: 81–97.
17 Greene CA, Chan G, McCarthy KJ, Wakschlag LS, Briggs-Gowan MJ. Psychological and physical intimate partner violence and young children's mental health: The role of maternal posttraumatic stress symptoms and parenting behaviors. Child Abuse Negl 2018; 77: 161–179.
18 Niehaus CE, Chaplin TM, Gonçalves SF, Semelsberger R, Thompson JC. Maternal stress and adolescent brain structure and function. Brain Behav 2019; 9(6): e01311.
19 Abbink MR, Schipper L, Naninck E, de Vos C, Meier R, van der Beek EM, Lucassen PJ, Korosi A. The effects of early life stress, postnatal diet modulation, and long-term Western-style diet on later-life metabolic and cognitive outcomes. Nutrients 2020; 12(2): 570.
20 Heim CM, Entringer S, Buss C. Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology 2019; 105: 121–137.
21 Valsamakis G, Papatheodorou D, Chalarakis N, Manolikaki M, Margeli A, Papassotiriou I, Barber TM, Kumar S, Kalantaridou S, Mastorakos G. Maternal chronic stress correlates with serum levels of cortisol, glucose and C-peptide in the fetus, and maternal non chronic stress with fetal growth. Psychoneuroendocrinology 2020; 114: 104591.
22 Kasture VV, Sundrani DP, Joshi SR. Maternal one carbon metabolism through increased oxidative stress and disturbed angiogenesis can influence placental apoptosis in preeclampsia. Life Sci 2018; 206: 61–69.
23 Zhang ZY (张治宇), Li J, Zuo Q, Gao Y, Xu YJ, Ni X, Gao L. Programming effect of glucocorticoid exposure during rat pregnancy on cardiac functions and expression of serum- and glucocorticoid-regulated protein kinase 1 in offspring. Acad J Sec Mil Med Univ (第二军医大学学报) 2016; 37(6): 661–676 (in Chinese).
24 Peng J, Zhou Y, Zhang Z, Wang Z, Gao L, Zhang X, Fang Z, Li G, Chen H, Yang H, Gao L. The detrimental effects of glucocorticoids exposure during pregnancy on offspring's cardiac functions mediated by hypermethylation of bone morphogenetic protein-4. Cell Death Dis 2018; 9(8): 834.
25 Garcia-Flores V, Romero R, Furcron AE, Levenson D, Galaz J, Zou C, Hassan SS, Hsu CD, Olson D, Metz G, Gomez-Lopez N. Prenatal maternal stress causes preterm birth and affects neonatal adaptive immunity in mice. Front Immunol 2020; 11: 254.
26 Ouchi R, Kawano T, Yoshida H, Ishii M, Miyasaka T, Ohkawara Y, Takayanagi M, Takahashi T, Ohno I. Maternal separation as early-life stress causes enhanced allergic airway responses by inhibiting respiratory tolerance in mice. Tohoku J Exp Med 2018; 246(3): 151–165.
27 Liang Y, Wang P, Zhao M, Liang G, Yin H, Zhang G, Wen H, Lu Q. Demethylation of the FCER1G promoter leads to FcεRI overexpression on monocytes of patients with atopic dermatitis. Allergy 2012; 67(3): 421–430.
28 McLean MA, Simcock G, Elgbeili G, Laplante DP, Kildea S, Hurrion E, Lequertier B, Cobham VE, King S. Disaster-related prenatal maternal stress, and childhood HPA-axis regulation and anxiety: The QF2011 Queensland Flood Study. Psychoneuroendocrinology 2020; 118: 104716.
29 Vale W, Spiess J, Rivier C, Rivier J. Characterization of a

41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981; 213(4514): 1391–1397.
30 Thomson M. The physiological roles of placental corticotropin releasing hormone in pregnancy and childbirth. J Physiol Biochem 2013; 69(3): 551–573.
31 Makrigiannakis A, Vrekoussis T, Zoumakis E, Navrozoglou I, Kalantaridou SN. CRH receptors in human reproduction. Curr Mol Pharmacol 2018; 11(1): 81–87.
32 Kim EY, Choi JE, Kim M, Hong J, Park Y. N-3 PUFA have antidepressant-like effects via improvement of the HPA-axis and neurotransmission in rats exposed to combined stress. Mol Neurobiol 2020; 57(9): 3861–3874.
33 Vaughan OR, Fisher HM, Dionelis KN, Jeffreys EC, Higgins JS, Musial B, Sferruzzi-Perri AN, Fowden AL. Corticosterone alters materno-fetal glucose partitioning and insulin signalling in pregnant mice. J Physiol 2015; 593(5): 1301–1321.
34 Murphy BE, Clark SJ, Donald IR, Pinsky M, Vedady D. Conversion of maternal cortisol to cortisone during placental transfer to the human fetus. Am J Obstet Gynecol 1974; 118(4): 531–541.
35 Benediktsson R, Calder AA, Edwards CR, Seckl JR. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clin Endocrinol (Oxf) 1997; 46(2): 161–166.
36 Salvante KG, Milano K, Kliman HJ, Nepomnaschy PA. Placental 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) expression very early during human pregnancy. J Dev Orig Health Dis 2017; 8(2): 149–154.
37 Shi XT, Zhu HL, Xiong YW, Liu WB, Zhou GX, Cao XL, Yi SJ, Dai LM, Zhang C, Gao L, Xu DX, Wang H. Cadmium down-regulates 11β-HSD2 expression and elevates active glucocorticoid level via PERK/p-eIF2α pathway in placental trophoblasts. Chemosphere 2020; 254: 126785.
38 Mina TH, Räikkönen K, Riley SC, Norman JE, Reynolds RM. Maternal distress associates with placental genes regulating fetal glucocorticoid exposure and IGF2: Role of obesity and sex. Psychoneuroendocrinology 2015; 59: 111–122.
39 Braithwaite EC, Kundakovic M, Ramchandani PG, Murphy SE, Champagne FA. Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. Epigenetics 2015; 10(5): 401–417.
40 Motta-Mena NV, Puts DA. Endocrinology of human female sexuality, mating, and reproductive behavior. Horm Behav 2017; 91: 11–35.
41 Bronson SL, Bale TL. The placenta as a mediator of stress effects on neurodevelopmental reprogramming. Neuropsychopharmacology 2016; 41(1): 201–218.
42 Valsamakis G, Papatheodorou D, Chalarakis N, Manolikaki M, Margeli A, Papassotiriou I, Barber TM, Kumar S, Kalantaridou S, Mastorakos G. Maternal chronic stress correlates with serum levels of cortisol, glucose and C-peptide in the fetus, and maternal non chronic stress with fetal growth. Psychoneuroendocrinology 2020; 114: 104591.
43 Valsamakis G, Papatheodorou DC, Chalarakis N, Vrachnis N, Sidiropoulou EJ, Manolikaki M, Mantzou A, Margeli A, Papassotiriou I, Chrousos GP, Mastorakos G. In pregnancy increased maternal STAI trait stress score shows decreased insulin sensitivity and increased stress hormones. Psychoneuroendocrinology 2017; 84: 11–16.
44 Montoya-Williams D, Quinlan J, Clukay C, Rodney NC, Kertes DA, Mulligan CJ. Associations between maternal prenatal stress, methylation changes in IGF1 and IGF2, and birth weight. J Dev Orig Health Dis 2018; 9(2): 211–222.
45 Hiden U, Maier A, Bilban M, Ghaffari-Tabrizi N, Wadsack C, Lang I, Dohr G, Desoye G. Insulin control of placental gene expression shifts from mother to foetus over the course of pregnancy. Diabetologia 2006; 49(1): 121–131.
46 Bronson SL, Bale TL. Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal antiinflammatory treatment. Endocrinology 2014; 155(7): 2631–2646.
47 Fowden AL, Sferruzzi-Perri AN, Coan PM, Constancia M, Burton GJ. Placental efficiency and adaptation: endocrine regulation. J Physiol 2009; 587(Pt 14): 3451–3472.
48 Ding GL, Wang FF, Shu J, Tian S, Jiang Y, Zhang D, Wang N, Luo Q, Zhang Y, Jin F, Leung PC, Sheng JZ, Huang HF. Transgenerational glucose intolerance with Igf2/H19 epigenetic alterations in mouse islet induced by intrauterine hyperglycemia. Diabetes 2012; 61(5): 1131–1142.
49 Mairesse J, Lesage J, Breton C, Bréant B, Hahn T, Darnaudéry M, Dickson SL, Seckl J, Blondeau B, Vieau D, Maccari S, Viltart O. Maternal stress alters endocrine function of the feto-placental unit in rats. Am J Physiol Endocrinol Metab 2007; 292(6): E1526–E1533.
50 Cuffe JS, Walton SL, Singh RR, Spiers JG, Bielefeldt-Ohmann H, Wilkinson L, Little MH, Moritz KM. Mid- to late term hypoxia in the mouse alters placental morphology, glucocorticoid regulatory pathways and nutrient transporters in a sex-specific manner. J Physiol 2014; 592(14): 3121–3141.
51 Hu C, Yang Y, Li J, Wang H, Cheng C, Yang L, Li Q, Deng J, Liang Z, Yin Y, Xie Z, Tan C. Maternal diet-induced obesity compromises oxidative stress status and angiogenesis in the porcine placenta by upregulating Nox2 expression. Oxid Med Cell Longev 2019; 2019: 2481592.
52 Ozmen A, Unek G, Kipmen-Korgun D, Cetinkaya B, Avcil Z,

Korgun ET. Glucocorticoid exposure altered angiogenic factor expression via Akt/mTOR pathway in rat placenta. Ann Anat 2015; 198: 31–40.

53 Sahay AS, Jadhav AT, Sundrani DP, Wagh GN, Mehendale SS, Chavan-Gautam P, Joshi SR. VEGF and VEGFR1 levels in different regions of the normal and preeclampsia placentae. Mol Cell Biochem 2018; 438(1–2): 141–152.

54 Reynolds LP, Vonnahme KA, Lemley CO, Redmer DA, Grazul-Bilska AT, Borowicz PP, Caton JS. Maternal stress and placental vascular function and remodeling. Curr Vasc Pharmacol 2013; 11(5): 561–593.

55 Kim SY, Lee EH, Kim EN, Son WC, Kim YH, Park SY, Kim IS, Kim JE. Identifying Stabilin-1 and Stabilin-2 double knockouts in reproduction and placentation: A descriptive study. Int J Mol Sci 2020; 21(19): 7235.

56 Waddell BJ, Hisheh S, Dharmarajan AM, Burton PJ. Apoptosis in rat placenta is zone-dependent and stimulated by glucocorticoids. Biol Reprod 2000; 63(6): 1911–1917.

57 Cuffe JSM, Saif Z, Perkins AV, Moritz KM, Clifton VL. Dexamethasone and sex regulate placental glucocorticoid receptor isoforms in mice. J Endocrinol 2017; 234(2): 81–100.

58 Er H, Acar N, Kipmen-Korgun D, Celik-Ozenci C, Ustunel I, Asar M, Korgun ET. Determination of PCNA, cyclin D3, p27, p57 and apoptosis rate in normal and dexamethasone-induced intrauterine growth restricted rat placentas. Acta Histochem 2015; 117(2): 131–147.

59 Panettieri RA, Schaafsma D, Amrani Y, Koziol-White C, Ostrom R, Tliba O. Non-genomic effects of glucocorticoids: An updated view. Trends Pharmacol Sci 2019; 40(1): 31–49.

60 Zhao X, Jiang Y, Jiang T, Han X, Wang Y, Chen L, Feng X. Physiological and pathological regulation of autophagy in pregnancy. Arch Gynecol Obstet 2020; 302(2): 291–303.

61 Sun QH, Peng JP, Xia HF, Yang Y. IFN-gamma promotes apoptosis of the uterus and placenta in pregnant rat and human cytotrophoblast cells. J Interferon Cytokine Res 2007; 27(7): 561–578.

62 Qin S, Zhang Y, Zhang J, Tian F, Sun L, He X, Ma X, Zhang J, Liu XR, Zeng W, Lin Y. SPRY4 regulates trophoblast proliferation and apoptosis via regulating IFN-γ-induced STAT1 expression and activation in recurrent miscarriage. Am J Reprod Immunol 2020; 83(6): e13234.

63 Leon-Martinez D, Robinson JF, Zdravkovic T, Genbacev O, Gormley M, Mcmaster M, Fisher SJ, Bianco K. Trisomy 21 is associated with Caspase-2 upregulation in cytotrophoblasts at the maternal-fetal interface. Reprod Sci 2020; 27(1): 101–109.

64 Ulmer-Yaniv A, Djalovski A, Priel A, Zagoory-Sharon O, Feldman R. Maternal depression alters stress and immune biomarkers in mother and child. Depress Anxiety 2018; 35(12): 1141–1157.

65 Jovanović Krivokuća M, Vilotić A, Stefanoska I, Bojić-Trbojević Ž, Vićovac L. Macrophage migration inhibitory factor in human early pregnancy events and association with placental pathologies. Placenta 2021; S0143-4004(21)00050-3. doi: 10.1016/j.placenta.2021.02.007.

66 Calandra T, Bucala R. Macrophage migration inhibitory factor (MIF): A glucocorticoid counter-regulator within the immune system. Crit Rev Immunol 2017; 37(1–6): 351–370.

67 Hamelin-Morrissette J, Dallagi A, Girouard J, Ravelojaona M, Oufqir Y, Vaillancourt C, Van Themsche C, Carrier C, Reyes-Moreno C. Leukemia inhibitory factor regulates the activation of inflammatory signals in macrophages and trophoblast cells. Mol Immunol 2020; 120: 31–42.

68 Ruiz-Rosado J, Olguín JE, Juárez-Avelar I, Saavedra R, Terrazas LI, Robledo-Avila FH, Vazquez-Mendoza A, Fernández J, Satoskar AR, Partida-Sánchez S, Rodriguez-Sosa M. MIF promotes classical activation and conversion of inflammatory Ly6C(high) monocytes into TipDCs during murine toxoplasmosis. Mediators Inflamm 2016; 2016: 9101762.

69 Segerer SE, Rieger L, Kapp M, Dombrowski Y, Müller N, Dietl J, Kämmerer U. MIC-1 (a multifunctional modulator of dendritic cell phenotype and function) is produced by decidual stromal cells and trophoblasts. Hum Reprod 2012; 27(1): 201–209.