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辅助生殖技术后代远期血压变化及影响因素

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摘要　自1978年以来, 辅助生殖技术(assisted reproductive technology, ART)的应用愈加广泛, 其安全性也一直备受关注, 人们对通过ART受孕出生的后代的健康和发育提出了担忧。目前大多数研究发现ART后代血压高于自然妊娠后代。既往文献报道ART后代血压升高可能与不良的围产期结局如早产、胎儿生长受限、胎盘功能不全的发生率增加, 器官结构功能的改变以及后代表观遗传的改变有关, 且ART后代青少年血压升高导致成年期心血管疾病发病风险增加。该文通过总结相关文献, 从ART后代远期血压变化、影响因素及其可能的机制进行详细综述。

关键词　生殖技术; 辅助; 儿童; 血压

Long-Term Blood Pressure Changes and Influencing Factors in the Offspring of Assisted Reproductive Technology

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Abstract　ART (assisted reproductive technology) has become more widespread since 1978, and there has always attention about the safety of this technology, raising concerns about the health and development of children conceived through ART. Most current studies have found an increased risk of elevated blood pressure in ART offspring, which may be related to adverse perinatal outcomes such as preterm birth, fetal growth restriction, increased incidence of placental insufficiency, alterations in organ structure and function, and posterior epi-

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genetic changes, and leads to an increased risk of cardiovascular disease in adulthood. This article summarizes the relevant literature and reviews the long-term blood pressure changes, influencing factors and possible mechanisms of ART offspring.

Keywords reproductive techniques; assisted; child; blood pressure

不孕症(infertility)在世界范围内发生率为10%~20%[1]。随着医疗技术发展, 辅助生殖技术(assisted reproductive technology, ART)被广泛应用于不孕夫妇。ART包括体外受精–胚胎移植(*in vitro* fertilization, IVF)及其衍生技术, 如卵胞质内单精子注射(intracytoplasmic sperm injection, ICSI)技术、胚胎种植前遗传学诊断(preimplantation genetic diagnosis, PGD)、胚胎的冷冻和解冻等。自ART诞生以来, 全世界已经有超过1 000万通过ART出生的婴儿[2]。目前已有较多研究关注于ART后代远期健康。在心血管健康方面, 既往研究发现ART后代青少年存在血管过早老化、血压轻度升高的现象[3-4]。因此, 考虑到青少年血压对成年期心血管疾病的重要性, 本文对于ART后代远期血压变化及其影响因素进行详细综述。

目前关于ART后代远期血压变化的研究结论尚存在争议[5](表1), 但我们认为ART后代血压在生理范围内高于自然妊娠后代。虽然有研究表明ART后代血压和自然妊娠后代血压无明显差异[6](表1), 但大多数研究在校正家族遗传等外界因素影响后发现通过辅助生殖技术出生的后代血压存在生理范围内的轻微升高[7-8](表1), 且一项纳入了2~26岁的自然妊娠(35 284名)和ART后代(654名)的荟萃分析表明, ART后代随年龄的增加, 血压逐渐高于自然妊娠后代[5], 揭示了ART后代和自然妊娠后代的不同血压变化轨迹, 即ART后代在青春期后血压升高显著快于自然妊娠后代。鉴于目前关于ART后代成年期后血压变化的研究尚且不足, 因此对于ART后代成年后的血压改变未来仍需要进一步随访。

1 ART后代血压变化对远期心血管健康的影响

青春期轻度的血压升高可能会通过导致动脉内膜中层厚度增加、影响左心室结构和功能等引起成年后的心血管疾病以及高血压的发病风险增加。有研究表明, 青少年期血压增长速度越快, 其成年期动脉内膜中层厚度(高增长速度组*vs*低增长速度组: 0.55 *vs* 0.5 mm)及左心室质量指数(高增长速度组*vs*低增长速度组: 79.23 *vs* 65.41 g/m^2)越大[11], 且青少年血压与成年期的内膜中层厚度呈正相关[12], 而颈动脉内膜厚度作为心血管疾病的亚临床标志物, 其升高提示心血管疾病的发病风险增加。同时, 一项纳入了5 035名受试者的多队列研究表明青春期血压升高与成年后的高血压疾病相关[青少年收缩压(systolic blood pressure, SBP)＞90百分位数, 成年人高血压患病几率显著增加, OR值为3.0(2.2, 4.1)][13]。综上所述, ART后代青春期的血压升高会影响其远期心血管健康, 进而导致心血管疾病发病和死亡风险增加。

2 影响ART后代血压变化的相关因素

ART过程包含超促排卵、胚胎培养、胚胎冷冻等多个环节, 目前仅有部分文献报道胚胎冷冻、卵巢过度刺激综合征以及胚胎延长培养与ART后代的血压的相关性。目前研究发现, 不同的胚胎移植方案例如冻胚和鲜胚移植后代的血压无显著差异, ZHANG等[9](表1)的一项纳入4~11岁的鲜胚(1 091名)和冻胚(685名)后代的研究证实冻胚和鲜胚后代血压无明显差异。ZHU等[10](表1)的一项纳入3~6岁的鲜胚(1 069名)和冻胚(487名)后代的研究也表明冻胚鲜胚后代血压无明显差异。卵巢过度刺激综合征是超促排卵过程中的并发症之一, 既往一项纳入3~6岁的卵巢过度刺激综合征(126名)和非卵巢过度刺激综合征(1 069名) ART后代的研究报道ART中发生卵巢过度刺激的后代血压显著高于自然妊娠后代[10], 提示超促排卵过程中的高雌激素水平可能对后代血压有不良影响; 另外, 胚胎延长培养也可能对后代健康有不良影响, ALJAHDALI等[14]的一项动物实验表明, 随着体外培养时间的延长, ART后代的血压升高[15]。但是目前尚无关于胚胎延长培养影响血压的人群流行病学研究。

3 ART后代血压升高的可能机制

ART后代血压高于自然妊娠可能与ART导致早产、胎儿生长受限和胎盘功能障碍等围产期并发症的风险增加从而进一步导致器官功能改变有关; 同

表1 ART后代血压纳入文献特征

Table 1 Characteristics of the included studies about ART offspring blood pressure

研究 Study	地区 Area	样本量 Sample size	平均年龄 Mean age	主要发现 Main findings	参考文献 References
ELHAKEEM A, et al. (2023)	Europe Australia Singapore	35 284 natural pregnancy offspring *vs* 654 ART offspring	2-26	The ART offspring have a trend towards increased blood pressure in early adulthood. 26 years old ART offspring *vs* natural pregnancy offspring, SBP (systolic blood pressure): 4.12 mmHg [0.19-8.06], DBP (diastolic blood pressure): 1.00 mmHg [–1.90-3.89]	[5]
WIJS L A, et al. (2022)	Australia	1 457 natural pregnancy offspring *vs* 163 ART offspring	0-17	There was no significant difference in blood pressure between ART offspring and natural pregnancy offspring [ART offspring *vs* natural pregnancy offspring, systolic blood pressure SBP: (120±3) mmHg *vs* (120±3) mmHg; DBP: (56±6) mmHg *vs* (57±6) mmHg]	[6]
CUI L, et al. (2021)	China	382 natural pregnancy offspring *vs* 382 ART offspring	6-10	The ART offspring had elevated BP and unfavorable changes in left ventricular structure and function [ART offspring *vs* natural pregnancy offspring, SBP: (105.5±6.9) mmHg *vs* (103.5±8.4) mmHg; DBP: (67.2±5.6) mmHg *vs* (62.2±6.3) mmHg; left ventricular ejection fraction: (64.61±3.20)% *vs* (66.70±3.89)%; left ventricular mass index: (31.97±5.04) g/m$^{2.7}$ *vs* (28.28±3.54) g/m$^{2.7}$]	[7]
MEISTER T A, et al. (2018)	Europe	43 natural pregnancy offspring *vs* 54 ART offspring	14-20	ART offspring had elevated blood pressure [ART offspring *vs* natural pregnancy offspring, SBP: (119.8±9.1) mmHg *vs* (115.7±7.0) mmHg; DBP: (71.4±6.1) mmHg *vs* (69.1±4.2) mmHg]	[8]
ZHANG B, et al. (2022)	China	1 091 fresh embryo transfer offspring *vs* 685 frozen embryo transfer offspring	4-11	There was no significant difference in blood pressure between frozen and fresh embryo transfer oofspring [fresh embryo transfer offspring *vs* frozen embryo transfer offspring, SBP: (98.3±8.81) mmHg *vs* (99.2±9.11) mmHg; DBP: (59.1±8.32) mmHg *vs* (61.0±8.51) mmHg]	[9]
ZHU Y, et al. (2022)	China	1 069 fresh embryo transfer offspring *vs* 487 frozen embryo transfer offspring 126 ovarian hyperstimulation syndrome offspring *vs* 1 069 non-ovarian hyperstimulation syndrome offspring	3-6	There was no significant difference in blood pressure between frozen and fresh embryo transfer oofspring, ovarian hyperstimulation syndrome leads to higher blood pressure in offspring than natural pregnancy [fresh embryo transfer offspring *vs* frozen embryo transfer offspring, SBP: (99.56±8.50) mmHg *vs* (99.49±8.91) mmHg; DBP: (42.74±9.50) mmHg *vs* (43.12±9.33) mmHg][ovarian hyperstimulation syndrome ART offspring *vs* non-ovarian hyperstimulation syndrome offspring, SBP: (101.93±8.17) mmHg *vs* (99.49±8.91) mmHg; DBP: (58.75± 8.48) mmHg *vs* (56.55±8.02) mmHg]	[10]

时ART可能会直接或者通过影响母体生殖内分泌系统导致身体各器官表观遗传的稳定性发生变化，引起器官结构功能的改变进而导致远期心血管疾病发生风险增加[16-19]。

3.1 心脏代谢

有研究指出通过ART受孕的儿童具有较差的心脏代谢特征[20]，ALCARAZ等[21]的一项包括6个月的由ART受孕的儿童(100名)和自然妊娠儿童(100名)的前瞻性队列研究显示ART受孕的儿童在胎儿时期存在心脏重塑，如具有更厚的心肌壁或出现球型心，而这种改变会在产后持续存在。ART受孕常导致早产和低出生体重，而早产和低出生体重可能引

起出生后生长加速, 新生儿早期生长加速可能会导致心脏亚硝化以及氧化应激水平和DNA损伤程度增加, 从而使得心血管疾病如高血压的发病风险增加[22-24]。ART的促排卵过程, 可能影响滤泡颗粒细胞的RNA和3′5′cAMP等分子跨透明带[25], 进而影响其与卵母细胞之间的通信, 导致卵母细胞的发育异常以及表观遗传改变[26], 进而引起胚胎的表观遗传改变(如*Mat2a*、*Dnmt1*、*Dnmt3a*、*Dnmt3b*、*Dnmt3l*、*Mecp2*、*Mbd3*、*Ezh2*、*Suz12*、*Rnf2*和*Yy1*的表达量增加)、胚胎发育障碍以及胎儿生长发育障碍(如胎儿发育迟缓、体重较轻、骨骼骨化迟缓或不完全), 导致后代心脏结构和功能的不利改变[27-29], 还可以通过影响宫内激素环境进而影响血压调节相关代谢系统的表观遗传修饰而发挥作用[25,30-31]。CHEN等[32]的研究发现, 在小鼠模型中, ART小鼠全基因组水平DNA甲基化变化可能和心脏代谢异常风险增加有关[33], 其后代印记基因*Dhcr7*、*Igf2*、*Mest*和*Smoc1*的表达水平降低, *Igf2*和*Mest*印记对照区的DNA甲基化水平异常升高, 而心脏中差异表达基因主要富集于RNA合成和加工以及心血管系统发育通路, 导致后代心脏发育以及代谢异常[32]。这些因素均可能会对ART后代的血压产生不利影响。

3.2 血管

SCHERRER等[34]纳入65名(11.1±2.4)岁的ART儿童和57名(11.9±2.3)岁的自然妊娠儿童的研究发现, 在体循环中, ART组儿童的血流介导的血管扩张比正常受孕的儿童低25%, 脉搏波传导速度作为动脉僵硬度的广泛使用的替代指标, 其在ART儿童中明显快于自然妊娠的后代[(6.6±1.8) *vs* (6.1±1.9) m/s], 同时ART儿童的颈动脉内膜–中层厚度也显著增加[(420±50) *vs* (360±60) μm], 说明ART后代较正常受孕的儿童有较差的动脉扩张性和血管弹性以及较高的血管僵硬度, 并发生了血管结构的改变, 2013年REX-HAJ等[35]的研究表示, 在ART后代小鼠中内皮功能缺陷可以转化为血压升高, 其内皮功能障碍与内皮一氧化氮合酶(endothelial nitric oxide synthase, *eNOS*)基因的表观遗传改变有关, ART改变了*eNOS*的启动子甲基化, 从而使得血管*eNOS*表达量降低, ART小鼠的一氧化氮血浆浓度下降导致内皮依赖性血管舒张功能降低, 是血管衰老和动脉高血压的基础[36]。此外, 印记基因*H19*、*Gtl2*和*Peg3*的甲基化在ART小鼠的主动脉中发生了改变, 与血管功能障碍密切相关[35]。血管的结构以及功能的不利改变会导致血压升高的风险增加[37]。

3.3 内分泌系统

3.3.1 *胰岛素抵抗* 胰岛素抵抗是一种影响很多器官的全身性疾病, 是心血管危险因素以及心血管疾病早期病理生理学的关键因素, 也被认为是高血压的重要致病因素[38-39]。GKOUROGIANNI等[40]的研究分别纳入了(6.8±2.1)岁的ART后代(42名)和自然妊娠后代(42名), 发现ART后代与自然妊娠后代相比, 与肥胖、胰岛素抵抗和代谢综合征相关的36种代谢物存在明显差异, 而胰岛素抵抗的易感性升高可能导致ART后代心脏代谢紊乱的风险增加, 动物研究也表明ART小鼠后代表现为胰岛素抵抗的风险增加, 其中ART后代肝脏胰岛素代谢的主要通路PI3K/AKT通路明显受损, 导致其糖原合成减少、糖酵解水平增加以及糖异生增强, 并且冻胚移植的后代代谢紊乱的风险比鲜胚移植更高[41-42]。胰岛素抵抗本身及其导致的代谢紊乱可以通过抑制PI3K-NO通路和激活MAPK-ET-1通路导致血管内皮功能障碍以及血管收缩, 进而导致血压调节功能受损, 引起血压升高[43-44]。此外, ARTUNC等[45]的研究表明, 远端小管钠潴留涉及PI3K-SGK1对上皮钠通道的刺激, 近端小管的钠潴留与IRS-2的表达和AKT的磷酸化有关[46], 提示胰岛素信号转导在足细胞活力和肾小管功能中具有重要作用, 说明盐敏感性动脉高血压与胰岛素抵抗有关联[47]。因此, ART后代胰岛素抵抗风险增加可能导致ART后代血压升高。

3.3.2 *生殖内分泌* ART过程中的卵巢刺激、胚胎移植、黄体支持等过程会导致母体的激素发生与自然妊娠不同的变化。如ART导致的母体更高的雌激素水平往往提示更高剂量的外源性促性腺激素, 这可能通过卵母细胞、胚胎及其微环境的表观遗传修饰和氧化应激状态影响下一代, 导致后代出现甲状腺功能异常等表现[48-51], 可能与ART后代血压升高有一定相关性。有研究发现ART后代促甲状腺激素水平明显增加[52]; GKOUROGIANNI等[40]的一项纳入(6.8±2.1)岁的ART(42名)和自然妊娠(42名)儿童的研究发现ART后代三碘甲状腺原氨酸水平增加。PENOVA等[53]的队列研究纳入了(14±0.9)岁的ART后代(134名)以及自然妊娠后代(1 359名)发现ART后代四碘甲状腺原氨酸水平升高[48]。促甲状腺激素、三碘甲状腺原氨酸、四碘甲状腺原氨酸水平

升高可以通过影响内皮细胞功能、升高动脉僵硬度从而导致动脉血压的增加[54], 进而引起其心血管系统的健康障碍; 此外, 卵巢刺激导致的孕激素升高也可能会导致后代的血压升高, 但目前其具体机制尚不明确[55]。

3.3.3 RAS(renin-angiotensin system, RAS)系统 RAS是调节血压以及体内液体和电解质平衡的主要生理系统。RAS在几种心血管疾病的发病机制以及心脏重塑中起着至关重要的作用, 除了经典的全身性RAS外, 局部RAS在心脏、大动脉、肾脏等器官中起作用, 甚至在单细胞中起作用, 以进一步参与心血管调节[56-57]。ART导致的母亲宫内环境改变会导致胎儿*At1r*的甲基化改变, 从而导致*At1r*下游信号通路和后代RAS的改变进而影响血压[25,31]。配子发生和早期发育是基因组印记擦除、获取和维持的关键时期, 早期胚胎中的表观遗传改变会影响其发育潜力[27,30,58]。在体外受精过程中, 当配子和胚胎暴露于非生理环境(如酸碱度改变、可见光暴露、氧压升高等)中时[59-60], 这种非生理的环境可以通过导致卵母细胞和受精卵的DNA损伤、线粒体变性以及细胞活性氧的产生引起RAS基因表达的改变[59]。在ART受孕小鼠心肌组织中RAS相关基因如*Ace*、*Agt*、*Agtr1b*、*Agtr2*、*Col1*和*Col3*以及蛋白质如REN1、ACE、AGTR1和CTGF表达与自然妊娠的后代有明显差异。其中*Col1*和*Col3*基因分布在心肌中, 对心肌壁的弹性起重要作用[61-62], *Col1*和*Col3*基因的异常表达会影响心血管结构的正常发育[63-64]。而血管紧张素原首先转化为血管紧张素I, 然后血管紧张素I通过血管紧张素转换酶水解为血管紧张素II发挥作用[65], *Agtr1*和*Agtr2*则通过影响血管紧张素II的功能来影响血压[65]。因此这些基因的改变可能通过造成RAS系统的功能障碍进而导致血压调节异常。此外, RAS系统中相应的基因DNA甲基化的修饰和miRNA表达的异常也可能参与调节心脏基因表达, 其中ART后代表现出*Col1*中CpG位点的甲基化水平降低, 以及miR-100、miR-297和miR-758的显著上调, miR-100、miR-297和miR-758分别通过与*Col3*、*Agtr1a*和*Col1a2*相互作用导致心肌细胞增殖, 从而影响ART后代的心血管健康[66]。

3.4 泌尿系统

目前关于ART对于后代肾脏的直接影响还尚不清楚, 但ART常与胎盘异常、胎儿生长受限、胎盘相关并发症如早产等产科不良结局的风险有关[67-68], 而这些因素会进一步影响肾脏的发育。SUTHERLAND等[69]对32位足月死产婴儿以及28位早产死产婴儿的肾脏进行病理学检查发现, 早产死产婴儿的功能性肾单位数目更少, 异形肾小球数目增加, 提示其存在肾脏过度滤过。肾单位缺乏的大鼠中, 肾小球滤过率降低、蛋白尿增加、尿钠排泄降低, 证实了BRENNER[70]等最初提出的先天性肾单位数量缺陷可能导致滤过表面积减小从而限制肾钠排泄进而导致原发性高血压的假设[71-72]。BASERGA等[73]的实验表明, 大鼠子宫胎盘功能不全导致出生时与肾脏发育有关的血管生成因子Vegf基因和蛋白的表达量降低, 导致肾单位数目减少。DOAN等[74]发现胎儿生长受限改变了对于肾脏发育具有重要作用的DNA甲基转移酶(DNMT1和DNMT3A)以及印记基因(*Peg3*、*Snrpn*、*Kcnq1*和*Cdkn1c*)的表达, 从而影响了肾脏表型改变, 如肾脏重量变轻。最近的一项研究对ART后代成年小鼠器官进行了RNA测序, 发现其中10个(*Lbp*、*Hspe1-rs1*、*Prxl2b*、*Pfn3*、*Gm9008*、*Bglap3*、*Col8a1*、*Hmgcr*、*Ero1lb*、*Ifi44l*)与肾脏疾病和功能有关的基因和自然妊娠的后代有差异, 但目前对于这些基因可能会对肾脏产生的具体影响还需要进一步的研究[75]。这些因素都可能与以后的血压升高、蛋白尿和肾脏疾病风险增加有关[76-77]。

4 研究总结及展望

全世界范围内通过ART受孕的儿童数量不断增加。ART过程中的非生理性环境和操作可能会通过影响配子胚胎发育及其表观遗传、器官结构和功能导致后代的远期血压升高, 同时也能够增加不良围产期结局的风险导致后代的不良心血管健康结局。但由于目前对于ART后代健康的研究多集中在青春期, 对ART后代远期健康追踪不足, 因此, 关于ART对后代血压的潜在作用还需要长期持续的队列研究。同时也需要进一步对ART后代血压升高的机制进行探索, 在生命早期及儿童期进行相关干预, 改善ART后代远期健康, 可能有助于预防成人疾病的发生发展, 对降低社会医疗压力具有重要的意义。

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