

辅助生殖技术受孕儿童健康状况的研究进展

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摘要: 辅助生殖技术(ART)自 1978 年问世以来,为治疗不孕不育开创了新时代。目前 ART 在全球广泛应用,累计已诞生超过 1 000 万名 ART 受孕儿童。ART 子代的健康状况和生活质量已成为全球医学界及社会各界关注的重要公共卫生问题。本文综述了近年来国内外关于 ART 受孕儿童健康状况的研究,重点探讨围产期结局、子代代谢状况及行为认知发育是否存在风险。结果显示,目前多数研究认为 ART 受孕儿童整体健康状况良好。建议推广单胚胎移植以减少多胎妊娠,从源头降低 ART 儿童围生期并发症及神经发育异常的风险;同时应持续关注其长期健康状况,为优化相关人群的医疗保健提供科学依据。

关键词: 辅助生殖技术; 糖代谢; 脂代谢; 神经发育; 儿童

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Advances in health status of children conceived through assisted reproductive technology

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Abstract: Since the advent of assisted reproductive technology (ART) in 1978, a new era has been opened for infertility management. Currently, ART is widely implemented across the globe, with over 10 million children born to date. The health status and quality of life of ART offspring have evolved into a critical public health concern, drawing extensive attention from the global medical community and society. This paper reviews recent domestic and international research on the health outcomes of ART-conceived children, with a specific focus on three core domains: perinatal outcomes, metabolic status, and potential risks associated with behavioral and cognitive development. Synthesis of the evidence indicates that the overall health status of ART-conceived children is favorable. It is recommended that single embryo transfer be prioritized to reduce multiple pregnancies, thereby mitigating the risks of perinatal complications and neurodevelopmental abnormalities at the source. Meanwhile, sustained surveillance of long-term health trajectories is warranted to facilitate the optimization of healthcare services for this population.

Keywords: assisted reproductive technology; glucose metabolism; lipid metabolism; neural development; children

不孕不育是 21 世纪影响人类生活和健康的三大主要疾病之一^[1]。辅助生殖技术(assisted reproduction technology, ART)的出现和发展为不孕不育夫妇孕育后代带来了希望。目前全球每年有超过 39 万 ART 受孕儿童出生,从 ART 应用至今约 40 年已经有超过 1 000 万 ART 受孕儿童出生^[2]。ART 受孕出生儿童的生命健康和生活质量是医学界、社会和 ART 群体关注的热点问题,也是一个重要的公共卫生问题。目前全球范围内已经建立了相关数据库,用于监测和观察 ART 母亲及儿童短期、

长期的健康状况^[3-4]。ART 儿童健康状况的证据仍然较少。本文就 ART 受孕儿童的短期、长期的健康状况进行综述,重点是身体代谢、心理运动发育情况,讨论潜在机制,以期为 ART 儿童的医疗保健提供参考。

1 辅助生殖技术受孕儿童的围生期结局

不少研究提出围生期并发症的可能性增加^[5-7]。从胎儿的角度来看,早产和宫内生长受限是目前讨论最多的内容。丹麦的一项大型全国性队列研究纳

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入了 57 964 名 ART 儿童和 1 183 070 名自然受孕 (natural conception, NC) 儿童, 结果显示 ART 受孕儿童更容易出现早产及低出生体重^[8]。Ohuma 等^[9]对 814 名 ART 受孕新生儿进行统计, 发现早产率是 32.8%, 远远高于 2020 年全球早产儿发生率 9.9%。但是多变量回归分析发现, 双胎妊娠是导致早产的重要因素, 使早产发生率增加了近 16 倍; 妊娠期高血压使早产概率增加了 2.6 倍^[10]。而 ART 亚群中多胎率较普通人群明显增高, 甚至达到 10~25 倍^[5, 11-12]。从另一个角度看, Waldaufova 等^[5]发现 2013—2018 年 ART 受孕新生儿出生体重逐年增长, 这种趋势很大可能和减少胚胎移植量、多胎妊娠发生率下降有关。2013 年, 冰冻胚胎移植 (frozen embryo transfer, FET) 多胎比例为 12%, 体外受精 (in vitro fertilization, IVF) 为 13%, 受体接受捐赠母细胞 (oocyte receipt, OoR) 为 24%; 而 2018 年 IVF 和 FET 均为 5%, OoR 为 12%。可见早产、低出生体重在 ART 儿童中发生率偏高主要归因于多胎妊娠^[13], 并不一定由 ART 本身引起。Pinborg 等^[13]认为 IVF、卵胞浆内单精子注射 (intracytoplasmic sperm injection, ICSI) 子代单胎婴儿在控制母亲年龄、胎次和胎儿性别后, 并未显示出不良的围生期结局。近年来随着 ART 技术的改进和提高, 从多胚胎移植逐渐转为单胚胎移植, 减少了多胎的发生率, 这显著改善了 ART 子代的早产、低出生体重等围生期并发症发生风险, 提高了 ART 儿童的健康状况, FET 的单胎更有可能出现大于胎龄儿^[10]。英国一项 ART 受孕出生的全国性队列研究显示 FET 单胎移植后出生的婴儿与自然受孕的对照组相比, 出生体重显著增高^[14]。

2 辅助生殖技术受孕儿童的代谢状况

2.1 肥胖 肥胖属于一种慢性代谢性疾病, 儿童期的肥胖可能会延续到青春期或者成年期。一方面有研究显示与 NC 儿童相比, ART 儿童在体重、体质指数 (body mass index, BMI) 方面无显著差异^[15-16]; 另一方面, ART 组儿童年龄特异性体重高于 NC 组儿童, ART 儿童男童肥胖发生率较 NC 儿童高 2 倍^[10-11, 17]。ICSI 受孕儿童中, 尤其是女童, 肥胖发生风险增加^[18]。近期丹麦一项 ART 儿童与 BMI 关系的队列研究, 纳入 327 301 名儿童 (随访年龄大部分为 5~8 岁), 结果并未发现 ART 与 5~8 岁儿童 BMI 之间存在关联, 但 FET 儿童肥胖风险高于新鲜胚胎移植, 约增加 1.5 倍, 尽管相对风险升高, 但绝对风险差异较低^[19]。另一项大规模人群队列研究

包含 122 429 名 ART 后代与 7 574 685 名自然受孕后代, ART 组随访时间为 8.6 (6.2) 年, 对照组随访时间为 14.0 (8.6) 年, 结果发现 ART 后代肥胖发生风险有微小但显著的增加^[20]。原因可能有以下几个方面: 1) ART 儿童的父母通常会对儿童成长表现出更高的关注度和参与度^[21], 这可能同样包括对儿童饮食支持更明显。2) 肥胖是一种不会立即引起严重症状的疾病, 所以对寻求治疗的意愿会有所影响, 可能自然受孕儿童父母寻求治疗的程度更高^[20]。3) 基于 DoHaD 假说-人类健康与疾病发育起源, 异常宫内环境会使胎儿“适应”, 这种“适应”可能会导致胰岛素抵抗, 并增加以后患肥胖的风险^[22]。4) 使用受精技术也会影响表观遗传学变化^[23], 其中 ICSI 比 IVF 显示出更多的表观遗传学改变, ICSI 会影响基因转录和表观遗传调节基因的甲基化, 如印记基因、X 连锁基因、逆转录转座子基因的改变^[24], 表观遗传机制也可能与肥胖相关^[25]。5) 动物研究显示, ART 的程序 (包括促排卵、温度、pH 值改变, 胚胎冻融等) 会引起代谢紊乱, 影响糖脂代谢、基因表达和胎盘大小的变化。胎盘异常对子代的生长发育及心血管健康可能产生长期影响^[26]。6) 由于男童和女童在日常生活中运动强度不一、机体脂肪含量及分布不同、基础代谢和激素水平均存在差异, 这些差异可能会导致肥胖发生风险存在性别差异, Lancet 杂志的数据也显示女童的肥胖发生风险可能更高^[27]。

体格发育是动态变化的, 一项前瞻性研究显示 ART 儿童出生后生长更快, 但在 17 岁时, 与 NC 组无显著差异^[28]。所以 ART 儿童是否具有更高的肥胖发生率, 还需要动态监测和长期随访, 即便出现肥胖, 在儿童时期的肥胖通过饮食指导、优化能量摄入、体力运动监督等干预措施, 往往能够成功改善体重结局^[29]。

2.2 脂代谢 一项研究纳入了 14 项出生队列, 发现 ART 儿童与 NC 出生儿童相比总胆固醇、高密度脂蛋白胆固醇、低密度脂蛋白胆固醇水平均上升^[30]。动物实验研究也显示, 在 ART 子代小鼠的肝细胞中观察到脂滴数量、体积增加以及脂滴融合, 肝脏甘油三酯含量显著增加^[31]; 与对照组相比, IVF 小鼠雌性后代中胆固醇增高, 雄性后代甘油三酯增高^[32]。究其原因可能有以下几个方面: 1) 小胎龄的早产儿脂代谢紊乱风险更高^[33], 而 ART 子代早产、低体重发生率较 NC 子代偏高^[8]; 2) 表观遗传学的改变: 在 ART 兔子模型的后代脂质代谢研究中, F3 代中因胚胎暴露 (胚胎移植、多次排卵等) 而导致 ART 后代肝脏 DNA 甲基化的变化, 这些变化主要

与脂质代谢(如多不饱和脂肪酸、类固醇、类固醇激素)有关;另外还发现 DNA 甲基化与脂质代谢和细胞凋亡基因的变化有关^[34]。而 Asserhøj 等^[35]发现新鲜胚胎移植受孕的男童胆固醇、低密度脂蛋白、甘油三酯显著低于 NC 男童,表现出更有利的血脂谱^[35]。另外也有研究显示与 NC 儿童相比,ART 儿童在脂代谢方面无显著差异^[15]。

2.3 糖代谢 ART 子代是否具有糖代谢调节异常风险一直是各种研究的焦点。一项涉及 2 112 名 ART 儿童和 4 096 名 NC 对照儿童的荟萃分析显示,ART 儿童从童年到成年早期的空腹胰岛素水平均有所升高^[36]。另外有研究显示 ART 儿童患 1 型糖尿病的风险未增加,但 FET 受孕单胎患 1 型糖尿病的风险升高^[37]。国内的一项研究比较了 6~10 岁 ART 子代和 NC 子代各 380 例,发现 ART 子代的空腹血糖、血清胰岛素和空腹胰岛素抵抗指数水平显著高于对照组^[38],饮食的差异可能在加速 ART 儿童中异常葡萄糖代谢的进展中起重要作用。而在动物研究中,IVF 一代雄性小鼠空腹血糖、空腹胰岛素水平均增加,IVF 对连续两代后代肝脏糖代谢具有影响^[39]。当接受高脂肪饮食时,ART 小鼠较 NC 小鼠更有可能出现肥胖、空腹高胰岛素血症和高血糖,并且 ART 小鼠胰岛素刺激的葡萄糖利用率比 NC 小鼠低 20%^[40]。ART 子代的糖代谢的改变可能受到以下因素影响:1)ART 儿童早产、低体重发生率偏高^[9],而低体重及极低体重早产儿成年后糖代谢异常的发生率比对照组高 4.03 倍,空腹血糖、餐后血糖、胰岛素抵抗指数均较对照组增高^[41];2)ART 儿童与 NC 儿童的代谢组学不同(如泛酸和丙酰基甘氨酸水平增高,5-氧脯氨酸水平下降等),而上述氨基酸均参与机体的糖脂代谢,这可能导致 ART 子代糖代谢的改变^[42];当然,也有研究显示与 NC 儿童相比,ART 儿童空腹血糖及患 2 型糖尿病的风险无显著差异^[15,20,43]。

3 辅助生殖技术受孕儿童的神经发育

精神运动、认知、行为和社会情感发展以及精神疾病都是神经发育的一部分。儿童精神性疾病主要包括智力残疾、孤独症谱系障碍(autism spectrum disorder, ASD)和注意力缺陷多动障碍(attention-deficit/hyperactivity disorder, ADHD)等。

3.1 认知能力和发展 随着生活水平的提高,社会、家庭对儿童智能发展的关注程度越来越高,同样 ART 子代的认知能力及发展受到广泛关注。一项基于 2006 年 6 月—2008 年 12 月招募的队列,包含

561 名 ART 及 600 名 NC 儿童,当儿童 7~8 岁时进行评估,内容包括考夫曼简明智力测验、儿童日常注意力测试、Beery-Buktenica 视觉运动整合发育测试等评估,排除混杂因素后发现 ART 儿童的认知、视觉运动能力、注意力和言语技能均与 NC 儿童一致^[44]。

但 Acharyya 等^[45]发现 ART 组儿童在 6 月龄和 12 月龄时,出现运动发育迟缓以及智力发育迟缓的比例显著高于 NC 组。在视觉感知和视觉整合的测试中,Wagener 等^[46]对 9~18 岁青少年的研究发现,IVF 组与 NC 组表现相近,但 IVF 组视觉感知得分较低,但两组结果均在国家标准之内。另一项前瞻性队列研究分析了 426 名 IVF/ICSI 儿童及 509 名 NC 儿童,两组儿童在运动能力、社交能力及总评分方面无差异,但在语言及协调性方面 IVF 组均较 NC 组偏低^[47]。Wienecke 等^[48]发现 IVF 儿童学习成绩较 NC 儿童差,但经过混杂因素处理,结论认为 IVF 过程本身并不是造成差异的原因。但丹麦一项针对 15~17 岁儿童学习成绩的大型队列研究发现,ART 单胎的平均成绩(7.16 ± 2.41)高于 NC 儿童(6.74 ± 2.46),且差异有统计学意义($P < 0.05$)^[49]。学习及认知能力可能随着时间的推移出现动态变化,正如 Barbuscia 等^[50]对 ART 儿童与 NC 儿童在多个年龄段的认知能力进行测评,发现 ART 儿童 5 岁前认知能力偏高(命名词汇测试中表现更好),但在 11 岁时,两组则无显著差异。本课题组前期的研究发现 ART 组婴儿在 6 月龄时精细运动发育商及语言发育商较 NC 组偏低,但在 6~12 月龄之间进行追赶,在 12 月龄时再次评估发现两组无显著差异^[6-7]。

3.2 孤独症谱系障碍和注意力缺陷多动障碍 北欧 ART 安全小组委员会的研究纳入了 1 160 909 例 ART 儿童和 4 959 535 例非 ART 儿童,在 ASD 发生风险方面,经粗略 COX 回归分析,ART 组 ASD 患病风险高于非 ART 组,经过调整后风险趋于升高,但在单胎方面分析,ASD 与 ART 无明显关联;在 ADHD 发生风险方面,经粗略 COX 回归分析,ART 组风险低于非 ART 组,经过调整后 ART 组儿童 ADHD 风险有所升高,但在单胎中两组的 ADHD、品行障碍风险均无显著差异;在调整后的模型中,ART 类型与神经发育障碍风险之间无显著关联^[51]。

既往有研究认为 ART 儿童 ASD 风险较高,但其中多胎妊娠比例相当大^[52]。ART 本身不会增加 ADHD 及 ASD 的风险,但 ART 儿童上述疾病发生

风险略微地增加可能与父母因素及多胎妊娠有关^[13]。一般情况 ART 儿童父母的年龄较 NC 儿童年龄偏高,而父母高龄与全面发育障碍及 ASD 有关^[53]。

有研究使用了迄今为止最大的数据来源评估 ART 与 ASD 发生的关系,发现 ART 受孕儿童与 ASD 发生风险增加有关系;但按多胎情况分层分析发现,ART 受孕与 ASD 的关联在很大程度上受多胎妊娠、早产及剖宫产的影响,而 ART 亚群中多胎率明显增高^[5,11-12],所以最终认为 ART 与 ASD 之间的关系可能是通过增加多胎妊娠、分娩和相关出生并发症而发生的^[54]。随着技术的更新和发展,目前 ART 中单胚胎移植的应用,减少了出生相关并发症(早产、低出生体重、多胎妊娠等),这可能是解决 ART 受孕儿童 ASD 发生风险的另一种策略^[54]。

ART 的应用成功地治疗了不孕不育症,这是现代医学的巨大成功之一,也为不孕不育夫妇带来了希望和幸福。目前在国内外 ART 儿童数量仍在不断增加,多数研究认为 ART 受孕儿童的健康状况良好,总体与 NC 儿童差别不明显,即使在部分层面与 NC 儿童存在差异(包括早产、低体重等),很大程度上与多胎妊娠相关,可能并非由 ART 自身引起。在肥胖发生、糖代谢、脂代谢方面则仍然存在很多争议,结论不一,有不少证据表明 ART 程序可能引起表观遗传学的改变,如 DNA 甲基化、印记基因等,这些变化可能对代谢方面产生影响,但仍有许多未知因素及机制需要进一步研究和长期随访;另外,国内相关的研究相对较少,希望能够开展相关大样本量的病例对照及随访队列研究,填补相关研究空白。

利益冲突声明 本文不存在利益冲突

数据可用性声明 本研究未生成新的数据,对于纳入的每项研究均已在参考文献列表中列出。

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