

# 冻融胚胎序贯移植策略改善反复胚胎种植失败的应用及内在机制

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## 摘要

胚胎种植失败, 尤其是多次失败的移植周期, 不仅给患者及家庭带来沉重的精神压力、情感创伤和巨大的经济成本。针对胚胎种植失败并非单一疾病, 而是由胚胎因素(遗传学异常、发育潜能差)、子宫内膜容受性因素(种植窗移位、免疫微环境异常、解剖结构异常)以及两者同步性共同作用的结果。序贯移植是卵裂胚胎移植和囊胚移植的结合, 可通过最大化“着床窗口”来提高子宫内膜容受性。将第一个胚胎移入子宫腔, 可以启动与子宫内膜的引发分子层面的相互作用, 从而促进第二个胚胎的着床。通过其“种植窗”和“优化胚胎-内膜对话”的双重理论优势, 为应对反复种植失败这一临床挑战提供了新的理论视角和潜在解决方案。虽然目前的临床证据需要进一步巩固, 但这种方法有望改善反复种植失败(Recurrent Implantation Failure, RIF)患者的妊娠结局, 为临床优化RIF治疗方案提供理论依据和实践参考。

## 关键词

反复种植失败, 冻融胚胎移植, 序贯移植, 子宫内膜容受性, 胚胎-内膜同步

# The Application and Underlying Mechanisms of Sequential Frozen-Thawed Embryo Transfer Strategy in Improving Embryo Implantation Failure

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## Abstract

**Embryo implantation failure, particularly after multiple unsuccessful transfer cycles, not only imposes significant psychological stress and emotional distress on patients and their families but also leads to substantial financial burdens. Recurrent Implantation Failure (RIF) is not a single disease entity but rather a complex condition resulting from the combined effects of embryonic factors (e.g., genetic abnormalities, poor developmental potential), endometrial receptivity factors (e.g., displaced window of implantation, immune microenvironment dysregulation, anatomical abnormalities), and asynchrony between the embryo and endometrium. Sequential embryo transfer, which combines the transfer of cleavage-stage embryos and blastocysts, aims to enhance endometrial receptivity by maximizing the “implantation window.” The initial transfer of an embryo into the uterine cavity may initiate molecular cross-talk with the endometrium, thereby facilitating the implantation of subsequent embryos. By leveraging the dual theoretical advantages of extending the implantation window and optimizing embryo-endometrial dialogue, this strategy offers a promising novel approach to addressing the clinical challenges of Recurrent Implantation Failure (RIF). Although current clinical evidence requires further consolidation, this approach holds promise for improving pregnancy outcomes in patients with RIF.**

## Keywords

**Recurrent Implantation Failure, Frozen-Thawed Embryo Transfer, Sequential Embryo Transfer, Endometrial Receptivity, Embryo-Endometrial Synchronization**

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## 1. 前言

尽管目前的促排卵方案日趋完善, 胚胎培养和冷冻技术也在不断优化, 但胚胎着床率仍然徘徊在 30% 左右, 这一现状给医务人员和不孕症患者带来了巨大的困扰[1]。成功怀孕取决于三个关键因素, 即胚胎、最佳移植时机以及胚胎 - 子宫内膜的相互作用[2]。对于胚胎种植失败而言, 获得单胎、健康的活产胎儿, 仍是巨大挑战。传统观点将反复种植失败的病因主要归结为胚胎因素(如非整倍体、发育潜能低下)与子宫内膜容受性因素(如种植窗偏移、免疫微环境异常)两大方面。然而, 越来越多的证据表明, 胚胎与子宫内膜之间的“对话”失调, 即二者在发育时空上的不同步性, 可能是导致着床失败的关键。冻融胚胎移植的优势主要体现在可以着床在一个更有利于胚胎着床的子宫内环境, 并优化胚胎选择, 能够成功复苏并继续发育的胚胎, 往往是发育潜能更好、更“强壮”的胚胎。近年来一些临床研究已显示出冻融胚胎序贯移植对于改善 RIF 患者妊娠结局的积极信号, 提出可以提高子宫内膜敏感性, 诱导胚胎着床, 提高妊娠率, 且其背后复杂的生物学机制, 如对内膜容受性标志物的调控、对局部免疫微环境的重塑等, 其是否是治疗 RIF 的有效方法仍待进一步探究[3]。因此, 寻找一种有效的移植策略, 包括筛查高质量胚胎、改善子宫内膜接受度以及促进子宫内膜与胚胎之间的相互作用, 可能对 RIF 患者有益, 以期为对序贯移植策略的深入研究, 指导临床合理应用提供理论参考。

## 2. 反复种植失败的定义

关于反复种植失败的统一诊断标准尚未形成。专家持有不同意见,目前多数学者倾向于将反复种植失败(RIF)定义为在接连三次接受体外受精-胚胎移植(IVF-ET)助孕后仍未能获得临床妊娠,并且每个移植周期须移植1~2枚优质胚胎[4]。然而,也有部分学者认为,应被界定为年龄不超过40岁的患者,在至少经历三个新鲜或冷冻胚胎移植周期,且移植的优质胚胎总数超过4枚后,依然未能成功实现临床妊娠[1]。目前RIF在辅助生殖助孕中发生率高达10%[5],这一问题不仅增加了患者在时间、精力和经济上的投入,还给他们带来了沉重的心理和身体压力,导致他们对成功妊娠的信心下降,甚至影响到对医生诊疗方案的配合度。现有研究表明,影响RIF的因素主要可以分为两个方面:胚胎质量和子宫内膜容受性以及胚胎与子宫内膜的同步性各占三分之一和三分之二[6]。优质胚胎需通过胚胎植入前遗传学检测(PGT-A)等手段,证实移植的胚胎是染色体正常的(整倍体)优质胚胎,以排除因胚胎自身染色体异常这一最主要的不着床原因,且需要通过宫腔镜检查等手段,确认宫腔形态正常,无粘连、息肉、肌瘤、炎症(慢性子宫内膜炎)等明显影响胚胎着床的解剖或病理问题。只有在排除了上述明确因素后,才能将多次优质胚胎移植失败归因于潜在的内膜容受性缺陷、免疫因素等更复杂、更微妙的“不明原因”领域。而冻融胚胎移植的核心优势,正是针对这些“不明原因”RIF中最常见的环节——优化子宫内膜的容受性与同步性——进行干预。

## 3. 序贯胚胎移植策略的提出

序贯胚胎移植,在同一个移植周期内,于不同时间点移植两个胚胎,旨在延长或覆盖更宽的着床窗口期,增加胚胎与内膜相遇的机会,又称二步移植法,是辅助生殖领域中的一项特殊技术。该方案指在同一治疗周期内,分两次进行胚胎移植:首先移植发育至第2或第3天的卵裂期胚胎,随后在第5或第6天继续移植囊胚阶段胚胎,形成所谓“D2/D3~D5/D6”的序贯移植模式[7]。更精细地模拟了自然妊娠中胚胎在不同时间点与内膜对话的过程,可能存在“先遣部队”改善内膜环境,为后续胚胎着床做准备的理论。在1988年,Abramovici等开展了一项早期研究,将可用胚胎数超过4枚的16例患者纳入序贯移植组,而可用胚胎数不足4枚的另一组16例患者则接受单纯卵裂期胚胎移植,其研究结果证实,序贯移植能够显著提升体外受精-胚胎移植的妊娠结局,其中序贯移植组的妊娠率达到25%,显著高于卵裂期移植组的6.2%。自此之后,学界对序贯移植机制与效果的深入探索逐步展开[8]。移植囊胚可改善RIF患者的预后,因其降低胚胎染色体异常风险及胚胎与子宫内膜间的相互作用改善,囊胚移植可以选择具有更大发育潜力、提升胚胎着床率和临床妊娠率的胚胎[9]。冻融周期(尤其是激素替代周期)允许医生完全掌控内膜的发育节奏,使用外源性激素精确模拟从增殖期到分泌期的转化,为分两次、不同阶段的胚胎移植提供一个同步且容受性持续良好的“舞台”[3],从而改善RIF患者的妊娠预后。序贯移植策略基于“子宫内膜容受性窗口动态调节”和“胚胎活力逐步筛选”的理念,在同一移植周期内分阶段移植胚胎,既避免了多次周期的繁琐,又显著提升了种植成功率。目前,序贯移植的临床证据仍在积累中,并非一线常规推荐,需在充分评估后个体化实施。若采用序贯移植策略,将其置于冻融胚胎移植的框架下进行是更合理和主流的选择。因为这结合了冻融胚胎移植优化内膜环境的核心优势与序贯移植精细调控着床时机的潜在好处,为RIF患者提供了当前技术条件下一种更为精密的治疗选择。

## 4. 序贯胚胎移植改善反复种植失败的内在机制

序贯移植代表了一种从“静态移植”到“动态同步”的转变。该策略通过在同一移植周期内,先后移植卵裂期胚胎与囊胚期胚胎,不仅理论上扩展了潜在的“种植窗”,更可能通过首次移植胚胎对内膜的“激活”与“适应”作用,优化后续胚胎着床的微环境,从而协同提升着床几率。

#### 4.1. 优化子宫内膜容受性, 延长种植窗口

序贯移植策略对子宫内膜的影响, 其核心理论在于: 第一次移植的早期胚胎(如 D3 卵裂胚)作为一个“生物刺激信号”, 通过胚胎与内膜间的“对话”, 上调或启动与内膜容受性建立相关的关键基因表达, 从而为第二次移植的胚胎(如囊胚)创造一个更优的分子环境[10] [11]。人类子宫内膜作为一种动态组织, 在月经周期中会定期再生, 子宫接受胚胎植入的时间很短, 子宫内膜容受性是胚胎成功种植的关键前提, 其核心特征是“种植窗”(Window of Implantation, WOI)的开放——即子宫内膜在特定时间内呈现“接受态”, 允许胚胎黏附、侵入[12]。如果胚胎移植时机与个体的种植窗不同步, 即使是高质量的胚胎也可能无法成功着床[13]。许多研究指出, RIF 患者的种植窗可能存在个体差异, 常存在 WOI 缩短、延迟或不稳定的问题, 甚至在不同月经周期中发生偏移, 导致胚胎与子宫内膜发育不同步[14]。序贯移植的策略是通过在不同时间点植入胚胎, 来覆盖一个更宽的、可能存在的时间段, 从而增加胚胎与子宫内膜“相遇”并成功着床的概率。

序贯移植利用胚胎不同发育阶段的“接力”优势。有相关研究表明在序贯移植中, 较早移植的卵裂胚可能会调节免疫反应, 并为第二次移植产生更好的子宫内膜环境[15]。初次进入子宫腔的卵裂期胚胎可作为“来使”, 促进子宫内膜血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)等表达, VEGF 是一种重要的血管生成因子, 它通过促进血管生长和重塑, 增加子宫内膜的血流量和营养供应[16], 使子宫内膜有着充足的营养为胚胎着床做准备[17]。国外也有相关动物实验表明, 子宫腔内的胚胎有助于提高子宫内膜的容受性, 促进其自身着床。在序贯移植过程中, 首次移植使用的胚胎移植管会对子宫内膜造成机械刺激, 子宫内膜受到刺激可以后募集一些与受精卵着床相关的细胞因子, 如  $\gamma$  干扰素(Interferon-gamma, IFN- $\gamma$ )、白介素 6(IL-6)、VEGF, 这些因子会增加子宫内膜螺旋小动脉及胞饮突数量, 通过这种方式改善子宫内膜容受性。因此, 在序贯胚胎移植中, D3 胚胎有可能开始在子宫内产生免疫耐受, 并为 D5 胚胎提供更好的子宫内膜环境[18]。当一个胚胎阶段与内膜不同步时, 另一个阶段可能恰好同步, 解决的“周期偏移”和“不稳定”问题。在胚胎种植失败患者行冻胚移植的过程中如何精准把控 WOI, 才是提高妊娠率的关键[19]。因此, 在患有反复种植失败的女性中, 卵裂期和囊胚期胚胎的序贯移植比传统的胚胎移植提供了更好的植入机会[20]。序贯移植的主要优点是获得囊胚移植的高植入潜力, 同时避免在计划仅进行囊胚移植的情况下可能出现的转移取消的令人沮丧的情况。

一种评估子宫内膜容受性的重要工具是子宫内膜容受性检测(Endometrial Receptivity Array, ERA), ERA 通过分析子宫内膜组织中特定基因的表达谱来确定个体的种植窗, 指导个性化胚胎移植(personalized Embryo Transfer, pET) [10] [21]。例如, 一项回顾性研究发现, 在 RIF 患者中, ERA 指导下的 pET 可能显著提高妊娠率和种植率[22]。另一项研究也指出, 与常规冷冻胚胎移植相比, ERA 指导下的 pET 对 RIF 患者的临床妊娠结局具有积极影响[23]。然而, 也有研究表明, ERA 检测并未显著改善 RIF 患者的妊娠结局[24] [25]。这可能提示 ERA 的应用效果存在个体差异或尚需更精确的筛选标准。除了种植窗的偏移, 子宫内膜的微环境异常也是导致 RIF 的重要原因[26] [27]。例如, 子宫内膜异位症、息肉等器质性病变以及子宫内膜微生物群的变化都可能影响子宫内膜容受性[26]-[28]。冻融序贯移植在某种程度上可能通过分次刺激子宫内膜, 诱导或优化局部免疫环境, 从而改善子宫内膜的整体健康状况。ERA 和序贯移植策略都旨在优化胚胎种植时机和环境。序贯移植通过在不同时间点移植胚胎(例如 D3 和 D5), 可能允许子宫内膜有更多时间对早期胚胎的存在作出反应, 从而潜在地改善容受性[29] [30]。这种“时间窗”的扩展或优化, 与 ERA 试图精确确定种植窗口的理念在某种程度上是互补的。

此外, 胚胎与子宫内膜之间的相互作用是一个复杂的分子对话过程[31]-[34]。冻融周期(尤其是自然周期或温和刺激周期)可以模拟更自然的生理状态, 或者通过人工激素精确调控内膜厚度和形态。这使得

医生能够在更“安静”、更接近自然的子宫环境下进行移植,显著提高了胚胎与子宫内膜的同步性,这是着床的关键。子宫环境细胞和分子水平的变化会影响子宫内膜的容受性[35][36]。生物化学方面,参与胚胎植入的侵袭机制包括细胞凋亡和其他上皮分解机制、有助于迁移的细胞-细胞或细胞-底物相互作用、血管和细胞外基质重塑,以及涉及适应性和先天免疫细胞的免疫反应[37]。尽管辅助生殖技术取得了进步,但有关胚胎植入的知识仍然不完整。子宫内膜组织的细胞和分子变化是胚胎植入成功或失败的最重要因素。序贯移植可能通过减少胚胎间的竞争,使得每个胚胎有更大的机会与子宫内膜进行充分的分子对话,从而提高种植成功率。

## 4.2. 筛选高活力胚胎, 提升种植潜能

胚胎发育潜能低下是 RIF 的另一重要原因。在冷冻和解冻过程中,质量较差、发育潜能不足的胚胎可能无法存活。因此,能够成功复苏并继续发育的胚胎,往往是发育潜能更好、更“强壮”的胚胎。对于 RIF 患者,这相当于进行了一次额外的自然选择,移植的是经过“考验”的胚胎。传统上,胚胎的形态学评分是评估其发育潜力和选择用于移植胚胎的主要依据[38]。囊胚期的胚胎通常具有更高的种植潜能,因为它们已经通过了体外培养的选择压力[39][40]。例如,有研究比较了卵裂期(第3天)和囊胚期(第5天/第6天)冻融胚胎移植的临床结局,发现囊胚移植可能在某些情况下更具优势[39][40]。在着床过程中,许多分子介质,包括细胞因子、脂质、粘附分子、生长因子等,支持怀孕的建立[41]。经期黄体期通过活检导管造成的子宫内膜损伤已被证明能改善后续治疗周期中的着床率和怀孕率[42]。在着床窗口期间,子宫内膜的准备不仅受母体因素影响,还受胚胎分泌的分子影响,如绒毛膜促性腺激素和白介素-1 $\beta$ [43]。因此,在序贯胚胎移植的首次 ET 手术后,导管插入及胚胎和子宫内膜产生的细胞因子引起的机械显微刺激,不仅可能有利于首次移植胚胎的着床,还可能促进更好的着床条件,并提高胚泡胚囊移植后的着床概率[44]。其次,人类的着床窗口是短暂的,超过此时间窗口的着床将导致妊娠失败[45]。对子宫内膜的机械刺激可能略微改变个体化胚胎植入窗口,对受体子宫内膜有益[46]。评估序贯移植机制时,未来需开展严格设计对照实验(如假移植组:仅进行导管插入但不移植胚胎),以区分机械刺激与胚胎特异性信号的作用。此外,与卵裂期胚胎第3天 ET 相比,体外培养3天至5~6天的胚胎可筛选出着床潜力更高的胚胎,从而提高妊娠率[47]。另一种可能的解释是,由于患者间的子宫内膜对类固醇激素的反应,导致两次移植时机增加,从而增加了达到“着床窗口”的概率[48]。因此,对于具有良好胚胎质量且反复着床失败的患者,建议采用顺序移植[49]。

## 4.3. 调节母体免疫微环境, 构建免疫耐受状态

女性生育能力下降是由复杂因素累积而成,其中免疫系统在女性生殖中被破坏是关键因素。成功的胚胎着床需要母体免疫系统从炎症反应向免疫耐受状态的转变[50][51]。子宫内膜作为胚胎着床的场所,其免疫细胞组成和细胞因子网络是影响胚胎容受性的重要因素[52][53]。调节性 T 细胞(Regulatory T cells, Tregs)是维持母胎免疫耐受的关键细胞,通过抑制效应免疫反应、控制炎症并支持母体血管适应性来促进滋养层细胞侵袭和胎盘对母体血液供应的获取[50]。序贯移植胚胎可能使母体免疫系统有更长时间逐步适应胚胎的存在。首先移植的 D3 胚胎可能作为一种“先行者”,诱导母体子宫内膜产生初步的免疫反应和调节,为后续囊胚的着床创造更有利的免疫环境[54]。序贯移植可能通过延长胚胎与子宫内膜的接触时间,促进子宫内膜细胞与胚胎之间的信号交流,从而增强子宫内膜的容受性[55][56]。序贯胚胎移植可能通过影响蜕膜免疫细胞亚群的募集和功能,蜕膜中的自然杀伤细胞、巨噬细胞、T 细胞和树突状细胞等免疫细胞的重塑对早期胚胎发育和蜕膜化至关重要[52][57], Tregs 通过抑制免疫效应、控制炎症并支持母体血管适应来促进滋养层细胞侵袭和胎盘血供,对胎盘的稳健发育和妊娠的持续至关重要[58]。例如

Tregs 的增殖与活化, 以及自然杀伤细胞的活性, 从而促进母胎免疫耐受[50][58]。Tregs 在妊娠期抑制效应免疫、控制炎症和支持母体血管适应方面发挥关键作用[50]。在小鼠模型中, 母体 Treg 细胞耗竭会损害胚胎着床, 而 Treg 细胞的过继转移可以纠正这种缺陷[58]。尽管序贯胚胎移植在临床实践中已被广泛应用, 其对母体免疫微环境的具体调节机制仍需深入研究。

## 5. 冻融胚胎序贯移植策略的临床应用现状

国内外有关于序贯移植单独应用于种植失败的研究, 例如, Abramovici 等学者在 1988 年首次将序贯移植策略应用于临床, 序贯移植组较对照组临床妊娠率由 6.2% 提高至 25%, 因此认为序贯移植可以改善体外受精 - 胚胎移植(In Vitro Fertilization and Embryo Transfer, IVF-ET)的妊娠结局[8]。Torky 等人的一项研究比较了 RIF 病例中且取回卵母细胞数量足够的情况下, 序贯胚胎移植与接受双囊胚移植的患者相比, 有较高的植入率和临床妊娠率有关, 因此提倡拥有足够数量的优质胚胎的患者进行移植[59]。同样, Arefi 等探究在第 3 天、第 5 天连续移植冻融胚胎比常规第 5 天 IVF-ET 更有效, 该研究表明, 序贯移植可以延长胚胎在植入窗口期的可用时间, 从而可能改善种植失败患者的妊娠结局[60]。Gao 等人探究冻融胚胎移植周期中的序贯胚胎移植与双卵裂期和双囊胚期移植相比可以改善种植失败患者临床妊娠率显著升高, 早期流产率和多胎妊娠率显著降低[3]。周燕等人探究冻融复苏胚胎序贯移植对胚胎种植失败患者临床妊娠结局的影响, 其研究表明冻融胚胎序贯移植可显著增加种植失败患者临床妊娠率[61]。Zhang 等人研究显示, 连续胚胎移植组的临床妊娠率和活产率高于卵裂胚胎移植组, 且序贯胚胎移植与囊胚移植无显著差异[15]。即使在卵巢反应较差的患者中, 有报告显示连续胚胎移植的活产率高于胚胎移植第 3 天, 且在冻胚移植周期中与囊胚移植的活产率相似[62]。一项 252 例回顾性研究分析接受冻融胚胎移植的反复种植失败患者, 序贯胚胎移植组的临床妊娠率显著高于卵裂期胚胎移植组和囊胚移植组[63], 同样, 2022 年一项随机对照研究, 按 1:1 的比例分为序贯移植组及囊胚移植组, 纳入 200 名 RIF 患者, 序贯移植组的临床妊娠率和着床率显著高于对照组, 因此 D3 和 D5 的胚胎序贯移植可能会改善患者的临床结局[60]。

然而, 有相关研究认为序贯移植对妊娠结局无改善作用, 一些研究显示序贯胚胎移植未改善反复种植失败患者的临床结局[64][65]。一项研究序贯胚胎移植( $n=136$  例)以及卵裂期胚胎移植( $n=139$  例), 其结果表示两组的妊娠率(36.8%, 37.4%)无统计学差异, 并未显示序贯移植相关显著优势[66]; 2019 年伊朗德黑兰一项纳入 120 名不孕患者的随机对照研究显示, 序贯移植组的临床妊娠率(40%)与囊胚期胚胎移植的临床妊娠率(38.3%)相似( $p$  值 = 0.085)[67]。在 2022 年一项纳入 311 名回顾性分析结果显示, 囊胚移植组(48.8%)、序贯移植组(48.1%)和卵裂胚胎移植组(48.1%)的临床妊娠率相当, 组间差异无统计学意义( $p > 0.05$ ), 因此序贯移植未能起到改善妊娠结局的作用[65]。相反, 有些研究认为序贯移植不利于胚胎的种植, 会降低胚胎的着床率。因为二次移植可能会对子宫内膜造成伤害甚至严重感染。序贯移植因为移植管的刺激作用, 可能会诱发宫缩, 导致胚胎着床失败, 还会给宫腔带来额外的微生物污染, 这些都可能干扰正常种植[65]。除此之外, 序贯移植因为需要进行二次胚胎解冻与复苏, 不仅增加了患者的就医次数, 还增加了胚胎解冻的金钱成本, 给患者造成了经济负担。这三种不同观点让序贯移植在临床的应用充满争议。

## 6. 冻融胚胎序贯移植策略的挑战

尽管这种胚胎移植策略在反复种植失败患者中表现出显著的临床优势, 但仍存在诸多亟待解决的问题, 比如缺乏统一的临床规范: 目前关于序贯胚胎移植的胚胎选择标准(如卵裂期胚胎的细胞数、囊胚的评分)、移植间隔时间(2 天 vs 3 天)、激素维持方案等尚未形成统一标准, 不同中心的临床实践差异较大; 尽管有理论支持其通过胚胎 - 内膜对话调控 HOXA10、LIF 等基因, 但这仍主要基于实验室研究与推论。

在人体内, 这一“胚胎生物刺激”效应是否确实发生、强度如何、是否存在个体差异, 仍需更多直接证据; 序贯移植对子宫内膜容受性的调节机制、胚胎-胚胎互作的具体分子机制、免疫调节的长期影响等仍需更多基础研究证实; 且多次胚胎移植可能增加子宫内膜感染的风险; 此外, 对于胚胎数量较少的 RIF 患者, 序贯移植可能导致胚胎消耗过快, 影响后续治疗; 尽管目标是提高单次移植周期的成功率, 但两次移植客观上增加了双胎甚至三胎妊娠的风险。多胎妊娠显著提升母体并发症(如妊娠期高血压、糖尿病)和围产期不良结局(如早产、低出生体重)的风险, 违背了辅助生殖“安全、单胎、足月、健康”的核心目标。这与当前全球倡导的选择性单胚胎移植趋势存在张力。

## 7. 结论

反复种植失败是辅助生殖技术领域的复杂难题, 冻融胚胎移植策略的核心优势在于将胚胎移植的时机从促排卵后混乱的激素环境中剥离出来, 转而寻求一个与胚胎发育高度同步、容受性最佳的子宫内膜状态, 从而最大程度地提高每一次移植的成功机会。同时序贯移植策略通过优化子宫内膜容受性、筛选高活力胚胎、调节母体免疫微环境等多维度机制, 显著改善了 RIF 患者的临床妊娠结局, 具有重要的临床应用价值。尽管该策略在临床规范、机制研究和潜在风险等方面仍存在挑战, 但随着精准医疗技术的发展和基础研究的深入, 序贯移植有望成为 RIF 治疗的标准化方案之一。未来需通过多中心、大样本 RCT 研究和基础机制研究, 进一步完善冻融胚胎序贯移植的临床应用体系, 为不孕不育患者提供更高效、安全的治疗选择。

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