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反复种植失败患者妊娠结局的影响因素分析

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摘 要

本综述旨在评估反复种植失败(Recurrent Implantation Failure, RIF)患者妊娠结局的多种影响因素。我们系统地回顾了最近几年的文献，探讨了从年龄、生殖系统疾病、子宫内膜容受性、胚胎质量、免疫因素、遗传因素等方面的影响。此综述为临床医师和患者提供了一个关于RIF患者管理和治疗的综合视角，以优化妊娠结果。

关键词

反复种植失败，妊娠结局，影响因素

Analysis of Factors Affecting Pregnancy Outcome in Patients with Recurrent Implantation Failure

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Abstract

The aim of this review was to assess the multiple factors influencing pregnancy outcomes in patients with Recurrent Implantation Failure (RIF). We systematically reviewed the literature of the last few years and explored the influence of factors ranging from age, reproductive disorders, endometrial tolerance, embryo quality, immunologic factors, and genetic factors. This review provides clinicians and patients with a comprehensive perspective on the management and treatment

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of patients with RIF to optimize pregnancy outcomes.

Keywords

Recurrent Implantation Failure, Pregnancy Outcome, Factors Affecting

1. 引言

反复种植失败(RIF)是在辅助生殖技术(Assisted Reproductive Technology, ART)中一个重要的挑战，影响着大量试图通过体外受精(*In Vitro* Fertilization, IVF)等技术来解决不孕问题的患者。RIF 的定义尚无统一标准，通常定义为 40 岁以下的女性，在至少三个新鲜或冷冻周期中移植至少四个优质胚胎后，未能实现临床妊娠[1]。RIF 的原因多种多样，本综述旨在探讨影响 RIF 患者妊娠结局的关键因素。

2. 影响因素

2.1. 年龄

随着女性受教育程度的提高，参与劳动力市场的女性也逐渐增多，女性生活的重点不完全在于生育问题，这一趋势导致女性生育年龄逐渐推迟[2]。而随着女性年龄的增长，线粒体功能与卵母细胞质量逐渐下降[3]。研究表明，胚胎－子宫内膜不同步率随年龄增加而增加，卵母细胞产量、囊胚形成率和子宫内膜厚度随年龄增加而降低。年龄 ≥ 35 岁的女性相比较年龄 < 35 女性来说，植入率较低，生化妊娠率较高，活产率显著降低[4]。因此，在研究和探讨辅助生殖技术及其妊娠结局时，女性年龄是一个不可忽视的关键因素。

2.2. 生殖系统疾病

宫腔环境是胚胎种植的基本条件，宫腔异常病变如子宫内膜息肉，宫腔粘连，子宫肌瘤，子宫腺肌病，慢性子宫内膜炎等，均可能会影响胚胎移植率。子宫内膜息肉是 RIF 患者较常见的子宫病变，会影响胚胎种植[5]。它不仅能引起子宫腔的形态改变，还通过改变子宫内膜分泌的细胞因子(如胰岛素样生长因子 1 结合蛋白和 TNF-α)来干扰着床过程[6]。一项研究指出，宫腔粘连的发生率在接受宫腔镜评估的 RIF 患者中约为 8.5%，宫腔粘连通常发生在清宫术后，粘连会损害子宫内膜的功能层，阻止胚胎附着，从而无法成功着床[7]。此外，子宫肌瘤可导致子宫腔变形和粘连，从而阻止胚胎附着在子宫内膜上。子宫肌瘤对妊娠结局的影响与其位置有关。特别是黏膜下肌瘤可能会降低接受试管婴儿的患者的着床和妊娠率，阻碍着床的机制包括子宫肌层收缩增加、血管形成异常和细胞因子谱紊乱[5]。一项系统评价指出，黏膜下肌瘤患者的着床率和活产率低于对照组[8]。子宫内膜异位症是一种雌激素依赖性炎症，在不孕妇女中的发病率高达 50% [9]，有研究表明子宫内膜异位症会降低患者生育力，其机制可能是破坏盆腔正常解剖结构、造成卵巢周围粘连、改变免疫系统功能、阻碍胚胎着床、降低卵子质量[10]。近年来，发现 RIF 患者合并慢性子宫内膜炎。慢性子宫内膜炎为微生物感染诱发，有研究表明，慢性子宫内膜炎是影响 RIF 患者活产率和临床妊娠率的一个独立因素，合并慢性子宫内膜炎的患者活产率及临床妊娠率显著降低[11]。因此，子宫腔的异常病变是影响胚胎移植成功率的重要因素，深入了解这些异常病变的特点及其对胚胎移植的具体影响机制，对于提高 RIF 患者的治疗效果和妊娠成功率具有重要意义。

2.3. 子宫内膜容受性

适当的子宫内膜功能以及子宫内膜和胚胎之间的动态相互作用是成功种植的必要条件。子宫内膜容受性是子宫环境接受胚胎和随后植入的时间窗，这个时期通常在月经周期的第 20 天和第 24 天之间，子宫内膜处于分泌期[12]。RIF 的病因复杂，如免疫因素，血栓前状态，感染因素，生殖系统解剖结构异常，内分泌因素，男性因素，染色体异常等，子宫内膜容受性欠佳是 RIF 的原因之一[13]。黄体酮对于建立子宫内膜容受性至关重要[14]。然而，子宫内膜种植窗的开放存在很短的时间，成功植入不仅取决于子宫内膜容受性，还取决于子宫内膜发育与胚胎之间的同步性[15]。在辅助生殖实施过程中，这种同步性可能会受到影响。一方面，血清黄体酮过早升高会降低新鲜胚胎移植周期的妊娠率，可能提示子宫内膜和胚胎之间存在不同步[16]。另一方面，在冻融胚胎移植(Frozen Embryo Transfer, FET)中，黄体酮给药的持续时间显著影响妊娠率[17]。在所有哺乳动物中胎盘滋养层黏附时，子宫内膜上皮雌激素受体 α (ERα)和孕酮受体(PR)基本消失。最近的证据表明，PR 的消失是由 P 通过调节 FOXO1 转录因子来调节的[18] [19]。此外，缺乏 PR 下调可能会阻止 FOXO1 促进白血病抑制因子(LIF)的表达，LIF 对多种胎盘物种中滋养层的附着至关重要[18]。因此，PR 下调、LIF 表达和 FOXO1 作用在子宫内膜上皮和子宫内膜容受性中都相互关联。细胞粘附分子在滋养层表面表达，并与子宫内膜细胞外基质表达的配体相互作用[20]。这些细胞粘附分子包括：(1) 选择素，参与滋养层黏附的碳水化合物结合糖蛋白[21]；(2) 钙粘蛋白，钙依赖性糖蛋白，有助于滋养层运动和侵袭[22]；(3) 整合素，参与胚胎子宫内膜附着和信号转导的跨膜糖蛋白[23]。

子宫内膜容受性可以通过无创方法进行研究，例如高分辨率经阴道超声(TVS)、三维超声(US)、多普勒超声、三维功率多普勒超声、磁共振成像(MRI)来检测子宫内膜组织血流。子宫内膜容受性阵列(ERA)是一种尝试，旨在临床上改善由于子宫内膜黄体期分化加速或延迟导致的胚胎－子宫内膜不同步的组织学检测[24]。一种较新的子宫内膜容受性测试是 ReceptivaDx 测试，该测试基于发现子宫内膜异位症女性子宫内膜 BCL6 的过表达[25]。在 ET 周期中，包括 ERA 和 ReceptivaDx 在内的新方法为改善妊娠结局提供了指导，特别是治疗患有 BCL6 缺陷的女性，可以显着降低子宫内膜异位症治疗后的流产率[15]。提高子宫内膜容受性可以通过以下方式来实现：(1) 改变生活方式，例如戒烟，补充营养，加强锻炼等；(2) 改善黄体缺陷，通常采用激素替代疗法；(3) 改善子宫血流，如口服小剂量阿司匹林[26]。

2.4. 胚胎质量

胚胎质量是辅助生殖过程中实现成功活产的关键决定因素之一，取决于形成胚胎的卵母细胞和精子的质量。卵母细胞的数量和质量是卵泡发育第一阶段的两个主要决定因素[27]。随着年龄的增长，线粒体 DNA 的不稳定性增加，这可能导致卵母细胞中的 mtDNA 突变，从而导致卵母细胞质量下降[3]。此外，卵巢储备随着年龄的增长而减少，可能是由于线粒体功能障碍、端粒缩短、黏附蛋白功能障碍等因素导致卵母细胞功能衰退，减少了卵巢中卵细胞的总量[28]。卵母细胞评估可能会有利于胚胎评估，以预测体外受精(IVF)的妊娠机会。在存在优质胚胎的情况下，卵母细胞评分较高的患者在接受辅助生殖技术后更有可能成功妊娠[29]。精子 DNA 损伤可能发生在氧化应激的情况下，例如生活方式不足、吸烟、既往手术史、放化疗、性传播疾病、鱼精蛋白缺乏症或 DNA 修复缺陷[30]。有研究表明，精子 DNA 片段化检测为自然或人工受孕提供了除常规参数之外的相关信息[31]。同样，另一项研究表明，精子 DNA 损伤的增加对 IVF 和/或 ICSI 后的临床妊娠率有负面影响[32]。卵胞浆内形态选择单精子注射(IMSI)技术通过大约 6300 倍的高倍率显微镜来细致观察精子的形态特征及头部中的液泡，旨在精选形态学上最优质的精子进行注射[33]。有研究将 IMSI 与传统的 ICSI 进行了比较，发现临床结局方面没有显著改善[34]。这提示虽然 IMSI 技术提供了对精子形态更细致的观察，但在提高临床妊娠率方面的实际效果仍需进一步研究与验证。

2.5. 免疫因素

各种免疫细胞类型，特别是 T 细胞的特殊亚群，在成功妊娠和生殖失败中具有不同的功能。具有抑制特性的调节性 T (Treg)细胞在胚胎移植和发育中至关重要。这些 Treg 细胞通过抑制 Th1 淋巴细胞的产生和功能(I 型炎症反应的主要介质)积极参与母体免疫适应。Th1 型免疫的下调是临床正常妊娠的基本要求，相比之下，Th2 介导的免疫反应在正常妊娠期间往往占主导地位。与正常妊娠相比，在复发性流产和 RIF 中，细胞因子的平衡发生了显著变化。具体来说，Th1 型细胞因子如干扰素(IFN)-γ 的水平显著提高，而 Th2 型细胞因子，包括 IL-6 和 IL-10 的水平则降低。这种细胞因子平衡的变化，暗示免疫应答在复发性流产和 RIF 中的重要作用[35] [36]。自然杀伤细胞可分为外周血自然杀伤(pNK)细胞和子宫自然杀伤(uNK)细胞。在外周血中，pNK 细胞被认为具有细胞毒性，相比之下，uNK 细胞的细胞毒性明显降低。在妊娠早期，uNK 细胞通过渗透到滋养层并参与控制滋养层侵袭及子宫螺旋动脉的重塑，从而增加母体血液和滋养层细胞之间的接触面积，这一过程是胎盘健康发育的主要过程。尽管 uNK 细胞似乎可以保护胚胎并支持植入，但在 RIF 和 IVF 后复发性流产的患者中发现了高水平的 uNK 细胞[37]，其机制有待进一步研究。一项研究[38]通过对 IVF 过程中 RIF 患者的子宫内膜进行全基因组甲基化和基因表达谱分析，研究子宫内膜容受性的变化情况，确定了 448 个差异甲基化位点，其中 242 个是低甲基化的，而 206 个是高甲基化的。这些与差异甲基化基因相关的最重要的生物学过程与抗原加工和呈递有关，包括 MHC I 类和 MHC II 类的内源性和外源性肽呈递。富集的途径属于吞噬体、同种异体移植物排斥反应、移植物抗宿主病、抗原呈递和炎症性肠病的途径。此外，转录起始位点的差异甲基化位点主要富集参与免疫功能的基因，如抗原加工和呈递、免疫球蛋白产生、IL-10 和 IL-4 调节、T 辅助细胞免疫应答以及由 HLA-DRB1 和 HLA-DRB5 基因组成的炎症应答。当与基因表达谱重叠时，大多数下调的基因在先天免疫和细胞防御反应、T 细胞增殖调节、趋化因子介导的信号通路、补体激活调节、急性和慢性炎症反应以及细胞趋化性中发挥作用。抗原加工和呈递途径、自然杀伤细胞介导的细胞毒性途径以及补体和凝血级联反应是下调基因中富集最多的三条途径。这些结果表明，子宫内膜的甲基化缺陷可能是子宫内膜局部免疫紊乱导致 RIF 的原因。

2.6. 遗传因素

一个能够成功种植的“优质”胚胎必须从高质量的成熟卵母细胞和精子开始，每个卵母细胞和精子都包含一组单倍体染色体。与年龄相关的不孕症可能部分归因于减数分裂错误数量的增加，特别是染色体分离错误。这导致产生的卵子和胚胎为非整倍体，降低了其着床率[39]。研究发现，在年长女性群体中，即便采用整倍体胚胎进行移植，其着床率、临床妊娠率(CPR)以及活产率(LBR)的降低仍然存在，这一结果指出年龄相关不孕症的成因可能不仅仅局限于胚胎的非整倍性问题。尽管面临这些挑战，选择性地移植整倍体胚胎仍可以在一定程度上提高年长女性的生育成功率，从而凸显了这一策略在缓解年龄相关生育能力下降方面的有效性[40] [41]。2014 年的一项研究表明，44 岁女性的囊胚非整倍体率可高达 53%，42 岁女性的非整倍体率高达 33% [42]。这表明高龄女性的囊胚往往总体质量较差[43]，且常染色体单体、单倍体和多倍体通常甚至不会进展到囊胚期[44]。母体易栓症相关基因，包括凝血因子 V Leiden (FVL)、凝血酶原和亚甲基四氢叶酸还原酶(MTHFR)基因突变，也在 RIF 的病因学中进行了研究[45] [46]。一项小型研究报告称，RIF 患者的 MTHFR c.677C > T 多态性，出现了显著的 Hardy-Weinberg 平衡偏差，特别是具有两种纯合基因型的夫妇(例如，男性为 677C 的纯合子和女性为 677T 的纯合子，反之亦然)的 4 倍过度表达，从而表明杂合子处于劣势。此外，携带 MTHFR 677T 纯合整倍体胚胎的移植失败率显著增高[47]。对母体 uNK 细胞免疫球蛋白样受体(KIR)基因型的研究表明 KIR A 抑制性单倍型具有优越性。一

项涉及 668 例整倍体单胚胎移植的大型研究报告称，与 KIR B 患者相比，KIR A 患者的妊娠丢失显著降低(分别为 16%和 28%)。这一差异受到移植胚胎的 HLA-C 基因型的显著影响，证实了母体和胚胎机制之间相互作用对成功种植的重要性[48]。

3. 结论

影响 RIF 患者妊娠结局的因素是多方面的，其作用机制复杂。通过综合全面的评估和干预这些影响因素，可以为 RIF 患者提供更有效的治疗方案，提高活产率，实现他们的生育愿望。已有大量研究从多角度出发分析 RIF 患者妊娠结局的影响因素的作用机制，但在未来的研究中，还需要进一步挖掘，以期制定更加有效的治疗方法，以提高反复种植失败患者的活产率。

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