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生长激素在女性生殖中的作用机制研究及临床应用进展

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摘　要

生长激素(GH)是由垂体前叶分泌的一种蛋白质，在调节多个靶组织中的细胞生长、发育和代谢中起关键作用。GH在妇女一生的各阶段都有分泌，且与年龄有一定相关性。自发现GH能够在控制性促排卵(Controlled Ovarian Hyperstimulation, COH)中增强促性腺激素(gonadotropic hormone, Gn)的作用后，就作为体外受精－胚胎移植(in vitro fertilization-embryo transfer, IVF-ET)的辅助治疗常用于卵巢低反应(POR)的不孕妇女中，后逐渐在各种不孕症的女性中广泛应用。目前GH在临床中的最佳添加剂量、应用时机以及其在女性生殖系统的具体作用机制仍在不断探索，是当前生殖领域的研究热点。本文将总结近年来GH在生殖领域中的机制研究进展及临床应用。

关键词

生长激素，辅助生殖，卵母细胞质量，原始卵泡，早期卵泡，颗粒细胞

Research on the Mechanism and Clinical Application of Growth Hormone in Female Reproduction

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Abstract

Growth hormone (GH) is a protein secreted by the anterior pituitary gland that plays a key role in

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regulating cell growth, development, and metabolism in multiple target tissues. GH is secreted in all stages of women's life, and has a certain correlation with age. Since the discovery that GH can enhance the role of Gn in IVF, it is often used as an adjunct treatment of IVF-ET in infertile women with low ovarian response (POR), and then gradually widely used in a variety of infertile women. At present, the optimal dosage, application time and specific mechanism of GH in the female reproductive system are still being explored, which is the current research hotspot in the reproductive field. In this paper, we will summarize the research progress and clinical application of GH in reproductive field in recent years.

Keywords

Growth Hormone, Assisted Reproduction, Oocyte Quality, Primitive Follicle, Early Follicle, Granular cell

1. 引言

生长激素(Growth Hydrogen, GH)是在调节细胞生长、发育和代谢的多个靶组织中起关键作用的垂体前叶分泌的蛋白质。在女性生殖中，GH 被认为是女性最佳生育的必需激素，因为研究发现，生长激素缺乏症妇女的生育能力下降，而 GH 替代治疗可以使这些不孕妇女成功怀孕[1] [2]。

从 1988 年首次在 IVF 中应用后，GH 在女性生殖中的作用越来越受到关注，现已成为生殖内分泌领域的研究热点。当前 GH 已在各种不孕症的女性中应用，但 GH 给药最佳方案仍未明确。相关机制研究表明，GH 可能通过 GH 受体直接作用或通过 IGF-I间接作用与卵巢内分泌信号系统产生交互作用，有利于原始卵泡激活、卵巢类固醇生成、卵泡生长发育和闭锁、卵母细胞成熟和子宫内膜容量的受性改善、影响胚胎植入和妊娠结局等[3]-[6]。全面了解 GH 在女性生殖中的作用机制及 GH 在生殖医学领域中的临床应用是必要的，为后续 GH 研究提供支持。

2. GH 在女性生殖中的作用基础

GH 主要产生部位是在垂体，由垂体的生长激素细胞产生，也可在其他多个组织中以旁分泌或自分泌的方式少量分泌来调节邻近细胞的增殖、分化和代谢[7] [8]。在女性生殖系统中，在卵巢的卵母细胞、基质细胞和颗粒细胞以及子宫内膜组织中可检测到 GH 蛋白及 GH 受体，因此认为 GH 可在卵巢及子宫内膜局部发挥一定作用，而 GH 作为一种抗氧化剂，也可改善局部内环境[8]-[10]。GH 的体内/体外给药优化了农业和临床的生育，所以 GH 被认为可改善生殖[11]。正常生殖需经过卵泡发生和卵子发生的两个关键过程，这些过程受到内分泌、旁分泌、自分泌和近分泌(通过间隙连接)方式的多重调节[12]-[14]。GH (垂体和卵巢来源)可能在这种复杂相互作用的信号中起重要作用。另外，肝细胞在 GH 作用下可合成分泌胰岛素样生长因子-I (insuline-like growth factor-I, IGF-I)，是 IGF-I 的主要产生部位，而 IGF-I 可以通过直接(垂体)或间接作用(下丘脑)抑制垂体对 GH 的分泌[14] [15]。研究发现，不同种 IGF 可在卵巢内不同的体细胞中表达，人颗粒细胞和卵泡膜细胞可分别主要表达 IGF-II mRNA、IGF-I mRNA，两者同时存在 IGF-I 受体。因此，卵巢是 IGF-I 基因的表达部位，GH 可作用于卵泡膜细胞使之分泌 IGF-I，而 IGF-I 可以通过远距离分泌或自分泌方式调节卵巢功能[16] [17]。越来越多的证据表明，GH 与 IGF-1 直接相互协调的

作用[18]。相关研究提示，GH 可能通过直接或 IGF-I的间接作用来调节女性的生殖功能，可能与以下女性生殖过程相关，包括激活原始卵泡、生成卵巢类固醇、卵泡生长发育与闭锁、成熟的卵母细胞和影响胚胎植入和妊娠结局的子宫内膜受性改善等方面的作用，从而改善女性的生育[18]。

3. GH 与原始卵泡发育之间的关系

原始卵泡数量从出生后就已固定，不再增长，其构成的原始卵泡池大小可代表女性的生殖能力的大小，也是卵细胞的唯一储备形式。在早期卵泡形成过程中不依赖于促性腺激素，是由许多局部产生的生长因子以旁分泌/自分泌方式调节。GH 在原始卵泡激活及生长过程中起重要作用。研究发现，GHR 也可在各种物种(包括人类、大鼠、猪和牛)的窦前卵泡的卵母细胞和颗粒细胞中表达[19]-[21]。在一项小鼠动物实验的研究中显示，GH 受体缺乏可使原始卵泡增多，而初级、次级、窦前和窦卵泡减少，这可能由于 GH 对原始卵泡的激活，及其生长发育为窦卵泡的过程中发挥有益影响，抑制卵泡闭锁，增加生长卵泡数量[3]。缺乏 GH 的哺乳动物(包括小鼠、水牛和绵羊)的发育卵泡数量减少，补充外源性 GH 可改善[22]-[24]。另外，ICF-I 治疗可增加 GHR 敲除小鼠的原始卵泡数目，阻止卵泡闭锁，这说明 IGF-I 可以弥补 GH 缺乏对原始卵泡的不利影响，能够对卵泡闭锁起到抑制效应[25]。因此，GH 和 IGF-I 对刺激原始卵泡发育起着重要的作用，它们在非促性腺激素依赖性的阶段相互配合。

4. GH 在促性腺激素依赖阶段对卵泡发育的影响

随着原始卵泡激活逐渐生长发育至促性腺激素依赖阶段，垂体分泌的促性腺激素和卵巢相关因子通过不同方式对卵泡的正常生长、分化及闭锁具有关键作用。GH (垂体和卵巢起源)是否参与调节这种复杂的相互作用的信号？GH 作为卵巢调节因子与内分泌信号系统之间存在串扰关联。促性腺激素(FSH 和 LH)与其受体(FSHR 和 LHR)结合后，激活下游环磷酸腺苷/蛋白激 A (cAMP/PKA)信号通路诱导一系列关键的卵泡内活动，包括类固醇生成、细胞增殖和分化[26]。研究发现，GH 通过上调颗粒细胞的 FSHR、LHR 及 GHR 的表达来增强 FSH 诱导的细胞分化，促进孕激素合成。因此，GH 可能通过上调 FSR 及 LHR，增强 LH 诱导的卵泡膜细胞的雄激素合成和 FSH 诱导的芳香化酶活性进而调节雌激素和孕激素的产生[27]-[29]。以上结果表明，GH 与内分泌信号系统之间的相关性可通过增强颗粒细胞对促性腺激素或 GH 刺激的敏感性和反应性，进而调节性类固醇合成影响卵泡发育。

另外，GH 可能作为卵巢因子还可通过自分泌或旁分泌以改变颗粒细胞增殖、分化和其代谢的方式达到对卵泡的生长发育的调控作用。研究发现，局部 GH 与 GHR 形成 GH：GHR 复合体，可触发 GHR 胞浆中 JAK2 (Janus 激酶)的募集和自磷酸化，进而诱导信号转导和转录激活因子(STAT)分子(包括 STAT5a、STAT5b、STAT1 和 STAT3)的磷酸化，这些分子可转位至细胞核并改变基因表达和细胞活动，包括细胞增殖、分化和代谢[30]。卵泡正常发育与颗粒细胞的良好增殖和代谢密切相关。有研究显示，GH 给药会使卵泡直径增加，增加卵泡大小、卵泡数量和卵巢重量，而颗粒细胞层明显增加，所以认为在卵泡发育过程中，GH 可以促进颗粒细胞增殖促进卵泡发育为优势卵泡[31] [32]。

所以，GH 及 IGF-I 作为细胞及卵巢内部因子可能通过增强颗粒细胞的增殖，促进颗粒细胞对促性腺激素或 GH 刺激的敏感性和反应性，进而调节性类固醇合成影响卵泡发育、闭锁，促进优势卵泡发育。

5. GH 与卵母细胞质量

卵母细胞质量是妊娠成功的主要限制因素，只有优质卵母细胞才能正常受精并支持早期胚胎发育。卵母细胞质量是由窦前卵泡发育到成熟卵泡的 2~3 个月生长阶段确定，高质量卵母细胞具备完全成熟能力及支持正常精卵结合发育和胚胎正常发育，进而使患者成功妊娠的能力[33]。线粒体生物能量减少和氧

化应激被认为是卵母细胞质量较差，导致减数分裂的染色体错误分离，最终导致非整倍体胚胎的主要因素[34] [35]。研究认为 GH 对卵母细胞核及细胞质成熟有积极作用，进而对卵母细胞质量具有有益影响。高质量的卵母细胞具备成熟的细胞核和细胞质。所以，GH 作为一种抗氧化剂，可对卵巢内环境有一定改善作用。研究发现，GH 可能通过促进并增强相关生物酶的表达来改善卵母细胞氧化应激水平，从而提高线粒体活性，达到增加卵母细胞成熟，提高卵母细胞质量的作用[36]。此外，卵母细胞与颗粒细胞及卵丘－卵母细胞复合体之间存在缝隙链接，相互作用影响。相关研究发现 GH 可以促进颗粒细胞及卵丘－卵母细胞复合体的增殖与分化，促进核成熟，抑制卵泡的闭锁，从而改善卵母细胞质量[37]-[41]。

在 IVF 相关研究中发现，卵泡液中 GH 和 IGF-1 的水平与卵母细胞数量、卵母细胞质量及胚胎质量的呈正相关，这说明 GH 及 IGF-I 可抑制卵泡闭锁，改善卵母细胞及胚胎质量，进而获得更好的 IVF 结果[42] [43]。GH 的辅助治疗可增加获卵数，提高卵母细胞质量和胚胎数量，并提高临床妊娠率和活产率[44] [45]。在一项体外研究中发现，在人类未成熟卵母细胞的培养基中补充 IGF-1 (以及表皮生长因子和脑源性神经营养因子)可以提高卵母细胞的成熟速率和质量，从而促进早期胚胎的发育和囊胚的形成[46]。因此，总的来说 GH 和 IGF-I 对卵母细胞质量及胚胎发育存在有益作用。

6. GH 与子宫内膜容受性

子宫内膜容受性是指胚胎种植窗，随着年龄的增长，其容受性下降(种植窗缩小)进而影响胚胎着床、临床妊娠以及女性整体生育力[47]。GH 已在临床应用多年，但大多研究局限于改善患者的卵母细胞和胚胎质量，而对子宫内膜容受性的研究较少。近年越来越多的证据显示，GH 对子宫内膜厚度的改善[48] [49]。研究发现，GH 在多种哺乳动物(包括人类)的黄体细胞、子宫肌层及蜕膜以及妊娠早期绒毛膜滋养层细胞中表达，可刺激黄体化颗粒细胞、子宫内膜和蜕膜细胞的增殖，抑制其凋亡，促进滋养层细胞的侵袭作用[50]-[52]。因此，GH 可以促进黄体功能及妊娠期间的蜕膜反应，增加胚胎侵入性，对人类子宫内膜及胚胎植入起重要的作用。有相关机制研究发现，GH 可促进内皮细胞有丝分裂，或通过介导 IGF-I 或 Janus 激酶/信号转导激活剂上调相关受体分子的表达，以加速细胞增殖并增加子宫内膜感受性相关基因的表达(如整合素 β3、白血病抑制因子(Lif)、基质金属蛋白 9 (Mmp-9)和血管内皮生长因子)，促进子宫内膜细胞增殖代谢和组织血管形成，从而提高子宫内膜容受性，调节胚胎植入[53] [54]。此外，GH 还可以通过调节 IGF-1 和白血病抑制因子等分子，增强子宫对雌激素的敏感性，优化子宫内膜的微环境[55] [56]。因此，GH 对子宫内膜的影响，可能通过改善内膜的受性，增强子宫内膜对雌激素的敏感性，调节着床因子之间的表达及相互关系，通过细胞因子等改善子宫内膜的局部血液循环，促进内膜代谢，促进内膜腺体的生长以及内膜细胞的增殖，进而改善患者临床妊娠。

7. GH 在 ART 中的应用

自 1988 年首次应用 GH 于 IVF 后，便一直被用于广泛治疗诱导排卵期间的女性不孕症，但关于 GH 作为 IVF/ET 辅助治疗的有益作用仍然存在争议[57]，至今无 GH 相关临床应用指南的发表，可能由于患者的异质性造成的。目前，在 ART 治疗期间，GH 较常应用于卵巢反应不佳、胚胎发育不良的患者，现在高龄、多囊卵巢综合征患者及卵巢反应正常不孕患者中也多有应用，甚至对子宫内膜薄的患者治疗中发现较好的疗效[58]-[60]。

良好的卵巢反应是 ART 治疗成功的重要基础，使 COS 过程能够获得足够的卵母细胞用以实现怀孕。卵巢反应不良(POR)在 ART 治疗中是生殖临床医生最具挑战性的任务之一，约在 ART 治疗中占 9%~24% [61]。POR 的发病因素可能与高龄、肥胖或医源性因素相关，包括卵巢手术、盆腔粘连等。为在 IVF 治疗中改善 POR 并提高妊娠成功率，临床中提出了许多辅助疗法，包括雄激素补充剂：睾酮和脱氢表雄酮

(DHEA)或雄激素调节剂：来曲唑(一种芳香化酶抑制剂)，类固醇激素：雌二醇和黄体酮，生长激素(GH)等。这里主要讨论 GH 在 POR 中的应用[62]-[64]。

有大量的随机对照试验(randomized controlled trials, RCTs)表明，GH 对 POR 的早期妊娠相关的因素有积极影响，包括取回的卵母细胞、成熟卵母细胞、优质胚胎[65]-[67]。然而，GH 对临床妊娠率和活产率的影响仍存在争议[68]。以往 POR 的定义一直以来存在一些争议并缺乏统一共识，因此患者之间可能存在较大异质性。至 2011 年为了标准化 POR 的定义，ESHRE 提出博洛尼亚标准，至此往后有较多研究采取该定义方法。2020 [69]年一项系统分析显示，GH 辅助治疗可获得更多的卵母细胞数量、HCG 日雌二醇水平和移植的胚胎数量，可降低促性腺激素使用剂量。因为更高剂量的促性腺激素可能会导致胚胎质量低下，这对于 POR 患者是不良因素。所以，GH 治疗对于 POR 患者可减少 Gn 用量，改善卵巢内分泌水平，获得更多卵母细胞，改善卵母细胞质量，对于后期妊娠有影响。一项涉及 17 项 RCT 的荟萃分析发现，GH 补充剂可能改善 POR 患者的子宫内膜厚度，获得更好临床妊娠率和活产率[70]。因此，当前研究认为 GH 可改善 POR 患者的卵巢内分泌水平，使其获得更多卵母细胞，也可同时改善了卵母细胞质量及子宫内膜厚度，进而对患者的临床妊娠及活产率产生有益影响，但缺乏统一的标准，仍需要不断地探索。

除在 POR 中应用，在正常反应、多囊卵巢综合征(PCOS)以及胚胎发育不良女性，甚至在获得卵母细胞捐献女性中应用也得到了不同程度的有益效果。在应用 GH 的同时，更应该关注其不利影响因素，短期使用 GH 可能不会给患者带来不良危害，但是长期使用仍需要严格把控 GH 用药标准。研究发现，GH 可能对机体代谢产生显著改变，包括胰岛素抵抗、葡萄糖耐量不良、胆固醇升高和肾素－血管紧张素系统紊乱，所以对于糖尿病患者等代谢相关疾病患者应谨慎使用[71] [72]。因此，关于 GH 在 IVF-ET 应用的最佳方案仍需进一步探索，考虑到患者的有益影响和风险应进行个体化选择。GH 在 ART 中的临床应用研究更多地集中在 GH 的添加时机及添加剂量方面，但目前尚无最佳定论。2023 [73]年一项研究发现，在高龄产妇中添加 GH，可以改善其妊娠结局，与 Gn 同时给药相比，Gn 刺激前长期预处理至 hCG 日的给药方案可能效果更佳。但该研究并未涉及 GH 对活产率及母婴并发症的研究。所以目前对于是否可以长疗程使用 GH 需要更多探索和观察，以期望更安全、更有效，确保对母婴的安全性。

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