

# 卵巢癌患者的生育力保存

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## 摘要

随着诊断技术的进步和治疗手段的提高, 卵巢癌患者生存比例明显增加, 但在癌症治疗过程中, 手术及某些放化疗手段均会对卵巢功能造成不可逆转的损伤, 随着卵巢癌患者生存时间的延长和生存率的提高, 很多患者不得不面临生育力折损的严重问题, 但人们目前对生育力保存时机、适用方法及存在的风险认识尚浅, 本文结合最近研究进展, 对临床常用的卵巢癌治疗手段对女性生育力产生的损伤及目前适用于卵巢癌女性的生育力保存方法进行了总结, 希望能够为临床上卵巢癌患者的诊疗及生育力保存提供依据。

## 关键词

卵巢癌, 治疗, DNA损伤, 生育力保存

# Fertility Preservation in Patients with Ovarian Cancer

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## Abstract

With the advancement of diagnostic technology and improvement in treatment methods, there has been a significant increase in the survival rate of ovarian cancer patients. However, in the course of cancer treatment, certain surgical procedures, as well as radiotherapy and chemotherapy treatments, can lead to irreversible damage to ovarian function. As the survival time extends and the overall survival rate improves for ovarian cancer patients, many individuals are confronted with

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the serious issue of fertility loss. Unfortunately, there is still limited awareness regarding the optimal timing, suitable methods, and associated risks of fertility preservation. This review summarized recent research progress on the detrimental effects on female fertility caused by commonly used clinical treatments for ovarian cancer and present current applicable fertility preservation methods for women with this condition. We hope to provide a basis for clinical management and fertility preservation in patients with ovarian cancer.

## Keywords

Ovarian Cancer, Treatment, DNA Damage, Fertility Preservation

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## 1. 引言

根据美国癌症协会数据统计, 女性一生中罹患卵巢癌的风险为 1/78 [1], 卵巢癌起病隐匿, 一般好发于绝经后女性中, 但育龄期妇女中仍有大量病例, 世界卫生组织预估 45 岁以下女性新发癌症类型中 4.5% 为卵巢癌, 高居所有癌症类型的前五位[2]。

卵巢癌通常根据起源分为上皮性卵巢癌(epithelial ovarian carcinoma, EOC)和非上皮性卵巢癌两大类, 其中非上皮性卵巢癌包括生殖细胞肿瘤、性索间质瘤和交界性肿瘤等[3]。随着癌症诊断技术和治疗方法的提高, 改善了卵巢癌患者的预后, 罹患卵巢癌的年轻女性生存比例明显增加, 小于 44 岁的 1A 期和 1B 期所有类型卵巢癌患者中, 5 年总生存率约为 91.2% [4]。卵巢具有分泌雌孕激素的功能, 是维持女性第二性征和保存生育能力的重要器官, 但癌症治疗过程中, 手术及某些放化疗手段均会对卵巢功能造成不可逆转的损伤, 很多患者不得不面临生育力折损的严重问题, 其中包括未性成熟的青少年、无婚育史的青年人及尚未来得及完成生育的已婚女性, 生育力保存需求日益增加[5] [6]。但人们目前对生育力保存时机、适用方法及存在的风险认识尚浅, 本文结合最近研究进展, 对临床常用的卵巢癌治疗手段对女性生育力产生的损伤及目前适用于不同类型卵巢癌女性的生育力保存方法进行了总结, 希望能够为临床上卵巢癌患者的诊疗及生育力保存提供理论依据。

## 2. 不同治疗方式对女性生育力的损伤

手术和化疗是卵巢癌的最主要治疗手段, 极少数早期卵巢癌患者只通过手术而治愈, 但卵巢癌起病隐匿, 发现时多为晚期, 多数患者需要手术联合放化疗等综合治疗方法, 治疗方案通常根据患者肿瘤类型、分期等情况进行制定[7]。

### 2.1. 手术治疗

手术治疗是卵巢癌最常见的治疗手段, 手术原则是尽量切除全部原发病灶及转移病灶, 或使残余病灶小于 2 cm, 手术根据肿瘤不同分型分期可能包括全子宫、双附件、大网阑尾及腹膜后系统淋巴结清除术[8], 全子宫、双附件的根治性手术会对女性生育力造成不可挽回的打击, 切除一侧或两侧卵巢会导致患者出现卵巢储备功能下降、卵巢功能不全或更年期症状[9]。交界性卵巢肿瘤及性索间质肿瘤预后良好, 5 年和 10 年生存率分别为 95% 和 90%, 单侧性肿瘤可切除患侧肿瘤及附件, 保留健侧附件和子宫[10] [11]。

对于 IA 或 IC 期的卵巢上皮癌, 也可行单侧附件切除 + 全面分期手术, 保留健侧附件和子宫, 有研究提示保留生育能力的手术和标准治疗之间的生存率没有差异, 但术中需要对切除组织进行冰冻病理诊断及临床评估, 权衡患者是否符合保存生育能力的条件[12]。有生育要求的任何期别恶性生殖细胞肿瘤, 如果子宫和对侧卵巢正常, 都可以考虑保留生育功能, 但 I 期透明细胞癌(ovarian clear cell carcinoma, OCC)恶性程度高, 应谨慎选择保留生育能力[13]。

## 2.2. 放疗

卵巢对放疗射线及其敏感, 研究证实 5 Gy 及以上剂量的射线会对各级卵泡产生不同程度的损伤, 导致 50% 以上的卵泡丢失, 高剂量的子宫辐射会导致不可逆的血管和子宫肌层损伤, 降低女性受孕和生育的可能[9] [14]。放疗过程中产生的电离辐射可以诱导 DNA 产生碱基损伤、碱基丢失、单链断裂(single strand break, SSB)、双链断裂(double strand break, DSB)以及 DNA-蛋白质交联[15], 当 DNA 被电离辐射破坏时, 细胞会启动修复机制试图修复损伤, 简单的损伤形式如单碱基的突变或损伤及单链断裂损伤将通过碱基切除修复(base-excision repair, BER)过程快速修复; 双链断裂损伤将通过同源重组(homologous recombination, HR)及非同源末端连接(non-homologous end joining, NHEJ)两种更为复杂的修复机制进行修复[16]。若修复成功, 细胞功能会恢复正常, 若修复不成功、不完整或出现错误, 细胞的遗传信息可能发生改变或丢失, 将会出现基因突变, 导致受损的细胞凋亡或坏死[17]。放疗同样会导致细胞染色体结构异常, 在细胞周期的 G1 期照射引起的 DNA 损伤如果在 DNA 复制之前未得到修复, 会引起原发性染色体畸变(primary chromosome-type aberrations), S 期或 G2 期照射将会导致原发性染色单体型畸变(primary chromatid-type aberrations), 因为卵母细胞的 DNA 复制通常在卵母细胞成熟之前就已完成, 因此放疗导致的染色体结构异常往往都是染色单体型的[18]。除此之外, 放疗还可以导致染色体数量异常, 染色体的分离错误导致非整倍体的产生, 这两种染色体异常虽然对患者个体没有直接影响, 但对子代健康产生严重威胁, 产生遗传性疾病, 如智力低下及先天性畸形等[14] [19]。

## 2.3. 化疗

化疗对于上皮性卵巢癌的治疗至关重要, 推荐用于卵巢癌的化疗方案为铂类化合物(顺铂或卡铂)和紫杉烷类药物(紫杉醇或多西他赛)组合使用, 比较不同化疗药物使用后患者的月经恢复率, 发现环磷酰胺对患者生殖功能损伤最为严重, 顺铂等铂类药物为中等风险, 紫杉醇导致患者不孕的风险相对较低, 但依然还是会对患者的卵巢储备功能造成一定程度的影响[20]。对卵巢功能损伤最严重的化疗药物为环磷酰胺等烷化剂, 在小鼠实验中, 环磷酰胺干扰小鼠的动情周期, AMH 水平明显降低, 各级卵泡都出现明显丢失, 闭锁卵泡增加, 卵巢储备功能显著下降, 这可能由于是激活了 HIF-1 $\alpha$ /BNIP3 相关自噬关键蛋白[21]。铂类化合物通过与 DNA 结合生成 Pt/DNA 结合物, 破坏 DNA 的结构, 使之易形成 DNA 交联产物, 从而使 DNA 维持解旋或发生弯曲, 降低 DNA 的稳定性, 诱导细胞死亡[22]。除此之外, 顺铂还能够诱导细胞产生活性氧(reactive oxygen species, ROS), 发生氧化应激, 产生有害的 8-氧 - 鸟嘌呤碱基突变, 导致 DNA 损伤[23] [24]。顺铂有明显的性腺毒性, 应用顺铂的患者出现卵巢早衰、卵巢纤维化、萎缩和血管损伤风险明显升高, 且风险与所使用的药物、给药剂量、疗程持续时间、患者年龄和卵巢储备情况有关[25], 顺铂等化疗药物会磷酸化 Akt、mTOR 及 FOXO3 等关键蛋白, 引发原始卵泡凋亡, 剩余卵泡过度激活, 抗苗勒管激素(anti-Müllerian hormone, AMH)水平下降[26] [27]。紫杉烷类药物是有丝分裂抑制剂, 通过诱导微管蛋白聚合, 抑制微管形成和纺锤体功能, 使得细胞停止分裂, 终止肿瘤细胞的生长, 动物实验发现紫杉醇会损害成熟的卵母细胞, 并影响短期生殖潜力[4]。因此, 在化疗开始前必须完成是否保留生育能力的选择, 同时研究人员也在努力寻找能够在治疗前或治疗期间减少或消除化疗药物的性腺毒

性作用的药物或方法。研究最多的也是唯一应用于临床实践的方案是给予促性腺激素释放激素激动剂(gonadotrophin releasing hormone agonist, GnRHa), 暂时性的抑制卵巢功能, 预防在治疗过程中可能出现的卵巢早衰[28]。研究证实使用 GnRHa 的患者能够更快的恢复月经和排卵[29], 但化疗引起的卵巢损伤的评估标准不应只局限于月经的恢复, 还应关注 AMH 水平, AMH 在卵巢周期中是一个恒定的数值, 是评估卵巢储备功能的可靠指标, 在现有的研究中, 鲜有实验证明 GnRHa 可以维持或挽救患者的 AMH 水平[30], 也没有证据表明治疗后妊娠率有所改善[31]。综上所述, GnRHa 对卵巢癌患者化疗药物行腺毒性的保护作用的证据尚不充足, 机制尚未阐明, 未来仍需进一步论证。

### 3. 卵巢癌女性生育力保存方法

与宫颈癌和子宫内膜癌等其他妇科肿瘤相比, 卵巢癌患者的生育力保存更具有挑战性[32]。若卵巢癌患者治疗过程中因放化疗的性腺毒性或手术导致不可避免的生育力损伤, 可以在癌症治疗之前借助辅助生殖技术(assisted reproductive technologies, ART), 促排卵(controlled ovarian hyperstimulation, COH)取卵后进行卵母细胞或胚胎冷冻来保存生育能力, 通常可以在 2~3 周之内完成, 并不会延迟肿瘤的治疗, 而对于需要立即进行肿瘤治疗的患者来说, 卵巢组织冷冻保存也可以实现患者保留生育能力的愿望[33]。

#### 3.1. 胚胎/卵母细胞冷冻

目前临床上常用的女性生育力保存手段包括胚胎/卵子冷冻及卵巢组织冷冻等保存方式, 胚胎或卵子冷冻适用于大多数卵巢癌患者, 但是冻胚或冻卵方案需要使用促性腺激素刺激卵泡生长, 诱导多个卵泡同时发育, 这就会导致循环中的雌二醇水平升高, 可能会刺激雌激素敏感的肿瘤细胞生长, 因此临床上会对卵巢癌患者采取更安全的促排卵方式, 使用他莫昔芬和来曲唑等芳香化酶抑制剂, 降低雌激素水平, 这类药物可以单独使用或与较低剂量的促性腺激素联合使用, 以提高卵母细胞的质量[34]。除此之外, 与传统的卵泡期促排卵周期启动方案相反, 研究人员还开发了“随即启动卵巢刺激”策略, 即不再受制于月经周期, 随时可以启动卵巢刺激而不会降低获卵数或胚胎数, 通过随机启动卵巢刺激策略, 可以缩短取卵周期, 为肿瘤患者争取更多的治疗时间[35]。

卵巢癌具有一定的遗传性, 目前已知的与卵巢癌相关的遗传易感基因有 20 多个, 其中最常见的是乳腺癌易感基因(breast cancer susceptibility gene, BRCA), BRCA1/BRCA2 基因突变的携带者属于卵巢癌的高发人群, 一生中发生卵巢癌的累积风险为 54% 和 23%, 同时这些突变可能与卵巢储备功能不全相关, 研究表明, 携带该突变的女性对促排过程中的卵巢刺激反应性较差, 获卵数相对较少[36] [37]。BRCA1/2 基因突变虽然会改变 DNA 修复机制, 但不会损害卵母细胞的体外成熟能力[38]。该人群应重视定期筛查, 同时尽早完成生育, 若有生育力保存需求, 应选择胚胎/卵母细胞冷冻或卵母细胞体外成熟, 而不应该选择卵巢组织冻存, 即使在筛查时并未检测到卵巢恶性肿瘤的可能[39]。胚胎植入前遗传学诊断(preimplantation genetic diagnosis, PGD)又叫第三代试管婴儿技术, 可以对获得的胚胎进行基因筛查, 筛选出无遗传突变的胚胎移植, 规避该基因遗传给后代的风险[40]。指南推荐该类女性在完成生育后可接受降低风险输卵管-卵巢切除术(risk reducing salpingo-oophorectomy, RRSO), 以降低卵巢癌及乳腺癌的发病风险[7]。

#### 3.2. 卵巢组织冻存

当患者没有足够的时间进行促排周期取卵, 或患者是未月经来潮的儿童时, 可以行卵巢组织冷冻保存(ovarian tissue cryopreservation, OTC), 通过手术切除整个卵巢皮质, 收集组织后进行病理学检查, 以确定是否存在恶性细胞以及评估卵巢储备情况[31] [41] [42]。OTC 的优点是无需外源性激素刺激, 并且当

卵巢皮质移植回患者体内后, 不仅可以恢复生育能力, 还可以恢复内分泌功能[43]。目前已经对卵巢组织冻存进行了大量的研究, 但无法排除癌细胞再植风险, 关于年轻女性早期卵巢癌保留生育能力手术的安全性数据也一直在累积中, 仍需更多证据论证卵巢癌患者进行 OTC 的可行性[44]。

#### 4. 结论

综上所述, 卵巢癌是女性生殖道肿瘤诊治中的“硬骨头”, 不断发展的规范化诊疗对改善患者生存至关重要, 随着患者生存期的延长, 在治疗方案制定之前需要兼顾患者的生育保存需求, 加强生殖医学科与肿瘤科之间的交流, 在治疗前进行详细评估和多学科联合会诊, 尽最大努力为有需求、有条件的患者保留生育能力, 提高患者的生存质量。

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