

# 子宫肉瘤患者保留生育功能治疗研究进展

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## 摘要

子宫肉瘤(Uterine Sarcomas, US)是一组罕见且异质性极强的子宫恶性肿瘤,虽多发于围绝经期,但仍有相当比例的育龄期女性受累。随着生育年龄的推迟及辅助生殖技术的进步,年轻患者对保留生育功能治疗(FST)的需求日益凸显。本文综述了对子宫肉瘤患者实施FST的最新研究进展,分析了低级别子宫内膜间质肉瘤(LG-ESS)、子宫腺肉瘤(UA)及子宫平滑肌肉瘤(uLMS)等不同亚型的保育治疗可行性、肿瘤学安全性及妊娠结局。现有证据表明,早期LG-ESS和无肉瘤样过度生长的UA患者行FST后妊娠结局相对较好,但复发风险仍需高度警惕;而uLMS及高级别子宫内膜间质肉瘤(HG-ESS)因侵袭性强、预后不良,保育治疗需极度慎重。此外,本文还阐述了保育手术、激素治疗及辅助生殖技术在子宫肉瘤FST综合诊疗中的应用策略。

## 关键词

子宫肉瘤, 保留生育功能治疗, 辅助生殖技术

# Advancements in Fertility-Sparing Treatments for Patients Diagnosed with Uterine Sarcoma

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## Abstract

Uterine Sarcomas (US) constitute a rare and highly heterogeneous group of malignant tumors

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affecting the uterus. While these tumors predominantly manifest during the perimenopausal period, a significant number of cases occur in women of reproductive age. The trend of delayed childbearing has led to an increased demand for fertility-sparing treatment (FST). This review critically examines the feasibility and safety of FST for various subtypes, including endometrial stromal sarcoma (ESS), uterine adenosarcoma (UA), and uterine leiomyosarcoma (uLMS). Current evidence indicates that early-stage low-grade ESS and UA without sarcomatous overgrowth are associated with favorable pregnancy outcomes, albeit with a risk of recurrence. In contrast, FST should be approached with extreme caution in cases of aggressive uLMS and high-grade ESS due to their poor prognosis. The review concludes by discussing comprehensive strategies that integrate surgical intervention, hormonal therapy, and assisted reproductive technologies.

## Keywords

Uterine Sarcoma, Fertility-Sparing Treatment, Assisted Reproductive Technology

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## 1. 引言

子宫肉瘤(uterine sarcoma, US)是一类起源于子宫间质或肌层组织的罕见恶性肿瘤, 约占所有子宫恶性肿瘤的 3%~7%, 在所有女性生殖器官恶性肿瘤中占比不足 1% [1]。尽管流行病学数据显示其中位诊断年龄为 50~60 岁, 但年轻化趋势不容忽视, 约 10%~15% 的患者在 40 岁以下确诊[2]。尤其值得关注的是, 在 15~49 岁的育龄女性中, 肉瘤在子宫体恶性肿瘤中的比例高达 12.5% [3]。目前, 全子宫切除术仍是子宫肉瘤治疗的基石[4]。随着辅助生殖技术(Assisted Reproductive Technology, ART)的进步及癌症生存率的提高, 越来越多的年轻患者在确诊时表达了强烈的生育愿望。调查显示, 高达 78% 的育龄期患者愿意为保留生育功能而承担更高的复发风险[4]。然而, 由于子宫肉瘤发病率低、病理亚型复杂, 且缺乏特异性的术前诊断标志物, 导致其保留生育功能治疗(fertility-sparing treatment, FST)缺乏高级别循证医学证据支持。临床数据显示, 子宫肉瘤的 FST 虽然能带来约 32% 的总体妊娠率, 但不同亚型的预后差异呈两极化: 低级别子宫内膜间质肉瘤(Low-grade endometrial stromal sarcoma, LG-ESS)复发率为 54%, 但死亡率仅为 1.1%, 且复发多为局部; 而子宫平滑肌肉瘤(Uterine leiomyosarcoma, uLMS)复发率高达 71%, 死亡率则达到 57.1% [5]。这提示临床医生在面对此类需求时, 必须在充分评估肿瘤风险的前提下, 制定高度个体化的诊疗方案。本文旨在通过梳理不同亚型子宫肉瘤的 FST 研究进展, 保育手术、激素治疗及辅助生殖技术在子宫肉瘤 FST 综合诊疗中的应用策略, 为临床决策提供参考。

## 2. 不同类型子宫肉瘤患者保留生育功能治疗的探索

### 2.1. 子宫内膜间质肉瘤

子宫内膜间质肉瘤(endometrial stromal sarcomas, ESS)可分为低级别(LG-ESS)与高级别(HG-ESS), 其中 LG-ESS 约占 ESS 总数的 80%, 是第二常见的子宫恶性间叶性肿瘤, 总体预后较好[6]。其临床特点为病程进展缓慢, 接受标准治疗的 I 期 LG-ESS 患者, 5 年疾病特异性生存率约为 90%, 中位复发时间为 65 个月, I~II 期患者的 5 年总生存率约为 90% [7]。而 HG-ESS 患者 5 年总生存率仅为 30%~40% [8], 因其高度侵袭性及不良预后, 原则上不建议实施保留生育功能治疗[9]。

LG-ESS 患者行 FST 的生育结局相对乐观。一项系统综述显示, 89 例 LG-ESS 患者接受保守治疗后的妊娠率为 41.5%, 活产率为 78.1% [7]。另一项纳入 63 例 I 期 LG-ESS 患者的荟萃分析结果表明, 结果显示 27 例患者成功妊娠(其中 1/3 借助辅助生殖技术), 34 例出现疾病复发(其中 3 例发生于妊娠期), 1 例死亡[10]。临床实践中, LG-ESS 患者的保留生育功能手术多限于 IA 期病例。IB 期患者接受该治疗后的妊娠成功率显著下降, 且复发风险大幅升高。一项多中心研究显示, 在 17 例 FIGO I 期 LG-ESS 患者(6 例 IA 期、11 例 IB 期)中, 经中位随访 39 个月, 共有 10 例(58.8%)复发, 且均为 IB 期患者[11]。虽在本项研究中显示在 17 例患者中复发率达 58.8%, 但其样本量有限, 需谨慎看待。研究显示, LG-ESS 的复发主要以局部复发为主, 而远处转移较为少见。这可能与肿瘤的生物学特性有关, 例如其较低的增殖活性和较高的激素受体表达, 这些特性可能限制了肿瘤的远处转移能力[12], 在充分知情同意及严密监测下, 实施 FST 具有可行性。近期一项针对 LG-ESS 保留生育功能治疗的专项研究纳入 135 例原发性 LG-ESS 患者, 其中 21 例(15.6%)接受了保育手术。在术后尝试受孕的 9 例患者中, 7 例成功分娩 8 名活婴, 且无流产事件发生。然而, 该研究同时指出, 接受 FST 患者的复发风险较标准治疗组提升了 3.5 倍, 虽未发现其与死亡率之间存在显著关联, 但仍需警惕[13]。JAZF1/SUZ12 基因融合大约存在于 50% 的 LG-ESS 病例中, 是 LG-ESS 的细胞遗传学标志, 有望成为一种特异性诊断工具[14]。JAZF1-SUZ12 融合基因的检测在术前和术中诊断中具有实际应用价值。通过内膜活检或术中组织学分析检测该基因融合, 可以帮助临床医生在手术前更准确地评估肿瘤的性质, 从而制定更为精准的保育治疗方案, 为患者提供了更为个性化的治疗选择[15] [16]。

## 2.2. 子宫腺肉瘤

子宫腺肉瘤(Uterine Adenosarcoma, UA)是一类罕见的混合性上皮-间质肉瘤, 占子宫肉瘤的 5%~8% [17]。该肿瘤由良性上皮成分与肉瘤样间质成分构成。临床根据肉瘤样成分占比将其分为两类: 肉瘤样成分占肿瘤体积  $\geq 25\%$  者为伴肉瘤样过度生长(Sarcomatous Overgrowth, SO)的 UA, 约占 10%; 占比  $< 25\%$  者为无肉瘤样过度生长的 UA。无肉瘤样过度生长的 I 期 UA 患者预后相对良好, 5 年总生存率可达 80% [18], 这为该亚型患者实施 FST 提供了理论依据。

然而, 现有研究表明子宫腺肉瘤患者行 FST 后的生育结局并不理想。数据显示, 19 例接受 FST 的患者中, 妊娠率仅为 21% [5]。一项单中心回顾性研究纳入 7 例未生育的 I 期 UA 保育治疗患者, 经 32 个月随访发现: 3 例无瘤生存(其中 1 例成功足月阴道分娩), 2 例病变持续存在, 2 例带瘤生存[19]。L'Heveder A 等曾报道 1 例 18 岁低级别 UA 患者行保育治疗, 术后通过严密的超声、宫腔镜联合子宫内膜活检监测, 随访 20 年间成功通过体外受精(IVF)受孕并诞下双胞胎, 完成生育后行腹腔镜全子宫切除术, 术后未见复发[17]。对于无肉瘤样过度生长的早期子宫腺肉瘤患者, 实施 FST 具有一定的临床可行性, 但术后必须建立严密的长期随访监测机制。

## 2.3. 子宫平滑肌肉瘤

子宫平滑肌肉瘤(Uterine Leiomyosarcoma, uLMS)是最常见的子宫肉瘤亚型, 约占 40%。其生物学行为具有显著侵袭性, 5 年总生存率仅为 30%~40% [20] [21]。鉴于该病高复发率及不良预后, 目前不推荐常规行保留生育功能手术, 相关报道亦十分有限。一项多中心研究显示, 11 例接受保守手术的年轻 uLMS 患者中, 5 例在术后 35 个月内复发, 仅 3 例成功分娩[9]。虽有个案报道显示, 部分误诊为子宫肌瘤的 uLMS 患者在接受肌瘤剔除及术后辅助治疗后成功自然受孕并分娩[22]。但需注意的是, 妊娠期高雌激素水平可能促进肿瘤增殖, 进而增加复发风险[23], 研究指出, 约 24% 的妊娠患者在产后 1 年内出现复发[24]。在生育结局方面, 接受保守手术的患者约 46.7% 可成功妊娠, 活产率约为 66% [24], 但妊娠并发症

(如早产、低出生体重)发生率较高,其中早产率约为 11.5% [25]。目前关于 uLMS 患者 FST 的安全性缺乏大样本循证医学证据,临床决策需极度谨慎。

## 2.4. 其他子宫肉瘤类型保育治疗研究

除上述亚型外,子宫胚胎性横纹肌肉瘤(Uterine Embryonal rhabdomyosarcoma, ERMS)和子宫尤因肉瘤(Uterine Ewing's sarcoma, UES)等罕见亚型的 FST 研究多限于个案报道。uERMS 多见于儿童,成年女性罕见,生物学行为相对温和,早期患者 5 年 OS 可达 78.2% [26]。有报道显示,年轻 uERMS 患者经化疗达到完全缓解后可成功自然受孕[27]。鉴于患者发病年龄通常较小,对于符合条件的病例,应积极评估 FST 的可行性。原发性子宫尤因肉瘤(UES)侵袭性极强,目前尚无统一治疗标准。对于有生育需求的育龄期患者,可尝试在多学科团队(Multidisciplinary team, MDT)指导下,采取肿瘤剔除术联合放化疗及辅助生殖技术(如卵巢移位术)的综合治疗模式[28]。已有成功案例提示,通过整合多种治疗手段,可在保障疗效的前提下最大程度满足患者的生育需求[28]。

## 3. 子宫肉瘤患者保留生育功能的综合治疗策略

### 3.1. 术前评估与鉴别诊断的挑战

经阴道超声在子宫肉瘤的初步筛查中的应用广泛,但其特异性较低,容易导致误诊或漏诊。相较之下,磁共振成像(MRI),尤其是扩散加权成像(DWI)和表观扩散系数(ADC)图,在鉴别良恶性方面具有重要价值[29]。一项研究指出,结合血清 LDH 水平和 MRI 特征,可提高 uLMS 的术前诊断准确率,这对于避免非意愿的肿瘤粉碎术至关重要[30]。

### 3.2. 保守手术治疗原则

子宫肉瘤患者的保守手术治疗核心原则是在彻底切除肿瘤的前提下,尽可能保留子宫及卵巢功能。术中必须确保肿瘤的完整切除,严格遵循无瘤原则,避免肿瘤破裂或播散[31]。术后需建立严格的随访机制,包括定期的 MRI 影像学检查及血清标志物监测[11]。关于卵巢保留的问题需审慎评估。Dimitrios 等的研究发现,保留卵巢组的肿瘤复发率显著高于双侧附件切除组(46.8% vs 24.2%),提示内源性激素暴露可能是导致复发风险增加的重要因素[32]。此外,术前分子诊断(如基因融合检测)有助于精准筛选适合 FST 的低危患者[33]。未来,优化术前评估体系、改进手术技术及加强术后监测将是该领域的主要发展方向。

### 3.3. 激素治疗的应用

激素治疗主要适用于激素受体(ER/PR)阳性的患者,其中 LG-ESS 是核心适用人群[34]。常用药物包括孕激素类(如甲地孕酮、甲羟孕酮)、芳香化酶抑制剂(AIs,如来曲唑、阿那曲唑)及促性腺激素释放激素激动剂(GnRH-a) [35]。孕激素作为 LG-ESS 的一线治疗药物,其客观有效率可达 60%~80% [36]。已有病例证实, LG-ESS 患者术后应用高剂量孕激素治疗可有效控制病情,并为后续辅助生殖创造条件[37]。芳香化酶抑制剂(如来曲唑)在控制 LG-ESS 进展的同时不影响卵巢储备功能,部分缓解率及疾病稳定率较为理想,且与孕激素联合使用可能进一步提升疗效,尤其适用于复发患者[35] [38] [39]。必须强调的是,他莫昔芬(Tamoxifen)因具有潜在刺激肿瘤生长的风险,被明确列为 LG-ESS 治疗的禁忌药物[35]。治疗期间需密切监测药物不良反应,如骨质疏松、血脂异常及血栓风险,并给予相应处理。

### 3.4. 子宫肉瘤患者的辅助生殖技术应用

对于年轻子宫肉瘤患者,辅助生殖技术主要用于肿瘤治疗前的生育力保存及治疗后的助孕。研究显示,使用 GnRH-a 联合芳香化酶抑制剂进行控制性超促排卵,可在有效获取卵母细胞的同时降低雌激素

水平, 避免刺激肿瘤进展[40]。此外, 卵巢组织冷冻保存与移植技术已显示出良好的有效性与可行性, 移植后卵巢内分泌功能恢复率高, 为年轻患者保留生育力提供了新的临床策略[41]。尽管目前尚无子宫肉瘤患者移植后妊娠的确切报道, 但该技术 in 生育力保护领域的应用前景广阔。

#### 4. 总结与展望

子宫肉瘤患者的保留生育功能治疗是一项充满挑战的临床决策, 需在肿瘤安全性与生育需求之间寻求平衡。现有证据表明, 对于 I 期(尤其是 IA 期)低级别子宫内膜间质肉瘤及无肉瘤样过度生长的早期子宫腺肉瘤患者, 在充分知情同意及严密监测下, 实施 FST 具有可行性, 且结合辅助生殖技术有望获得良好的妊娠结局。然而, 对于高侵袭性的子宫平滑肌肉瘤及其他高危亚型, FST 应被视为极高风险的探索性医疗行为, 原则上不予推荐, 或仅在极个别严格筛选的病例中谨慎实施。

未来, 子宫肉瘤的 FST 应依托于多学科团队(MDT)的协作模式, 治疗策略应涵盖精准的分子病理诊断、彻底的肿瘤切除、个体化的术后辅助治疗以及终身的随访监测。随着分子生物学研究的深入及生育力保存技术的成熟, 期望能建立更为精准的风险分层体系, 为年轻子宫肉瘤患者提供更安全、有效的生育保护方案。

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