

卵巢组织冷冻保存和移植在青春期前女童中的应用进展

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[摘要] 针对罹患需化疗、放疗或骨髓移植等恶性肿瘤,或有骨髓移植指征的免疫性、代谢性和血液系统疾病等良性疾病,以及其他早发性卵巢功能不全高危疾病的青春期前女性患儿,卵巢组织冷冻保存和移植是目前唯一可行的生育力和卵巢内分泌功能保护方法。该技术的标准流程为:通过腹腔镜微创手术获取卵巢组织,并进行慢速程序化冷冻保存;待原发病治愈且患者有生育或恢复卵巢内分泌功能需求时,经多学科评估和个体化决策后选择适当时机和策略进行移植。目前多采用卵巢原位移植。对于卵巢携癌风险高的患者,建议移植前采用组织病理学和分子生物学等方法检测卵巢皮质微量残留。全球范围内,借助卵巢组织冷冻保存和移植技术已诞生超过300名健康婴儿,移植使用的组织多数来源于青春期后冷冻保存的卵巢组织,而源自青春期前冷冻保存的卵巢组织在移植后成功诱导青春期发育并实现妊娠和活产案例较少。本文综述了卵巢组织冷冻保存和移植在青春期前女童中的适应证、应用现状、冷冻保存和移植时机及策略、移植后肿瘤细胞引入风险评估以及临床结局等研究进展,并探讨了其联合卵母细胞体外成熟技术的潜在价值和现实挑战,以期为临床实践提供参考。



[关键词] 生育力保存;青春期前女童;卵巢组织冷冻保存;卵巢移植;卵母细胞体外成熟;青春期诱导;综述

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Advances in ovarian tissue cryopreservation and transplantation for fertility preservation in prepubertal patients

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[**Abstract**] Ovarian tissue cryopreservation and transplantation is currently the only feasible method for preserving both fertility and ovarian endocrine function in prepubertal females. It is indicated for those requiring gonadotoxic therapies such as chemotherapy, radiotherapy, or bone marrow transplantation for malignant diseases, as well as for non-malignant diseases, including immunologic, metabolic, and hematologic benign diseases requiring bone marrow transplantation, and other populations at high risk of premature ovarian insufficiency. The procedure involves laparoscopic retrieval of ovarian tissue, followed by slow-programmed cryopreservation. When the primary disease is cured and fertility or hormonal function restoration is desired, the tissue is thawed and transplanted, most commonly to an orthotopic site. For patients at high risk of ovarian malignancy, pre-transplantation assessment of minimal residual disease in the ovarian cortex is performed using histopathology and molecular biology techniques. Globally, while ovarian tissue cryopreservation and transplantation has led to over 300 live births, the majority result from tissue cryopreserved after puberty. Successful restoration of puberty and subsequent live births following transplantation of tissue frozen before puberty, although demonstrated in reported cases, remain less common. This review systematically summarizes recent advances in the indications, current application status, timing and strategies of ovarian tissue cryopreservation and transplantation, risk assessment of tumor cell reintroduction, and clinical outcomes in prepubertal patients. It also discusses the potential value and current challenges of combining this approach with *in vitro* oocyte maturation techniques, aiming to provide practical references for clinical practice.

[**Key words**] Fertility preservation; Prepubertal girls; Ovarian tissue cryopreservation; Ovarian transplantation; Oocytes *in vitro* maturation; Puberty induction; Review

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[**缩略语**] 早发性卵巢功能不全(premature ovarian insufficiency, POI); 微量残留病(minimal residual disease, MRD); 聚合酶链反应(polymerase chain reaction, PCR)

女孩的青春期通常始于9~11岁、结束于15~17岁,以月经初潮(通常发生在12岁左右)为最重要的标志。从生物学角度看,青春期前女童的卵巢中储备着大量原始卵泡,具有巨大的生育潜力^[1]。然而,一些疾病的治疗方案可能会对卵巢造成不可逆的医源性损伤^[2]。全球每年新增约40万名儿童肿瘤患者^[3],随着医疗水平进步,其5年存活率已超过85%^[4],但抗癌治疗(包括手术、化疗、放疗和造血干细胞移植等)常对患儿的卵巢功能造成损伤^[2]。研究显示,不孕症已成为儿童期肿瘤幸存者面临的常见问题,严重影响其生活质量^[5]。即便是良性疾病,若需接

受造血干细胞移植,几乎所有接受清髓处理的患儿均会发生卵巢功能衰退,从而引发POI,阻碍子宫等生殖器官的正常发育^[6]。此外,半乳糖血症这种罕见的先天性代谢性疾病会导致绝大多数患儿在成年前耗尽卵巢储备^[7-8];而特纳综合征患儿仅10%~30%能自发经历青春期发育,5%~10%可经历月经初潮,自然妊娠率低至2%~10%^[7,9]。因此,生育力保护的必要性已扩展至所有面临高POI风险的青春期前女童。

卵巢组织冷冻保存(以下简称冻存)和移植是目前针对上述患儿的主要且有效的生育力保存技术。该技术通过腹腔镜微创手术获取患儿卵巢组

组织(青春期前患儿推荐单侧卵巢取材)进行冻存,待未来需要时再进行移植^[10-11]。2019年,美国生殖医学学会宣布此技术不再是试验性技术,可作为临床常规的生育力保存技术^[12]。截至2021年,通过此技术出生的健康婴儿已超过200例,目前估计已达300例以上^[13-14]。尽管如此,全球范围内源自儿童的冷冻卵巢组织在移植后成功诱导青春期发育并实现妊娠和活产案例较少^[15-17],青春期前女童卵巢组织冻存的临床实践信息匮乏,其生育力保护领域的临床经验有限。与此同时,PanCareLIFE联盟和国际儿童癌症远期效应指南协调小组明确强调,所有儿童肿瘤患者及其家属均有权了解治疗可能带来的性腺损伤风险及现有的生育力保存技术^[18]。本文围绕卵巢组织冻存和移植及其在青春期前女童生育力保护中的应用进展作一综述,以期为临床实践提供参考。

1 卵巢组织冷冻保存和移植概述

目前,临床主要的生育力保存技术包括胚胎冻存、卵母细胞冻存以及卵巢组织冻存等,但对青春期前女童而言,卵巢组织冻存和移植是目前唯一可行的生育力保存方案^[19]。尽管有研究尝试从青春期前女童卵巢组织中获取未成熟卵母细胞进行体外成熟后冷冻,但由于其下丘脑-垂体-卵巢轴尚未成熟,卵母细胞的体外成熟率低,因此该技术仍处于探索阶段,不作为常规方案推荐^[2, 20]。相比之下,卵巢组织冻存不依赖于月经周期,通过微创手术获取卵巢组织即可进行,整个流程仅需数日,不会延误后续的疾病治疗,是所有需要紧急进行生育力保存患者的推荐方案^[2, 20]。

卵巢组织冻存技术的临床探索可追溯至1996年Hovatta等^[21]的研究,随后的临床实践充分证实了其安全性^[13, 22]。卵巢组织冻存前需行腹腔镜下卵巢组织取材术,以获取用于冻存的卵巢组织^[23]。Beckmann等^[24]研究显示,腹腔镜下卵巢组织取材的并发症发生率较低。针对青春期前女童,因其年龄小,腹腔镜手术应首先考虑采用5 mm光学套管针操作;又因其卵巢体积小且髓质少,推荐单侧卵巢切除,该方案能在有效控制出血和卵巢损伤风险的同时,获取足够量的卵巢组织,以增加未来移植的机会^[25]。在冻存环节,目前认为慢速程序化冷冻是卵巢组织冻存的标准方法^[2, 12, 26]。

目前,临床上多采用原位移植卵巢组织,包括移植到卵巢内、卵巢上或卵巢对应位置的盆腔腹膜袋中。由于放疗、化疗后的卵巢组织可能出现萎缩,因此移植于盆腔腹膜更有利于血液循环的建立。Ruan等^[27]用冷刀切开盆腹膜,钝性分离形成腹膜袋,将复苏的组织块平行植入袋内,术后未观察到并发症。目前借助卵巢组织冻存和移植技术诞生的婴儿大部分通过原位移植实现,原位移植有利于移植后患者的自然妊娠。盆腔粘连严重不宜进行原位移植时可进行异位移植。卵巢组织异位移植即移植到盆腔外,包括前臂或腹壁肌肉等部位。异位移植可避免腹腔侵入性操作,可多次移植且成本较低,便于监测移植组织中恶性肿瘤复发。然而,异位移植可能面临卵泡提前闭锁和临床结局不佳的双重挑战^[28],其妊娠率和活产率均显著低于原位移植^[29]。此外,不建议一次性将所有冻存的卵巢皮质移植回体内,可根据冻存卵巢皮质数和卵巢皮质内卵泡密度移植部分组织,以备在卵巢功能丧失后再次移植。

2 卵巢组织冷冻保存和移植的适应证及青春期前女童应用现状

卵巢组织冻存和移植的适应证主要包括需化疗、放疗或骨髓移植等恶性肿瘤疾病,有骨髓移植指征的免疫性、代谢性和血液系统疾病等良性疾病,以及其他POI高危疾病^[2, 10-11]。

从全球多个中心的临床实践来看,青春期前女童卵巢组织冻存的主要适应证为各类肿瘤性疾病^[30-32]。研究显示,14岁及以下肿瘤患儿中,患白血病最常见(约占28%),其次为神经系统肿瘤(约占26%);15~19岁肿瘤患者中,患神经系统肿瘤占比升至首位(约占21%),其次为淋巴瘤(约占20%),且霍奇金淋巴瘤的病例数约为非霍奇金淋巴瘤的两倍^[33]。尤因肉瘤作为儿童第二常见的恶性骨肿瘤,约占所有儿童恶性肿瘤的3%,由于患儿存活率已超过70%,尤因肉瘤也成为卵巢组织冻存的重要适应证之一^[34]。此外,在非肿瘤性疾病中,遗传性血红蛋白病是卵巢组织冻存的重要适应证:全球每年约有30万~40万新生儿患有该病,以地中海贫血和镰状细胞病最为常见^[35]。另外,对于拟行造血干细胞移植的患儿,也建议提前进行卵巢组织冻存^[36]。

欧洲多个中心报道了可观的卵巢组织冻存

病例数^[30, 37-38]。意大利博洛尼亚临床中心为超过千名患者提供了卵巢组织冻存,其中青少年占比近25%^[30];比利时多个团队也报道了上百例患者进行卵巢组织冻存的案例,其中青春期前女童占10%~20%^[31-32]。在中国,卵巢组织冻存技术也已成功落地并实现了规模化应用。阮祥燕教授团队已为超过300例15岁及以下患儿成功实施了卵巢组织冻存,患儿疾病涵盖从特纳综合征到需行造血干细胞移植的良恶性疾病,均采用腹腔镜下卵巢组织取材术,无一例发生术中、术后并发症,证明了该技术在人群中应用的安全性和普适性^[39-41]。梁晓燕教授团队也报道了百余例月经来潮前女童冻存卵巢组织的经验,可见该技术在国内已进入稳步发展阶段^[42]。上述临床实践数据表明,卵巢组织冻存已从探索性技术逐步转变为临床常规服务,随着病例的积累和技术的持续优化,卵巢组织冻存将为更多面临POI风险的青春期前女童提供生育力和卵巢内分泌功能保障。

3 卵巢组织冷冻保存和移植的时机、策略及肿瘤复发风险评估

选择恰当的冻存时机是确保卵巢组织冻存安全有效的关键。原则上,卵巢组织冻存应在性腺毒性治疗前进行,但对于白血病等卵巢携癌风险高的患者,为降低移植后肿瘤复发的风险,建议在化疗达到完全缓解后实施卵巢组织冻存^[2]。欧洲五大中心对285例冻存卵巢组织移植患者的分析显示,其中50例患者在卵巢组织冻存前经历过化疗,其卵巢功能恢复率与冻存前未接受化疗者相比无显著差异(分别为90.0%和85.3%),单变量与多变量分析进一步表明,冻存前是否行化疗对移植后的妊娠结局无显著影响^[13],这与先前研究结果一致^[22, 43-44]。但化疗药物的种类和累积剂量仍是关键的影响因素,如卵巢组织冻存前接受烷化剂化疗的女性,移植后的妊娠率显著低于未接受烷化剂化疗的女性(分别为32.1%和68.4%)。因此,在卵巢组织冻存前须综合评估患者的卵巢储备功能^[2, 45]。值得注意的是,两项关于生育力保护的指南提出即使化疗已经开始,卵巢组织冻存仍应被视为生育力保存的首选方法^[2, 26]。总之,须根据患儿原发病治愈情况、生长发育状态、卵巢功能、临床症状和实验室指标进

行综合判断,并充分尊重患者的移植意愿,最终需与患者、肿瘤专科医生及移植专家充分沟通评估后进行个体化决策^[2, 46]。

目前,多数证据报告卵巢组织冻存和移植后原发疾病未复发,但血液肿瘤学家仍担心卵巢组织皮质有携带白血病恶性细胞的风险^[13, 46-47]。为降低卵巢组织被白血病细胞浸润的风险,建议在患者经化疗达到完全缓解后再进行卵巢组织取材和冻存,但即便骨髓中检测不到,部分患者的卵巢组织中仍可能存在白血病细胞^[48-49]。因此,提倡应用多种技术检测卵巢皮质中可能存在的MRD,包括分子生物学技术(如荧光原位杂交、逆转录定量聚合酶链式反应)和组织病理学技术(如苏木素-伊红染色、免疫组织化学染色)等,检测时需根据原发肿瘤类型和起源选择细胞或分子水平的特异性标志物。值得注意的是,组织病理学染色的敏感度通常低于PCR检测^[50]。Rosendahl等^[51]研究发现,针对已知的特异性染色体易位或融合基因,利用PCR法进行MRD检测,在敏感性和准确性上均优于免疫组织化学染色。然而,PCR不适用于缺乏单克隆分子标志物的肿瘤,因此对于肿瘤标志物表达水平低或特异性差的患者,可采用多色流式细胞术来评估卵巢皮质组织的污染风险。此外,还可利用免疫缺陷小鼠异种移植试验评估风险^[47]。目前,MRD阳性通常定义为采用至少一种检测技术在至少一个卵巢组织片段中检测到MRD,敏感度阈值一般为万分之一至十万分之一。全球已有26例白血病患者进行卵巢组织冻存和移植,移植前进行MRD检测未见异常,移植后长期随访均无白血病复发^[45, 52]。本研究团队纳入5例接受冻存卵巢组织移植的白血病患者中,移植前MRD检测未见异常,移植后随访时间最长近2年、最短2个月,所有病例均无复发,仍在随访中。

4 冷冻保存卵巢组织移植后临床结局

4.1 通过恢复内分泌功能诱导青春期发育

冻存卵巢组织移植诱导患儿青春期发育临床明确有效。2012年《柳叶刀》报道了一例镰状细胞性贫血患儿10岁时行卵巢组织冻存(慢速程序化冻存23片卵巢皮质组织),在造血干细胞移植后27个月接受自体异位移植(左侧腹壁皮下组织)3片卵巢皮质组织,随后2个月内即出现双乳

房发育,4个月达到Tanner S2期,8个月时出现月经初潮且乳房发育达到Tanner S3期,标志着完整的青春期进程被激活^[53]。类似地,一例尤因肉瘤和一例重度地中海贫血患儿也分别在移植后12个月和5个月出现月经来潮,进一步证实了该技术在儿童内分泌功能重建上的可行性^[54-55]。

虽然移植后内分泌功能的激活时间通常在几个月内,但其维持时间可能因移植部位、移植组织块存活情况及原始卵泡储备等而异。例如,一例镰状细胞贫血患儿的规律月经持续了约2年^[53],而一例尤因肉瘤患儿则在19个月后可能因移植部位血供问题导致卵巢内分泌功能减退^[54],提示优化移植策略对于获得稳定的内分泌功能至关重要。鉴于儿童卵巢体积较小且冻存的卵巢皮质组织有限,可权衡后将移植时机推迟至有生育需求时;对于暂无移植条件但有诱导青春期发育需求者,可经专科评估后采用雌激素或雌激素联合孕激素等方案进行外源性激素治疗以诱导青春期发育^[56]。

4.2 通过恢复生殖功能实现妊娠及活产

冻存卵巢组织移植的另一目的是恢复患者的生殖功能并实现健康活产,这已在青春期前冻存卵巢组织的病例中获得成功。全球多个中心的成功案例证实了卵巢组织冻存和移植在恢复生育力方面的巨大潜力。2015年比利时团队报道了一例14岁因镰刀型细胞贫血症冻存卵巢组织的患儿于十年后移植,移植后5个月月经来潮,两年后自然妊娠并顺利分娩一名健康男婴^[15]。后续案例涵盖了多种疾病,包括 β 地中海贫血(卵巢组织冻存时患儿9岁,14年后移植并成功分娩一名健康婴儿)^[16]及其他疾病^[38, 57]。提示青春期前冻存的卵巢组织即便经过长期低温保存,其卵泡在移植后仍保留完整的发育潜能,最终成熟、受精并完成胚胎发育全过程。长期随访数据证实,通过此技术出生的子代,其遗传异常、出生缺陷及癌症的风险并未增加^[45, 58-59]。

综上,尽管青春期前冻存卵巢组织移植后的活产案例总数尚有限,但现有证据已表明该技术不仅安全可行,能通过自然方式实现妊娠,且子代健康状况良好。尤为重要的是,青春期前女童卵巢组织在血管结构和细胞外基质等方面的独特生物学特点为其在移植后的长期存活及功能维持提供了有利的微环境^[60],这从理论上解释了为何青春期前冻存的卵巢组织在成年后移植仍

有强大的生育潜能。未来的核心任务是积累更多案例,持续优化技术,以期为青春期前冻存卵巢组织的患儿在成年后获取长期、稳定的卵巢内分泌功能和生育能力提供保障。

5 卵巢组织冷冻保存与卵母细胞体外成熟联合策略

对于卵巢组织移植引入恶性肿瘤细胞风险高的患者,采用卵巢组织冻存与卵母细胞体外成熟联合策略是理想选择。该技术从一次取材中实现双重保障:既冻存了富含原始卵泡的卵巢皮质,又尝试获取并冻存成熟卵母细胞,为患者未来生育提供了可进行体外受精-胚胎移植的备用方案^[61]。然而,该技术在青春期前女童中的应用面临挑战。从青春期前女童卵巢组织中获取的未成熟卵母细胞,其获取数量和体外成熟率均显著低于青春期后女性^[62-63],这可能与青春期前女童卵巢组织中异常卵泡比例更高以及静止卵泡的体外激活机制尚不明确有关^[64]。

2025年美国临床肿瘤学会相关指南提到,卵母细胞体外成熟是一项新兴的生育力保存方法,然而,该技术妊娠率和活产率目前尚不明确,成功活产的案例有限,面临整体效率偏低的瓶颈^[26]。为攻克这一瓶颈,研究者正积极探索各种优化方案。多项研究已证实,在青春期前女童中实施卵母细胞体外成熟在技术上是可行的^[65-68]。促性腺激素预处理可能是提升效率的关键,如梁晓燕教授团队的最新研究表明,对月经初潮前女童进行为期3 d的150 U卵泡雌激素预处理,可将其卵母细胞总成熟率从36.2%显著提升至49.2%,且在低龄儿童中获益尤为明显^[40],但此预处理是否影响卵巢皮质中原始卵泡密度等尚未明确。未来研究亟须聚焦于提升体外成熟卵母细胞的受精率、妊娠率和活产率等,并通过前瞻性临床试验来验证卵母细胞体外成熟对活产结局的实质性影响。

6 结 语

目前,卵巢组织冻存和移植已被视为一种安全有效的生育力和卵巢内分泌功能保护方法,适用于成人和儿童。对于青春期前女童,推荐腹腔镜下完整切除单侧卵巢组织并进行冻存,尽可能高效且安全地保存其生育和卵巢内分泌潜能。

青春期前冻存的卵巢组织移植,无论是用于诱导青春期还是满足生育需求,在技术上均是可行的,对于未来发生POI风险高的女童,保护其生育力及卵巢内分泌功能对其心理健康也至关重要。尽管青春期前女童卵巢组织冻存的例数正逐渐增加,但儿童成长至产生移植需求存在较长的时间间隔,未来仍需更多关于青春期前女童卵巢组织冻存和移植的长期随访数据及研究证据。

本文附加文件见电子版。



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· 学术动态 ·

宋培歌研究员团队组织制订儿童青少年身心共患研究
优先议题国际共识

2025年10月9日,浙江大学公共卫生学院宋培歌研究员团队在《柳叶刀》子刊*eClinicalMedicine*发表题为“Research priorities on physical-mental comorbidity in children and adolescents: an international consensus”的卫生政策类研究论文(DOI: 10.1016/j.eclinm.2025.103559)。

近年来,儿童青少年身心共患问题呈高发态势,已成为影响儿童健康的重要公共卫生挑战。然而,全球相关研究呈现碎片化、不均衡状态,难以形成系统性、协同化的应对格局。研究人员聚焦该领域的研究议题优先排序,采用“儿童健康与营养研究倡议”(CHNRI)方法,邀请来自25个国家的82位专家参与,形成全球共识。结果显示,早期干预、治疗策略优化、教育与社会支持体系建设以及促进健康公平是当前全球儿童身心共患领域的优先研究方向。不同收入水平国家关注重点有所差异,高收入国家聚焦数字化干预,中低收入国家则更重视跨领域整合和服务体系建设。该研究为全球儿童身心健康研究提供了系统性议题框架和循证策略依据,有助于推动研究资源优化配置,并为制订更具公平性和可操作性全球卫生政策提供方向支撑。

浙江大学医学院蒋德楠硕士研究生和周佳丽博士研究生为论文第一作者。研究得到国家自然科学基金资助。