

·综述·

隐睾睾丸受损评价指标在术后随访中的意义

夏杰¹, 屈振繁^{2*}

(1. 湖北医药学院附属太和医院 小儿外科, 湖北 十堰 442000;

2. 深圳市妇幼保健院 小儿外科, 广东 深圳 518000)

摘要: 隐睾是小儿外科常见疾病, 各种因素会导致隐睾睾丸受损, 且隐睾术前睾丸受损程度与成年期生育能力相关, 本文将结合现有文献对隐睾的治疗、隐睾睾丸受损评价指标及其与生育潜力关系和术后随访重要程度进行综述, 以期提高临床医师对隐睾术后随访的重视度及最大程度预防发生成年期非梗阻性无精子症。

关键词: 隐睾; 非梗阻性无精子症; 超声检查

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Significance of evaluation indicators of testicular damage in cryptorchidism in postoperative follow-up

Xia Jie¹, Qu Zhenfan²

1. Department of Paediatric Surgery, Taihe Hospital Affiliated to Hubei University of Medicine, Shiyan, Hubei 442000, China;

2. Department of Paediatric Surgery, Shenzhen Maternal and Child Health Hospital, Shenzhen, Guangdong 518000, China

Corresponding author: Qu Zhenfan, E-mail: 13593741676@163.com

Abstract: Undescended testis is a common disease in pediatric surgery. Various factors can lead to testicular damage in cryptorchidism, and the degree of testicular damage before cryptorchidism surgery is related to fertility in adulthood. This article reviews the treatment of cryptorchidism, the evaluation indicators of testicular damage in cryptorchidism and their relationship with fertility potential, and the importance of postoperative follow-up. This article aims to increase the attention of clinicians to postoperative follow-up of cryptorchidism and to prevent the occurrence of non-obstructive azoospermia in adulthood.

Keywords: Undescended testicles; Non-obstructive azoospermia; Ultrasonography

隐睾亦被称为睾丸未降, 是指男性患儿出生后单侧或双侧睾丸从腹膜后下降过程中移行至阴囊以外的异常位置, 是儿童最常见的泌尿生殖系统先天性畸形之一^[1]。一般认为, 出生时未下降至阴囊的睾丸在出生后6个月内还有自发性下降的可能, 而6个月以后睾丸的自发性下降则不常见。持续性隐睾会导致睾丸发生一系列生理和病理变化, 导致生育能力受损和睾丸恶性肿瘤的发病率增加^[2]。因此, 早期对隐睾进行治疗可以减少生育能力受损, 改善术后睾丸追赶性生长并预防睾丸恶性肿瘤的发生^[3]。

1 隐睾的治疗

正常下丘脑-垂体-性腺轴在男性睾丸下降过程中

起着重要作用, 从性腺分化上讲, 胎儿睾丸间质细胞产生的雄激素、胰岛素样因子3和睾丸支持细胞产生的抗缪勒管激素 (anti-mullerian hormone, AMH)、抑制素B负责正常男性内生殖器的发育, 睾丸下降过程中相关激素的调控为激素治疗提供了重要的理论依据^[4-5]。LI等^[6]研究表明, 对隐睾患儿在术前或术后给予鼻内激素治疗可能会增加睾丸的生育指数 (每个小管的精原细胞数量)。BARTOLETTI等^[7]认为隐睾可能与成年男性的激素水平和精液分析相关, 单纯手术治疗的患儿在成年期的精子质量会受损, 而手术联合激素治疗对患儿成年期的精子密度、精子活动率和形成正常形状的精子细胞方面有显著的疗效, 因此, 建议早期行睾丸固定术, 并在术后进行激素治疗以获得更好的生育力, 从而进一步减少

*通信作者: 屈振繁, E-mail: 13593741676@163.com

不育症的发生。但隐睾的激素治疗一直存在争议性,激素治疗可能会优化生殖细胞的成熟并促进精子的产生,以至于成年期得到更好的精子质量,但人绒毛膜促性腺激素(human chorionic gonadotropin, HCG)在治疗后存在诸多副作用,比如HCG可使生殖细胞凋亡增加,导致不育、频繁勃起、阴茎过度发育、注射部位和生殖区的疼痛等^[8]。所以大多数情况下,并不鼓励使用激素,因为激素治疗的总体有效率很低并可能延误患儿接受外科治疗的时机,并且激素对于睾丸发育和睾丸功能的远期预后依然是未知的。

2014年发布的《美国泌尿外科协会指南》^[9]、2016年发布的《欧洲泌尿外科指南》^[10]均不推荐对隐睾使用激素治疗,睾丸固定术依然是隐睾治疗的金标准,手术的目的也是为了保持生育能力并预防恶性肿瘤的发生。考虑到睾丸在6个月内还有自发性下降的可能性,6个月后未下降睾丸的生殖细胞数量将进行性下降,因此,目前主流意见认为隐睾手术治疗的最佳时机是出生后6~18个月龄之间,以保持现有的生育潜力^[11]。隐睾的延迟治疗可能会对精子的产生和激素的分泌造成影响从而导致生育功能的减退,并增加睾丸肿瘤的发生率^[12-13],而早期对隐睾进行手术干预并不会增加睾丸的萎缩率^[14]。

2 隐睾睾丸受损与生育潜力的关系

有研究表明,由于80%~90%的睾丸质量由含有生殖细胞和支持细胞的生精小管组成,睾丸体积(testicular volume, TV)在很大程度上反映了精子的发生^[15]。隐睾在组织学上表现为睾丸间质细胞数量的减少和生殖细胞转化为精原细胞的过程发生了改变^[16]。TASIAN等^[17]证实了隐睾的这种组织病理学上的改变代表了生育力的降低,会影响到隐睾的生育指数;并强调隐睾是一种以生殖细胞和间质细胞持续性损伤为特征的进行性疾病,这种持续性的受损与年龄呈线性关系;并且睾丸受损与隐睾睾丸的位置也密切相关^[18]。这种组织学的变化导致生殖细胞的凋亡使隐睾成为成年后非梗阻性无精子症的主要病因之一^[19]。

KOLLIN等^[20]通过对不同年龄隐睾患儿进行手术时的睾丸组织活检,提出手术时的TV与生殖细胞和支持细胞的数量显著相关,并认为睾丸位置越高,每个生精管的精原细胞数量越少。ALLIN等^[21]进行荟萃分析时指出1岁前手术的隐睾患儿的TV、曲细精管直径、精原细胞数量明显高于1岁后,这表明患儿在1岁前接受手术具有更高的生育潜力。20%

的无精子症或不育男性既往患有隐睾, BARBOTIN等^[19]在排除了所有可能有其他生精障碍原因后,对既往患隐睾的成年人进行精液提取分析实验的结果指出双侧隐睾患者以生精小管内没有生殖细胞最常见,单侧隐睾患者以生精功能低下最常见。BELLURKAR等^[22]报道称TV与无精子症和少精子症显著相关,并且可以用作预测不孕不育的参数。隐睾患者的术前TV与其生殖细胞数量、精子密度和睾丸的生精活性呈正相关,TV的缩小也在一定程度上反映生育能力受损,这种相关性对评估生育潜力具有重要意义。

3 睾丸受损的评价指标

关于对睾丸受损程度的评估,对睾丸进行组织活检是金标准,但此方法对幼儿不适宜。血清标志物抑制素B、AMH似乎可以作为生育能力的预测因子。抑制素B、AMH在促卵泡雌激素(follicle stimulating hormone, FSH)刺激下由睾丸支持细胞分泌,睾丸间质细胞分泌的睾酮同样受黄体生成素(luteinising hormone, LH)的调节。由此认为抑制素B、AMH、FSH、LH和睾酮水平被认为是睾丸功能不同方面的直接或间接标志^[23]。MA等^[24]也指出抑制素B水平低提示睾丸功能障碍,并且可作为隐睾手术的短期评价指标。KATO等^[25]认为抑制素B、AMH是支持细胞功能的直接标志和精子发生的间接标志,并认为双侧隐睾患儿中低抑制素B/FSH和低AMH/FSH比值可能反映了生殖细胞的受损和未来的不育风险。

隐睾术前TV的缩小在一定程度上可以反映生育潜力受损,但对成年后生育能力的预测价值暂不可知。首选的监测TV的方法是超声检查(ultrasonography, US),US可以探测到97%的腹膜外型隐睾的睾丸位置和大小,TV的丢失量与精子生成障碍的程度有关,使用US测量TV可作为间接评价未来精子发生可能性的指标^[26]。对于隐睾术后TV的评价,建议随访至青春期是较为客观的,SADOV等^[27]表明隐睾患儿与正常患儿睾丸开始生长的平均年龄为11岁,而隐睾患儿青春期后的TV小于正常患儿。对于评价TV,可引用睾丸萎缩指数(testicular atrophy index, TAI)这一评价指标,定义为(对侧TV-受损TV)/对侧TV。NIEDZIELSKI等^[28]于2003年指出TAI是监测隐睾患儿治疗效果的一个客观的评价指标。LI等^[29]指出TAI可用于评价隐睾术前睾丸的受损程度,提出需在睾丸随年龄增长而受损增加之前进行手术以得到更好的预后。

睾丸位置和可触及性是隐睾睾丸受损的独立危

险因素, YOU等^[30]根据US所监测的睾丸活动度将单侧腹膜外隐睾患儿分为活动组和受限组, 结论表明睾丸活动受限组术前、术后的TAI均高于活动组。在活动组中, 各年龄组术后TAI均显著下降。相比之下, 在限制组中, 有效的体积增长只体现在1岁前接受过手术的患儿中。这表明隐睾睾丸位置越高, 睾丸受损程度越大。

4 隐睾的术后随访价值

早期对隐睾进行手术治疗已成为共识, 但是延迟手术的现象普遍存在。SCHMEDDING等^[31]针对2009年公布的德国指南, 分析了德国指南发表10年后的实施情况, 表明即使在指南发表10年后, 隐睾患儿在出生后1年内行睾丸固定术的概率仍然非常低, 国内隐睾的手术年龄也相对晚于最佳手术年龄。这与儿科医师对指南中手术时机的重视程度有很大关系, 需要让临床医师认识到隐睾手术时机的重要性, 及时做出准确诊断并转诊给外科医师是治疗的关键^[32-33]。已有相关研究证实了US在隐睾术前诊断中的价值所在, 但隐睾术后定期的US随访对术后TV进行监测以判断睾丸发育也至关重要, 可目前临床缺少术后随访数据作为标准进行评估^[34-35]。TAI可作为监测隐睾治疗成功的临床有效性的一个标准, TSENG等^[36]引用生长百分率比率(growth percent ratio, GPR)作为隐睾体积的一个评价指标, 即受损睾丸的生长百分率/对侧睾丸的生长百分率, 睾丸的生长百分率定义为术后TV/术前TV $\times 100\%$, 由于睾丸的生长百分率取决于随访时间, 在不同随访时间的回顾性研究中, GPR更适合于作为单侧隐睾术后恢复的评价指标。同时临床需重视隐睾患儿的术后随访率, 目前需要足够的证据来证明术后睾丸受损程度与成年后的生育能力之间是否存在相关性。

5 结论

综上所述, 隐睾作为小儿外科的常见疾病, 隐睾的早期治疗与保持生育能力、保持令人满意的睾丸大小和预防成年肿瘤转化的风险有关, 早期识别隐睾患儿并对其进行手术可最大程度上减少对睾丸的损害。US作为一种客观的评价工具, 可以对隐睾进行长期的术后随访, 同时US更有利于监测睾丸癌发病的风险。但TAI和GPR是否能作为睾丸受损的一个评价指标, 需要临床数据进行评判; 而血清标志物这一评价指标因其价格和需获得家属知情同意而在临床上实施受限。关于上述, 考虑是否能用

US作为隐睾术后的初步随访标准, 以筛选出需要进行血清标志物测定的人群, 从而对隐睾术后睾丸功能恢复进行更进一步的检查, 比如在青春期的监测及成年后的精液分析(精子密度、正常精子细胞数量和精子细胞活力的信息), 从而早期发现并进行干预以最大程度减少隐睾术后成年期非梗阻性无精子症的发生。

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