

在反复种植失败患者中应用宫腔镜检查 及宫腔搔刮术的临床意义

刘 玮, 陈 成, 向卉芬, 曹云霞

摘要 **目的** 探讨宫腔镜检查及宫腔搔刮术在反复种植失败患者中应用的临床意义。**方法** 选择反复种植失败的不孕患者 205 例, 根据是否行宫腔镜检查 and 宫腔搔刮术分为 3 组: A 组: 行宫腔镜检查联合宫腔搔刮术 ($n = 101$); B 组: 单纯行宫腔搔刮术 ($n = 39$); C 组: 未予任何干预措施 ($n = 65$)。将 A 组按照检查情况分为宫腔形态正常组 (A1 组) 和宫腔形态异常组 (A2 组), 分析 A 组宫腔镜检查情况, 并比较 4 组患者再次移植周期的临床妊娠率、胚胎种植率及不良妊娠率。**结果** A 组 57.4% 宫腔形态正常 (A1), 42.6% 显示宫腔内微小病变 (A2), 包括子宫内膜炎、子宫内膜息肉及增生、宫腔黏连等。A1 组、A2 组及 B 组临床妊娠率与胚胎种植率均明显高于 C 组, 差异有统计学意义 ($P < 0.05$), 但

A1、A2 及 B 组间比较无统计学意义。**结论** 宫腔镜能显示子宫腔内微小病变, 宫腔镜检查联合宫腔搔刮术和单纯搔刮术均有助于提高反复种植失败患者的临床妊娠率, 但前者与后者相比并未提高临床妊娠率。

关键词 反复种植失败; 宫腔镜; 宫腔搔刮术

中图分类号 R 711.6

文献标志码 A **文章编号** 1000-1492(2017)08-1240-04
doi: 10.19405/j.cnki.issn1000-1492.2017.08.031

体外受精 - 胚胎移植 (*in vitro* fertilization-embryo transfer, IVF-ET) 的成功率不断提高, 累计成功率达 40% 左右^[1], 但仍有相当一部分患者需经历反复种植失败 (repeated implantation failure, RIF)。此类患者约 60% 左右系因为子宫内膜容受性有缺陷, 造成胚胎着床困难^[2]。因此, 改善子宫内膜容受性, 就成为了提高 RIF 患者妊娠率的研究关键。宫腔镜能直观了解宫腔及子宫内膜情况, 且可以同时进行治疗, 是评价宫腔环境的金标

2017-04-18 接收

基金项目: 卫生部公益性行业科研专项 (编号: 201402004); 国家自然科学基金青年基金项目 (编号: 81501232)

作者单位: 安徽医科大学第一附属医院生殖中心, 合肥 230022

作者简介: 刘 玮, 女, 硕士研究生;

曹云霞, 女, 教授, 博士生导师, 责任作者, E-mail: caoyunxia6@126.com

cal spondylotic myelopathy (CSM), and discuss effect of the surgery on cortical reorganization in functional recovery. **Methods** 19 cases with CSM intrial group underwent cervical vertebra canal decompression surgery according to clinical routine. Cases in trial group completed clinical assessment using the modified Japanese Orthopaedic Association Scores (mJOA) prior to decompression and 12 months following surgery, and underwent cerebral functional MRI and conventional MRI in the same time. 19 controls also carried out cerebral functional MRI and conventional MRI. All subjects performed a finger-tapping paradigm with right hand during processing functional MRI. The imagings and data of trial group were divided into preoperative group and postoperative group in accordance with the time of completed and than analysed. **Results** The mJOA score of postoperative group was increased significantly ($P < 0.001$). Cortical volume of activation (VOA) of preoperative group was significantly higher than the control group ($P < 0.05$). VOA was lower in the postoperative group, but still significantly higher than the control group ($P < 0.05$). The preoperative group was able to detect and activate the signal only in the left precen-tral gyrus. The postoperative group was able to detect and activate the signal in the l left postcentral gyrus, the pre-motor area and the supplementary motor area, and the right cerebral cortex could also detect a small amount of activation signal. **Conclusion** CSM patients undergo cerebral cortical remodeling, causing sensory and motor function activation areas to expand and shift. The changes of cortical reorganization after cervical vertebra canal decompression surgery are associated with functional recovery. The surgical treatment may promote the compensating cortical reorganization.

Key words cervical spondylotic myelopathy; functional magnetic resonance imaging; canal decompression surgery; cortical reorganization

准^[3],其在辅助生殖技术中的应用逐渐增多,有研究^[4]指出对于RIF患者,最重要的干预措施之一是宫腔镜的诊治。另外近年来部分学者认为,机械性搔刮子宫内膜也能改善子宫内膜的容受性,提高RIF患者的妊娠率。该研究回顾性分析了在再次行冻融胚胎移植(frozen embryo transfer, FET)的205例RIF患者的资料,其胚胎种植率、临床妊娠率显著提高,现报道如下。

1 材料与方法

1.1 病例资料 选择2015年1月~2016年6月在安徽医科大学第一附属医院生殖中心采用经典长方案或拮抗剂方案超促排卵助孕的患者205例,所有患者既往有RIF经历,拟再次行FET。

纳入标准:①患者年龄<40岁,因输卵管不通或堵塞不孕;②基础卵泡刺激素(follicle stimulating hormone, FSH)<10 U/L;③行胚胎移植 ≥ 2 次,均着床失败,每次移植时至少有1枚优质胚胎(均为囊胚)且内膜厚度 ≥ 7 mm;④夫妻双方无重大疾病及活动期传染病,且染色体均正常。

排除标准:①患者有内分泌疾病或其他疾病导致不孕;②既往B超显示内膜异常回声或宫腔镜检查发现内膜病变(包括内膜息肉、宫腔粘连、内膜结核等);③输卵管积液;④最近3个月内服用过避孕药或其他激素类药物;⑤男方有严重精液异常导致不育。

1.2 分组及方法 将符合上述条件的205例患者按照有无内膜干预及干预方法不同分为3组:A组:行宫腔镜检查联合宫腔搔刮术($n=101$);B组:单纯行宫腔搔刮术($n=39$);C组:未予任何干预措施($n=65$)。其中根据宫腔镜检查情况再将A组分为:A1组:宫腔形态正常组($n=58$)和A2组:宫腔形态异常组($n=43$)。

宫腔镜检查联合宫腔搔刮术:患者于再次进入FET周期前1个月经周期的第8~10天行宫腔镜检查(日本奥林巴斯纤维宫腔镜,型号HYF-XP),膨宫介质选用5%葡萄糖,膨宫压力13.332~15.999 kPa。根据宫腔镜检查结果分为A1组和A2组,宫腔正常患者直接行宫腔搔刮术;宫腔异常组包括子宫内膜炎、子宫内膜息肉、轻度宫腔粘连等。宫腔异常患者均进行了相应的治疗,所有宫腔刮出组织送病理检查,术后常规口服抗生素预防感染。单纯宫腔搔刮术:患者于再次进入FET周期前1个月经周期的第8~10天行宫腔搔刮术。操作者以宫颈扩张

棒扩张宫颈管口至5.5号,在超声引导下用5号刮匙均匀且轻柔地搔刮宫腔1~4周。

1.3 FET方案和妊娠结局判断 根据患者既往月经周期情况选择内膜准备方案:①如患者既往月经规则,行自然周期:月经周期第11天开始监测卵泡及内膜发育情况,当卵泡破裂,内膜 ≥ 7 mm且内膜无明显异常回声时,予黄体支持,排卵后第5天行囊胚解冻移植术;②如患者既往月经不规则,则行激素替代周期:从月经周期或撤退性出血的第2天起,每天口服戊酸雌二醇2~8 mg,当内膜 ≥ 7 mm且无异常回声时,每天肌注黄体酮40 mg转化内膜,转化的第5天行囊胚解冻移植术。移植以后继续给予黄体支持。

于胚胎移植术后5周行B超检查,宫腔内见孕囊者定义为临床妊娠。不良妊娠包括早期流产、胚胎停育及异位妊娠。

1.4 统计学处理 采用SPSS 19.0统计软件对数据进行分析,计数资料使用率(%)表示,计量资料使用 $\bar{x} \pm s$ 表示,组间比较使用方差分析。组间比较使用 χ^2 检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 宫腔镜检查异常类型分析 宫腔镜检查异常组(A2)具体异常类型:24例子官内膜息肉,占23.76%;9例子官内膜过度增生,占8.91%;6例子官内膜炎,占5.94%;2例宫腔轻度粘连,占1.98%;1例子官黏膜下肌瘤,占0.99%;1例鞍状子宫,占0.99%。

2.2 4组患者一般情况比较 4组患者的一般情况如年龄、不孕年限、原发性不孕率、基础FSH值、自然周期所占比率、黄体酮转化日的内膜厚度等均差异无统计学意义,见表1。

2.3 4组患者FET结局比较 A1组、A2组、B组的临床妊娠率(49.1%、55.3%、52.8%)和胚胎着床率(26.9%、30.7%、29.6%)显著高于C组(23.8%、13.5%),差异有统计学意义($P < 0.05$),另外A2组的临床妊娠率和胚胎着床率虽高于A1和B组,但3组间差异无统计学意义,4组间的不良妊娠率也差异无统计学意义,见表2。补充说明:在各组患者中均有数例患者因各种原因未再次移植。

3 讨论

RIF是指优质胚胎移植2~6次以上或移植胚胎数量总计超过10枚仍未妊娠者。很多夫妇反复

表 1 4 组患者一般情况比较 [n(%), $\bar{x} \pm s$]

| 项目 | A1 组(n =58) | A2 组(n =43) | B 组(n =39) | C 组(n =65) | F/ χ^2 值 | P 值 |
|----------------------------------|----------------|---------------|---------------|----------------|---------------|-------|
| 年龄(岁, $\bar{x} \pm s$) | 29.88 ± 3.11 | 30.81 ± 3.61 | 30.60 ± 3.75 | 30.12 ± 4.14 | 0.663 | 0.576 |
| 不育年限(年, $\bar{x} \pm s$) | 3.98 ± 1.75 | 4.01 ± 1.55 | 4.13 ± 1.81 | 4.26 ± 2.01 | 0.293 | 0.830 |
| 原发不育率 [n(%)] | 30(51.72) | 23(53.49) | 20(51.28) | 33(50.77) | 0.080 | 0.994 |
| 基础 FSH 值(U/L, $\bar{x} \pm s$) | 6.83 ± 1.75 | 7.19 ± 1.83 | 7.14 ± 2.11 | 6.94 ± 1.98 | 0.385 | 0.764 |
| 转化日内膜厚度(mm, $\bar{x} \pm s$) | 10.48 ± 1.87 | 10.06 ± 1.94 | 9.87 ± 1.96 | 10.15 ± 1.76 | 0.920 | 0.432 |
| 自然周期所占比例 [n(%)] | 29/55(52.73) | 21/38(55.26) | 19/36(52.78) | 33/63(52.38) | 0.089 | 0.993 |
| 种植周期数($\bar{x} \pm s$) | 3.18 ± 1.15 | 3.17 ± 1.11 | 3.16 ± 1.02 | 3.17 ± 1.05 | 0.003 | 0.999 |
| 移植胚胎数($\bar{x} \pm s$) | 1.98 ± 0.59 | 1.86 ± 0.65 | 2.01 ± 0.54 | 2.12 ± 0.58 | 1.719 | 0.164 |
| 优质胚胎比例 [n(%)] | 61/108(56.48) | 43/76(56.58) | 39/73(53.42) | 71/108(55.47) | 3.395 | 0.335 |

表 2 4 组患者临床结局比较 [n(%)]

| 项目 | A1(n =55) | A2(n =38) | B(n =36) | C(n =63) | χ^2 值 | P 值 |
|-------|---------------|--------------|--------------|---------------|------------|-------|
| 临床妊娠率 | 27/55(49.1) | 21/38(55.3) | 19/36(52.8) | 15/63(23.8) | 14.052 | 0.003 |
| 胚胎种植率 | 29/108(26.9) | 23/75(30.7) | 21/71(29.6) | 17/126(13.5) | 11.228 | 0.011 |
| 不良妊娠率 | 2/27(7.4) | 2/21(9.5) | 2/19(10.5) | 2/15(13.3) | -* | 0.957 |

* : 由于不良妊娠率变量理论频数小于 5 的个数占 50% ,用确切概率法,所得检验统计量为 0.777

助孕失败,对其经济及心理造成极大负担。约 2/3 的 RIF 患者是因子宫内膜容受性不良导致不孕,因此改善子宫内 膜容受性就可以提高该类患者的妊娠率。一项资料荟萃分析指出 IVF-ET 失败患者宫腔异常率在 26.7% ~ 59.6% ,提示宫腔异常是影响子宫内 膜容受性,且导致 RIF 的重要原因之一^[5]。宫腔异常主要有子宫内 膜息肉、宫腔粘连、子宫内 膜炎等,这些宫腔内的隐性微小病变改变了宫腔内环 境,影响了子宫内 膜容受性^[6]。

目前临床上,最常使用阴道超声和输卵管造影观察宫腔形态,但二者都属于间接性的检查。Guimarães Filho et al^[4] 研究报道指出输卵管造影检查出的宫腔异常假阳性率达 15.6% ,假阴性率更高达 35.4% 。Oliveira et al^[7] 对 2 次 IVF-ET 失败,且输卵管造影检查未显示异常的患者进行宫腔镜检查,其中 25 例(45%) 患者显示子宫内 膜病变,而这些病变阻碍了胚胎植入。宫腔镜检查是诊断宫腔内病变的金标准,程丹等^[8] 研究指出,宫腔镜检查能显示宫腔内的微小病变,对提高 IVF-ET 患者成功率有良好的帮助。Lorusso et al^[9] 研究指出宫腔镜在不孕患者中检出宫腔病变率约为 40.6% ,其能在检出宫腔病变的同时进行治疗,建议作为不孕症患者的常规检查方法,但是他同时指出在 IVF-ET 前使用宫腔镜诊治不能显著提高不孕症患者的临床妊娠率。但其他多项研究^[10] 表明反复多次 IVF-ET 失败后最主要的干预措施是宫腔镜诊治,无论宫腔正常与否,均能提高患者的临床妊娠率。在本研究中,101 例曾行阴超或输卵管造影检查无异常的 RIF 患

者中,43 例(42.6%) 显示有宫腔内微小病变(A2 组),且 A2 及 A1(宫腔正常) 组进行干预后的临床妊娠率及胚胎种植率均高于未干预的 C 组。说明宫腔镜检查确实能显示宫腔内微小的病变,并且能提高 RIF 患者的临床妊娠率,这是因为对于宫腔异常的患者,在宫腔镜诊治过程中,可以将病灶直接摘除或进行针对性处理,从而改善了子宫内 膜的血液循环及胚胎着床环境,提高了临床妊娠率。而对于宫腔正常的患者,膨宫液冲刷子宫内 膜,均匀、机械性地扩张宫腔可能使某些内 膜基因表达发生了短时改变,促使内 膜释放了有利于胚胎着床的生长因子及细胞因子,利于胚胎种植,提高了临床妊娠率^[11-12]。

本研究所使用的宫腔搔刮术与常规诊断性刮宫和清宫不同,强调的是轻柔的搔刮或吸刮子宫内 膜,避免伤及内 膜基底层。近年来国内外部分学者将宫腔机械刺激用于 RIF 患者,以提高其妊娠率。Potdar et al^[13] 进行了一项资料荟萃分析指出: 子宫内 膜机械性的刺激提高子宫内 膜的容受性,改善了 RIF 患者的妊娠结局,本研究的结果与此报道一致。其中 B 组患者就是进行单纯宫腔搔刮术的 RIF 患者,其临床妊娠率和胚胎种植率显著高于未干预的 C 组患者,说明单纯宫腔搔刮术确实改善了子宫内 膜容受性,提高了 RIF 患者的临床妊娠率。这可能是因为宫腔搔刮术可以清除不规则的子宫内 膜,刮除局灶性的异常组织,促进了子宫内 膜螺旋动脉生成,增加子宫内 膜血流,促进了子宫内 膜腺体的发育,并使基质细胞水肿和蜕膜化;另外宫腔搔刮术可能激活

了一些参与建立子宫内膜容受性的相关因子,这些因子共同作用,改善了子宫内膜容受性,从而提高了临床妊娠率。

参考文献

- [1] Zeyneloglu H B, Onalan G. Remedies for recurrent implantation failure [J]. Semin Reprod Med, 2014, 32(4) : 297 - 305.
- [2] 刘杰, 郑洁, 陶海龙, 等. 子宫内膜轻创术对体外受精 - 胚胎移植治疗结局的影响 [J]. 实用医学杂志, 2012, 28(5) : 748 - 50.
- [3] Kasius J C, Broekmans F J, Fauser B C, et al. Antibiotic prophylaxis for hysteroscopy evaluation of the uterine cavity [J]. Fertil Steril, 2011, 95(2) : 792 - 4.
- [4] Guimarães Filho H A, Mattar R, Pires C R, et al. Comparison of hysterosalpin gography, hysterosonography and hysteroscopy in evaluation of the uterine cavity in patients with recurrent pregnancy losses [J]. Arch Gynecol Obstet, 2006, 274(5) : 284 - 8.
- [5] 牛婷, 李爱斌, 沈兰, 等. 宫腔镜用于体外受精 - 胚胎移植失败患者改善妊娠结局 Meta 分析 [J]. 生殖医学杂志, 2014, 23(10) : 828 - 33.
- [6] Rama Raju G A, Shashi Kumari G, Krishna K M, et al. Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome [J]. Arch Gynecol Obstet, 2006, 274(3) : 160 - 4.
- [7] Oliveira F G, Abdelmassih V G, Diamond M P, et al. Uterine cavity findings and hysteroscopic interventions in patients undergoing *in vitro* fertilization-embryo transfer who repeatedly cannot conceive [J]. Fertil Steril, 2003, 80(6) : 1371 - 5.
- [8] 程丹, 杨菁, 胡静, 等. 宫腔镜在再次体外受精 - 胚胎移植前的应用价值 [J]. 生殖与避孕, 2007, 27(2) : 150 - 1, 154.
- [9] Lorusso F, Ceci O, Bettocehi S, et al. Office hysteroscopy in an *in vitro* fertilization program [J]. Gynecol Endocrinol, 2008, 24(8) : 465 - 9.
- [10] Hosseini M A, Ebrahimi N, Mahdavi A, et al. Hysteroscopy in patients with repeated implantation failure improves the outcome of assisted reproductive technology in fresh and frozen cycles [J]. J Obstet Gynaecol Res, 2014, 40(5) : 1324 - 30.
- [11] Narvekar S A, Gupta N, Shetty N, et al. Does local endometrial injury in the nontransfer cycle improve the IVF-ET outcome in the subsequent cycle in patients with previous unsuccessful IVF? A randomized controlled pilot study [J]. J Hum Reprod Sci, 2010, 3(1) : 15 - 9.
- [12] Bosteels J, Weyers S, Puttemans P, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review [J]. Hum Reprod Update, 2010, 16(1) : 1 - 11.
- [13] Potdar N, Gelbaya T, Nardo L G. Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis [J]. Reprod Biomed Online, 2012, 25(6) : 561 - 71.

Clinical significance of hysteroscopy and endometrial scratch in patients with recurrent implantation failure

Liu Wei, Chen Cheng, Xiang Huifen, et al

(Reproductive Medicine Center, The First Affiliated Hospital of Anhui Medical University, Hefei 230022)

Abstract Objective To investigate the clinical significance of hysteroscopy and endometrial scratch in the patients with recurrent implantation failure. **Methods** 205 patients with recurrent implantation failure were enrolled. Based on the use of hysteroscopy and endometrial scratch, patients were divided into three groups: hysteroscopy combines endometrial scratch(group A, $n = 101$), endometrial scratch alone(group B, $n = 39$) and no specific treatment(group C, $n = 65$). Group A was then divided into two groups according to the outcome of hysteroscopy, including normal uterine cavity(group A1) and abnormal uterine cavity(group A2). The outcome of hysteroscopy was analyzed, and rates of clinic pregnancy in next transfer cycle, implantation rates and the rates of abnormal pregnancy were compared among groups. **Results** In group A, 57.4% were normal uterine cavities(group A1), and 42.6% were observed with small endometrial lesions(group A2), including endometritis, endometrial polyps and intrauterine adhesions. Clinical pregnancy rates were significantly higher in group A1, A2, and B than that in group C($P < 0.05$). However, there were no significant difference between group A1, A2, and B. **Conclusion** Small endometrial lesions can be found by hysteroscopy, the treatment using hysteroscopy combines endometrial scratch or endometrial scratch alone can increase clinic pregnancy rates in the patients with recurrent implantation failure, but there is no differences between the two groups.

Key words recurrent implantation failure; hysteroscopy; endometrial scratch