



生殖与避孕

SHENGZHI YU BIYUN

月刊 1980年12月 创刊

2014年7月第34卷第7期

主管

国家卫生和计划生育委员会

主办

上海市计划生育科学研究所

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计划生育药具重点实验室

辉凌医药咨询(上海)有限公司

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编辑出版

《生殖与避孕》编辑部

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http://www.RandC.cn

印刷

上海竟成印务有限公司

广告经营许可证

3100420100002

国内总发行

上海市报刊发行处

国内订购

全国各地邮政局

国外发行

中国国际图书贸易公司

(北京399信箱)

报刊代号

4-294(国外代号: M389)

国内统一连续出版物号

CN31-1344/R

定价

每期15.00元

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Directed by

National Health and Family Planning
Commission of PRC

Sponsored by

Shanghai Institute of Planned
Parenthood Research

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and Contraception No.779, Lao-
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China

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+86-21-64438169

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+86-21-64438975

E-mail

randc_journal@163.com

Website

<http://www.RandC.cn>

Printing

Shanghai Jingcheng Printing
Co., Ltd.

Domestic Distribution

Shanghai Post Office

Domestic Subscription

Local Post Offices

Foreign Distribution

China International Book
Trading Corporation
(GUOJI SHUDIAN)

Postal Code

4-294(Foreign Code: M389)

CSSN

ISSN 0253-357X
CN 31-1344/R

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· 述 评 ·

胚胎种植失败, 是内膜更重要吗?

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辅助生殖技术经历了36年的发展历程, 取得长足的进步, 妊娠率不断提高, 但是也存在胚胎反复种植失败的老大难问题。多年来对研究的投入是不平衡的, 对胚胎的研究比较深入, 也取得较好的效果, 如植入前遗传学筛查(PGS)、Time-Lapse, 已经从分子生物学水平跨越到生物物理学动态的胚胎发育监测, 降低了流产率, 提高了妊娠率。但是对内膜的接受性研究太少, 首先因为没有良好的体外模型; 我们对围种植期在体内内膜的认识太少; 种植期内膜的环境, 如免疫学、内分泌状态、代谢组学、蛋白组学的动态改变、胚胎内膜对话认识有限, 足以影响我们临床水平的提高。

作为对内膜接受性的研究, 最早通过月经周期卵巢内分泌的变化, 采用内膜的活检的方法提出了黄体期至排卵后6 d, 即月经周期第20~24日, 这5 d内称之为种植窗, 允许胚胎植入。而辅助生殖技术(ART)也是根据胚胎的年龄选择移植时间, 选择第3日胚胎(即取卵后第3日)或第5日囊胚(即取卵后第5日)进行移植。按照种植窗规律, 我们移植胚胎的时间是早了吗? 成功妊娠是因为改变了胚胎的培养环境, 是子宫不是培养箱。妊娠成功胚胎发育应该是正常的, 内膜与胚胎的对话是成功的。

着床是指处于活化状态的胚泡与处于接受态的子宫内膜相互作用, 最后导致胚胎滋养层与子宫内膜建立紧密联系的过程。着床失败是指胚胎与子宫内膜在建立这种紧密联系过程之前的某个环节发生异常, 导致胚胎不能着床。这些环节通常是免疫相容和免疫排斥的过程, 免疫调节通常处于动态平衡, 在免疫相容可以获得着床的机会, 免疫排斥胚胎不能着床。这是胚胎种植的头一关。胚胎已经开始着床, 滋养外胚层侵入子宫蜕膜层, 胚胎分泌的 β -hCG进入母体血液并达到可检测出的水平, 由于某种原因, 这种免疫动态平衡从免疫相容倾向于免疫排斥, 妊娠不能继续, 血或尿中的 β -hCG一过性的升高, 称为生化妊娠。

着床过程与内分泌是相关的, LH/hCG是通过卵巢颗粒细胞黄素化产生黄体酮启动种植窗, 雌、孕激素同样增加了内膜螺旋血管的增生及腺体的分泌, 为蜕膜化提供了基础。子宫内膜上的雌、孕激素受体不足也是造成内膜的发育异常, 包括内膜的厚度及形态的变化, 胚胎难以植入。近年来对内膜的研究有了一点进步, 从微阵列基因芯片研究围种植期内膜的变化。但是作为指导临床实践应用得还不多。

改善内膜对胚胎接受性的临床研究也不少, 如宫腔灌注hCG、粒细胞-巨噬细胞集落刺激因子(GM-CSF)、外周血单个粒细胞(PBMC)等, 子宫内膜搔刮增加免疫促炎作用, 有利于血管增生实现蜕膜化。国内同道发展了中医中药针灸以及物理治疗改善子宫内膜血流, 达到增加妊娠率的目的。

兰州大学生殖医学专科医院以张学红教授带领的团队早年已关注子宫内膜容受性的研究, 从子宫内膜炎性改变对助孕结局影响的研究, 基于炎症是病原体激发机体的免疫反应, 产生大量致敏的活性细胞并产生多种细胞因子, 炎性细胞, 免疫抗体可干扰正常胚胎和内膜间的组织相容性, 从而不利于胚胎着床和发育。我们所需要的促炎是对一些免疫反应对胚胎刺激弱或不产生反应的患者给予一定的刺激会带来好处。

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博士生导师, 兰州大学第一医院副院长, 兰州大学第一医院生殖医学专科医院暨甘肃省生殖医学专科医院院长, 中华医学会生殖医学分会常务委员, 国家人类辅助生殖技术评审组专家, 中华医学会妇产科分会内分泌学组委员, 甘肃省生殖医学专业委员会主任委员。主要致力于生殖内分泌及辅助生殖技术的临床研究。带领团队填补了“试管婴儿”研究领域西北地区多项技术空白。主编及参编专著4部, 译著2部。发表学术论文80余篇, 在研及完成国家级省部级课题十余项, 曾获“中华医学科技三等奖”, “甘肃省医学科技一等奖”, “甘肃省科技进步一等奖”等。



寻找子宫内膜种植窗, 提高子宫内膜容受性

张学红

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体外受精-胚胎移植(IVF-ET)技术发展至今, 在控制性超促排卵技术、取卵、体外受精、胚胎培养、胚胎移植及配子胚胎冷冻技术等方面取得了很大进展, 但是对于胚胎种植环节的认识还有待于进一步提高。大量临床实践表明, 未能准确把握子宫内膜种植窗及各种原因导致的子宫内膜容受性降低是胚胎着床失败的重要原因之一。因此, 重新认识胚胎种植的关键环节已成为目前国内外生殖医学界研究的热点。

子宫内膜种植窗和子宫内膜容受性的评价指标有很多, 目前应用较广泛的是各种超声形态学参数、超声下血流指标、动态物理学指标、血液激素测定、分子生物学指标和基因标记等等。子宫内膜种植窗的调控受到全身神经内分泌因素的影响, 呈现典型的个体化差异。子宫内膜容受性的调控涉及到胚胎与母体子宫内膜细胞间的多重复杂的相互作用, 受到激素、细胞因子、机体状态、基因、免疫因子以及精神心理状态等多种因素的调控。

在自然周期和控制性超促排卵周期中子宫内膜与卵子发育、胚胎发育都存在同步化差异的问题, 子宫内膜种植窗的开放及子宫内膜容受性的维持需要学术界较为统一的认识, 目前各种改善措施尚无定论。多囊卵巢综合征(PCOS)、子宫内膜异位症(EMs)、输卵管积水、炎症、子宫肌瘤等疾病其子宫内膜种植窗及容受性会发生变化, 需要根据其“种植窗”时期特征进行干预调控同时改善其容受性。有关改善子宫内膜容受性的有效措施除药物治疗、手术治疗、激素调节外, 近期有内膜创伤性修复、宫腔灌注治疗以及中医治疗等尝试性手段。

自2003年以来, 兰州大学第一医院生殖医学专科医院每年在甘肃兰州举办“全国生殖医学新进展学习班”, 重点围绕胚胎种植环节邀请国内、外专家同道及年轻学者开展研讨与交流。2013年会议主题为“种植失败, 是内膜更重要吗?”, 这一专题从胚胎种植的基础环节与调控角度进行全方位阐述, 共同探讨了影响种植窗口开放和内膜容受性的各种因素及其相互作用, 讨论了多种控制性超促排卵方案治疗过程中的“种植窗”以及PCOS等常见疾病患者的“种植窗”特点, 对改善内膜容受性的一些有效措施进行了指导和研究成果展示, 同时就临床上遇到的一些疑难病历以及目前存在的瓶颈问题进行了专家论坛, 更好地明确了一些问题, 并提出了更多的研究方向, 指导临床工作。

“寻找子宫内膜种植窗, 提高子宫内膜容受性”是目前国内外生殖医学界在胚胎种植方面共同面临的难点问题, 也是制约IVF-ET技术提高的瓶颈, 值得深入研究与探讨。

• 专题讨论 •

人粒细胞集落刺激因子(G-CSF)宫腔灌注 改善子宫内膜容受性的临床研究

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【摘要】目的: 探讨人粒细胞集落刺激因子(G-CSF)宫腔灌注对于子宫内膜状况欠佳患者的子宫内膜容受性的影响。方法: 将进行体外受精-胚胎移植(IVF-ET)的子宫内膜厚度不足或基底低回声、反复种植失败的患者按2:1随机分为G-CSF组和对照组, 进行前瞻性研究, G-CSF组($n=60$)行IVF-ET前进行1~6次G-CSF宫腔灌注, 对照组($n=30$)则不给予G-CSF, 观察子宫内膜厚度、回声、基底回声、血流动力学等指标。结果: 与对照组相比, G-CSF组在早卵泡期、晚卵泡期的子宫内膜厚度增加明显, 基底回声优于对照组, 差异有统计学意义($P<0.05$); 围排卵期内膜厚度与对照组相比无统计学差异($P>0.05$), 基底回声优于对照组, 差异有统计学意义($P<0.05$)。早卵泡期、晚卵泡期及围排卵期G-CSF组子宫内膜基底区(EMI)动脉搏动指数(PI)均高于对照组, G-CSF组早卵泡期及围排卵期阻力指数(RI)高于对照组, 差异均有统计学意义($P<0.05$); 晚卵泡期RI与对照组无统计学差异($P>0.05$)。在已行ET的患者中, G-CSF组的妊娠率为62.5%(35/56), 显著高于对照组的33.3%(9/27), 差异有统计学意义($P<0.05$)。结论: G-CSF宫腔灌注可改善子宫内膜的厚度及基底回声, 对于内膜较薄、基底低回声及胚胎反复种植失败的患者具有较好的临床治疗效果, 妊娠率较高。

关键词: 人粒细胞集落刺激因子(G-CSF); 子宫内膜容受性; 体外受精-胚胎移植(IVF-ET); 三维多普勒超声; 动力指数(PI); 阻力指数(RI)

中图分类号: R711.71

文献标识码: A

文章编号: 0253-357X(2014)07-0527-007

Granulocyte Colony-stimulating Factor Uterine Perfusion for Inadequate Endometrium

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【ABSTRACT】 Objective: To study the effect of granulocyte colony-stimulating factor (G-CSF) intrauterine perfusion on inadequate endometrium. **Methods:** 1) Totally 90 women were collected in a prospective study, who had inadequate endometrium, thin or exudative change on endometrial-myometrial interface (EMI), and repeated implantation failure. They were randomly divided into G-CSF group ($n=60$) and control group ($n=30$). The patients in G-CSF group received intrauterine perfusion with G-CSF for 1–6 times before IVF-ET, while the patients in the control were not given G-CSF. Thickness and echo of endometrium, echo of EMI under transvaginal ultrasonography, haemodynamics and other indicators were compared. **Results:** 1) Compared with the control, in the early follicular phase and the late follicular phase, endometrial thickness in G-CSF group increased significantly, the EMI's echo was better, the difference was statistically significant ($P<0.05$). There was no significant difference in endometrial thickness in ovulation-around phase between the two groups ($P>0.05$), but EMI's echo was better than the control ($P<0.05$). Artery pulsation index (PI) of EMI in G-CSF group was higher in all these three phases, and resistance index (RI) in the early follicular phase and ovulation around phase in G-CSF group were higher, the difference was statistically significant ($P<0.05$). There was no significant difference in RI of the late follicular phase between the two groups ($P>0.05$). The pregnancy rate in G-CSF group and the control was 62.5% (35/56) and 33.3% (9/27), respectively, the difference was statistically significant ($P<0.05$). **Conclusion:** G-CSF intrauterine perfusion can improve endometrial thickness and inflammatory exudative changes of EMI. It is effective for patients with thin endometrium, inflammatory exudate changes of EMI and repeated implantation failure, and get a better clinical pregnancy rate.

Key words: granulocyte colony-stimulating factor (G-CSF); endometrial receptivity; *in vitro* fertilization and embryo transfer (IVF-ET); three-dimensional ultrasound; pulsatility index (PI); resistance index (RI)

2种剂量戊酸雌二醇对宫腔粘连切除术后 辅以人工周期的疗效影响

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【摘要】 目的: 评价应用不同剂量戊酸雌二醇对宫腔粘连切除术(TCRA)后辅以人工周期疗效的影响。方法: 选择临床确诊为宫腔粘连(IUA)的患者230例, 行TCRA后, 先放置球囊引流再放置宫内节育器(IUD), 并随机分为A组和B组, A组给予戊酸雌二醇(E_2)3 mg/d($n=128$), B组9 mg/d($n=102$), 所有患者均联合孕激素口服行人工周期治疗, 上述术后治疗连用3个周期。定期随访药物反应及月经改善情况, 3个月后B超及宫腔镜检查了解术后子宫内膜厚度及宫腔情况, 评价临床疗效。结果: TCRA后辅以人工周期治疗, IUA患者子宫内膜较术前增厚, 差异有统计学意义($P<0.05$); B组患者较A组患者更明显, 组间差异有统计学意义($P<0.05$)。TCRA后B组行人工周期的临床疗效优于A组, 治愈率及有效率均高于A组($P<0.05$)。结论: TCRA后联合人工周期治疗, 能促进IUA患者术后受损子宫内膜增生, 且B组优于A组; B组较A组的临床疗效更好, 且是安全的。

关键词: 戊酸雌二醇; 人工周期; 宫腔粘连(IUA); 宫腔粘连切除术(TCRA)

中图分类号: R713.4

文献标识码: A

文章编号: 0253-357X(2014)07-0534-04

Therapeutic Effects of Different Doses of Estradiol Valerate after TCRA Combined with Postoperative Artificial Cycle Treatment

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【ABSTRACT】 Objective: To evaluate the therapeutic effects of different doses of estradiol valerate after transcervical resection of adhesion (TCRA) combined with postoperative artificial cycle treatment. **Methods:** A total of 230 patients diagnosed as intrauterine adhesions (IUA) were included in this study and randomly divided into two groups (groups A and B). The patients firstly received transcervical resection of adhesion following the balloon drainage and placement of intrauterine device (IUD). After operations, the patients were given estradiol valerate 3 mg/d (group A, $n=128$) and were given 9 mg/d (group B, $n=102$) for artificial cycle treatment with progesterone for 3 cycles. All patients were regularly followed up to monitor the drug reaction and the improvement of menstruation. After three months, the ultrasound and hysteroscopy were performed to detect the endometrium thickness and the changes of adhesion. **Results:** After TCRA combined with postoperative artificial cycle treatment, the endometrium thickness was increased significantly compared with that before treatment ($P<0.05$), and it was more obvious in group B than in group A ($P<0.05$). The therapeutic effect in group B was better than that in group A, and the curative rate and the effective rate were also higher than these in group A ($P<0.05$). **Conclusion:** The postoperative estrogen combined with progesterone increased the proliferation of endometrium after the injuries induced by transcervical resection of adhesion. Moreover, the high dose of estrogen (9 mg/d) had better effects in the endometrium restoration and decrease of intrauterine adhesion than 3 mg/d estrogen. And the therapy is safe with no significant side effects.

Key words: estradiol valerate; artificial cycle treatment; intrauterine adhesion (IUA); transcervical of adhesion; transcervical resection of adhesion (TCRA)

冻融胚胎移植3种内膜准备方案 成功妊娠者的临床比较

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【摘要】 目的: 探讨冻融胚胎移植(FET)3种内膜准备方案成功妊娠者的临床特征。方法: 回顾性分析188个FET周期, 其中98个成功妊娠, 比较自然周期(A组, $n=42$)、激素替代周期(B组, $n=46$)和促排卵周期(C组, $n=10$)这3种方案成功妊娠者在年龄、移植日及移植第4日血清激素水平、移植胚胎数、I级胚胎比例、移植位置和黄体酮的用量上是否存在差异。结果: ① B组移植日、移植第4日血清 E_2 水平、 E_2/P 值、黄体酮的用量均明显高于A组, 而P水平明显低于A组, 差异均有统计学意义($P<0.05$); 年龄、移植胚胎数、I级胚胎比例及移植位置上A、B无统计学差异($P>0.05$)。② C组可移植胚胎数明显少于A组和B组, 差异均有统计学意义($P<0.05$); 而在年龄、移植日及移植第4日血清激素水平、I级胚胎比例、移植位置和黄体酮的用量与A组和B组间无统计学差异($P>0.05$)。结论: B组方案者黄体支持时黄体酮的用量应高于A组, B组方案在移植日及移植第4日孕酮值低于A组, 但并不影响妊娠, C组方案者可移植胚胎数减少可能并不影响妊娠率。

关键词: 冻融胚胎移植(FET); 内膜准备方案; 成功妊娠

中图分类号: R711.1

文献标识码: A

文章编号: 0253-357X(2014)07-0538-05

Clinical Comparison among Successful Pregnant Patients with Three Different Therapies in Frozen-thawed Embryo Transfer Cycles

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【ABSTRACT】 Objective: To explore the clinical characteristics of successful pregnant patient with different therapy in frozen-thawed embryo transfer (FET) cycles. **Methods:** A total of 188 FET cycles were retrospectively analyzed. Among them, 98 cycles got successfully pregnant, the differences of successful pregnant patients' age, the concentration of serum hormone on the 1st and 4th day of embryo transfer (ET), the amount of transplanting embryos, the rate of best embryo, the location of embryo and the dose of progesterone used were compared when they were treated by natural cycle (group A, $n=42$), hormone replacing cycles (group B, $n=46$) or superovulation treatment (group C, $n=10$). **Results:** 1) Compared with group A the patients in group B had a higher concentration of serum E_2 , E_2/P on the 1st and 4th day of embryo transfer, and lower dose of progesterone on the 1st and 4th day of embryo transfer, and they used higher dose of progesterone. There were no significant differences in age, the amount of transplanting embryos, the rate of transferrable embryos and the location of embryo. 2) Compared with group A and group B respectively, the patients in group C had lower amount of transferrable embryos, and there were no significant differences in the age of the patient, the concentration of serum hormone on the 1st and 4th day of embryo transfer, the rate of grade I embryos, the location of embryo transplanted and the dose of progesterone. **Conclusion:** Compared with group A, the patients in group B should be given larger dose of progesterone, and the concentration of serum progesterone on the 1st and 4th day of embryo transfer was lower which had no impact on pregnancy. For the treatment of superovulation, the reduce of the number of embryo transferrable also has no influence on pregnancy rate.

Key words: frozen-thawed embryo transfer (FET); endometrial preparation program; successful pregnancy

MircoRNA 在胚胎反复植入失败患者 子宫内膜的免疫调控作用

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【摘要】辅助生殖中不明原因反复胚胎植入失败可能涉及子宫内膜环境微观水平的改变, 包括由免疫细胞、免疫因子构成的免疫调控网络。microRNA 作为转录后调控因子参与免疫因子的合成及生物学作用的发挥, 其表达失衡可破坏良好免疫微环境, 导致子宫对胚胎进行免疫攻击, 阻碍胚胎的顺利着床。明确和分析胚胎着床中相关 miRNAs 在子宫内膜免疫网络的调控作用以改善胚胎种植率是目前国内外学者研究的热门话题。

关键词: 胚胎反复植入; 治疗失败; 微小RNA(miRNA); 免疫

中图分类号: Q492.6; Q556 文献标识码: A 文章编号: 0253-357X(2014)07-0543-05

Role of microRNA in the Regulation of Immunological Pathogenesis in Recurrent Embryo Implantation Failure

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【ABSTRACT】 In clinical, recurrent/repeated implantation failure is a frustrating condition for clinicians and patients alike. The implantation failure may involve the precisely controlled immune molecular and cellular events. microRNAs (miRNAs, miRs) are small RNAs that function posttranscriptionally to regulate gene activity. The unbalanced expression of microRNAs may change the endometrial immune environment, leading to an adverse effect in the process of embryo implantation. Thus, we highlight the role of microRNAs during the dialogue between the maternal endometrium and the implanting embryo and discuss the hot topic of the methods to implantation rate improvement.

Key words: microRNA (miRNA); immunology; embryo implantation; implantation failure

趋化因子及其受体与复发性流产

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【摘要】母-胎界面免疫调节功能的异常是导致复发性流产(recurrent spontaneous abortion, RSA)的一个重要病因,其作用机制尚不清楚。趋化因子及其受体参与调控母-胎界面免疫细胞的定向招募和活化,在免疫耐受状态的维持、新血管的生成、滋养层细胞的增殖和侵袭过程中发挥重要作用。因此,母-胎界面趋化因子及其受体功能的异常,可能会打破免疫耐受状态,导致胚胎植入和胎盘形成障碍,从而引起流产。

关键词:母-胎界面;复发性流产(RSA);趋化因子;趋化因子受体;免疫耐受

中图分类号: R714.21

文献标识码: A

文章编号: 0253-357X(2014)07-0548-08

Roles of Chemokines and Their Receptors in the Recurrent Spontaneous Abortion

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【ABSTRACT】 Immune dysregulation at the maternal-fetal interface has been recognized as a critical pathogeny of the recurrent spontaneous abortion (RSA), but the mechanisms underlying such a local immune dysregulation are not fully understood. Chemokines and their receptors have been demonstrated to be involved in the specific recruitment and activation of corresponding leucocytes, and play essential roles in maintaining the status of immune tolerance, angiogenesis, as well as regulating the proliferation and invasion of trophoblasts. Thus, the dysfunctions of chemokines and their receptors at the maternal-fetal interface would cause the failures of embryo implantation and placenta formation that initiating the early pregnancy loss.

Key words: maternal-fetal interface; recurrent spontaneous abortion (RSA); chemokines; chemokine receptor; immune tolerance

子宫内膜自然杀伤细胞与妊娠关系的研究进展

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【摘要】 子宫内膜自然杀伤(uNK)细胞是胚胎植入前内膜和早孕期蜕膜中数量最多的一类免疫细胞。母体的uNK细胞与胎儿的滋养层细胞相邻且相互作用。uNK细胞分泌一系列细胞因子和血管生长因子, 调控滋养层细胞入侵并参与子宫螺旋动脉的重塑。uNK细胞数量的增多与反复种植失败(RIF)、复发性流产(RSA)有关。但仍需更多的研究阐明uNK细胞在胚胎种植过程中的具体作用、对内膜容受性的影响, 以此作为临床治疗的依据。

关键词: 子宫内膜自然杀伤(uNK)细胞; 反复种植失败(RIF); 复发性流产(RSA)

中图分类号: R711

文献标识码: A

文章编号: 0253-357X(2014)07-0556-04

Progression of Uterine Natural Killer Cells and Pregnancy

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【ABSTRACT】 Uterine natural killer (uNK) cells are the most abundant immune cells in preimplantation endometrium and early pregnancy deciduas. Maternal uNK cells are adjacent to, and have the ability to interact directly with fetal trophoblasts. uNK cells can secrete an array of cytokines and angiogenesis factors that are important in regulation of trophoblast invasion and involved in remodeling of uterine spiral arteries. The increased number of uNK cells is associated with recurrent implantation failure and recurrent spontaneous abortion (RSA). More work needs to be done to establish a specific role for uNK cells in the process of embryo implantation and effect on endometrial receptivity and to use uNK cells as the basis for clinical treatment.

Key words: uterine natural killer (uNK) cell; recurrent implantation failure (RIF); recurrent spontaneous abortion (RSA)

控制性促排卵与子宫内膜容受性

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【摘要】 控制性促排卵(COS)致内分泌环境的改变是影响子宫内膜容受性的医源性因素。研究显示 COS 中孕激素水平增高可致围排卵期 and 排卵后子宫内膜分泌期改变提前;且 COS 高血清类固醇水平可影响子宫内膜基因表达及分泌因子的变化,从而改变子宫内膜上皮-基质层的发育,影响胚胎着床。预防卵泡期孕激素水平上升,降低卵泡期雌激素水平及 COS 高反应是改善 COS 子宫内膜接受性的关键。有文献报道采用高纯度人绝经期促性腺激素(hMG-HP)促排卵,提前扳机及微刺激等预防措施可降低卵泡期孕激素水平上升的发生,若孕激素水平已升高至危险阈值,可考虑全部胚胎冷冻,待以后行冻融胚胎移植(FET);但这些措施的临床有效性尚需更多研究加以证实。

关键词: 控制性促排卵(COS); 子宫内膜容受性; 着床

中图分类号: R711

文献标识码: A

文章编号: 0253-357X(2014)07-0560-04

Controlled Ovarian Stimulation and Endometrial Receptivity

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【ABSTRACT】 Endocrine changes induced by controlled ovarian stimulation (COS) can affect endometrial receptivity. The serum progesterone elevation during COS may cause secretary advancement in the peri- and post-ovulatory period. The high steroid levels after COS also change the endometrial gene expression profile and endometrial secretion, which alters epithelial-stromal development and affects embryo implantation. The keys to improve endometrial receptivity are preventing progesterone elevation before hCG injection, decreasing high estrogen levels during follicular phase and reducing high ovarian response. Therefore, preventive measures to reduce the occurrence of progesterone elevation during COS include high purity menopausal gonadotropin (hMG-HP) for ovarian stimulation, early trigger and minimal stimulation. If progesterone rises to a dangerous threshold, frozen embryos are considered. The clinical effectiveness of these measures still need more studies.

Key words: controlled ovarian stimulation (COS); endometrial receptivity; implantation

胚胎反复着床失败的病因及处理措施

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【摘要】 胚胎反复着床失败是一种病因复杂的综合征, 涉及到胚胎因素、子宫内膜因素及免疫因素等方面。对反复着床失败的患者来说, 可考虑采用胚胎筛选、囊胚移植, 机械刺激子宫内膜、序贯性胚胎移植以及免疫治疗等来提高临床妊娠率。此外, 还包括宫腔镜检查以及B超检查, 以除外子宫畸形、子宫内膜息肉、子宫肌瘤、子宫内膜异位症等, 以及处理输卵管积水、多囊卵巢综合征等疾病。

关键词: 反复胚胎着床失败(RIF); 机械刺激; 子宫内膜; 免疫治疗

中图分类号: R711.71

文献标识码: A

文章编号: 0253-357X(2014)07-0564-07

Etiology and Treatment Measures of Recurrent Implantation Failure

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【ABSTRACT】 Recurrent implantation failure is a complex syndrome, which refers to embryo factors, endometrial factors, immune factors, and so on. For those patients, managements, such as embryo selection, blastocyst embryo transplant, stimulation of endometrium, sequential embryo transfer and immune therapy should be considered. In addition, uterine malformation, endometrial polyps, uterine myoma, endometriosis should be excluded by ultrasonography and hysteroscopy, and hydrosalpinges, polycystic ovarian syndrome should be treated.

Key words: recurrent implantation failure (RIF); mechanical stimulation of endometrium; immunotherapy

多囊卵巢综合征患者子宫内膜容受性的特点

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【摘要】有生育障碍的多囊卵巢综合征(PCOS)患者子宫内膜容受性受损是近年来生殖领域研究的热点, 研究发现子宫内膜的厚度、容积及内膜下血流的减少, 子宫内膜间质的异常、性激素及其受体的不均衡表达, 以及子宫内膜容受性标志物的降低等均可导致子宫内膜容受性受损。本文将多囊卵巢综合征患者的子宫内膜容受性特点从超声影像学、病理组织学特点、性激素受体及着床期分子表达、基因芯片、转录组学等五个方面来阐述。

关键词: 多囊卵巢综合征(PCOS); 子宫内膜容受性

中图分类号: R711.6

文献标识码: A

文章编号: 0253-357X(2014)07-0571-05

Uterine Receptivity in Women with Polycystic Ovary Syndrome

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【ABSTRACT】 The research of endometrial receptivity damaged in women with polycystic ovary syndrome (PCOS), whose fertility was impaired, has become a hot pot in the area of reproduction. Researchs had indicated the reduction of endometrial thickness, volume and the endometrial blood flows, the abnormality of endometrial stromal, the imbalances expression of sex hormone and its receptors, and the decrease of endometrial receptivity markers can result in a reduction of endometrial receptivity. All above will be analyzed in five aspects in this article, such as ultrasound image, histopathology, sex hormone receptor and molcular expression at implantation phase, gene chip and transcriptomics.

Key words: polycystic ovary syndrome (PCOS); endometrial receptivity; infertility

子宫肌瘤对子宫内膜容受性的影响

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【摘要】 子宫内膜容受性是影响胚胎着床的重要因素之一, 子宫肌瘤是生育期女性最常见的良性肿瘤, 对子宫内膜容受性的影响备受关注, 其对子宫内膜容受性的影响不是局限于肌瘤表面而是遍布整个宫腔。除了引起宫腔形态改变外, 子宫肌瘤可通过局部血供受损、子宫内膜免疫状态失衡、细胞因子分泌异常、着床相关因子改变等损害子宫内膜容受性; 但子宫肌瘤是否影响子宫内膜着床尚未达成一致意见。

关键词: 子宫肌瘤; 影响; 子宫内膜容受性

中图分类号: R711.74

文献标识码: A

文章编号: 0253-357X(2014)07-0576-04

Effect of Leiomyoma of Uterus on Endometrial Receptivity

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【ABSTRACT】 Endometrial receptivity plays a key role in the establishment of successful pregnancies. Leiomyomas of uterus are the most common solid pelvic tumors in women. Several studies have shown an unfavorable effect of fibroids on endometrial receptivity. Its effect on endometrial receptivity is not confined to the myoma surface but throughout the whole of the uterine cavity. In addition to cause the change of uterine cavity shape, uterine fibroids may affect the endometrial receptivity by damaging the local blood, endometrial immune imbalance, abnormal secretion of cytokines, implantation related factors. But whether the leiomyomas affect endometrial implantation have not yet reached consensus.

Key words: leiomyoma of uterus; effect; uterine receptivity

子宫内膜炎性改变对胚胎植入及助孕结局的影响

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【摘要】在胚胎种植过程中,需要促炎因子与抗炎因子相互平衡,才能保证成功妊娠的建立与维持。子宫内膜炎或亚临床子宫内膜感染破坏了各因子之间的平衡状态,形成具有细胞和胚胎毒性的子宫内膜微环境,不利于精子成活和胚胎着床;引起炎症的病原体还可激发机体的免疫反应,产生大量致敏的活性细胞及多种细胞因子、炎性细胞,杀灭和吞噬精子;免疫抗体可干扰正常胚胎和内膜间的组织相容性,影响胚胎着床和胚胎发育;导致胚胎种植失败、自然流产、早产等不良妊娠结局。临床上应给予重视并积极治疗,以提高 IVF-ET 的妊娠率。

关键词: 子宫内膜容受性; 体外受精; 胚胎种植; 炎性因子

中图分类号: R711.6

文献标识码: A

文章编号: 0253-357X(2014)07-0580-04

Effect of Endometrial Inflammatory Changes on Embryo Implantation and the Pregnant Outcomes

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【ABSTRACT】 In the process of embryo implantation, hormones, nervous, immune, genes and cytokines play roles together and ultimately achieve the synchronous development between embryo and endometrium. It needs a balance state of cytokines between pro-inflammatory and anti-inflammatory in this process of the establishment and maintenance for the successful pregnancy. Endometrial inflammatory exudative changes may undermine the balance among the factors, and cause a toxic endometrial microenvironment which is harmful to embryo implantation and assisted reproductive outcomes, so we need pay enough attention in order to improve the IVF-ET pregnancy rates.

Key words: endometrial receptivity; *in vitro* fertilization (IVF); embryo transfer (ET); inflammatory factors

输卵管积水及其治疗对胚胎种植影响的评价

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【摘要】 输卵管积水患者行体外受精-胚胎移植(IVF-ET)后妊娠率降低, 积水对IVF的负面影响包括: ①机械性冲刷; ②对配子及胚胎的毒性作用; ③子宫内膜容受性下降等。改善此类患者IVF结局的主要方法是阻断输卵管积水返流至宫腔; 输卵管积水的处理方式应根据患者的临床症状、既往助孕结局而个体化地选择输卵管切除术、近端输卵管结扎术、输卵管造口术等。对输卵管病变较轻、功能尚可者应行输卵管造口术引流积水; 对于重度积水或伴积脓、确无功能者可在IVF前切除患侧输卵管或行近端输卵管结扎术; Essure近端栓塞术对有手术禁忌证的IVF患者不失为一种选择, 但有效性有待进一步观察; 输卵管穿刺积水抽吸术可作为超促排卵过程新发积水的一种临时处理方式。输卵管积水最优化的治疗方案仍有待进一步评估。

关键词: 输卵管积水; 体外受精-胚胎移植(IVF-ET); 治疗; 胚胎; 着床

中图分类号: R711.6

文献标识码: A

文章编号: 0253-357X(2014)07-0584-06

Assessment of Effections of Hydrosalpinx and Its Treatment on Embryo Implantation

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【ABSTRACT】 Patients with hydrosalpinx are a recognized group with poor prognosis in *in-vitro* fertilization (IVF). The negative effects of hydrosalpinx have generally been attributed largely to: 1) mechanical washout; 2) gamete and embryo-toxicity; 3) alterations in endometrial receptivity by the reduced expression of cytokines and integrins important to implantation. The rationale for treatments to improve the results of IVF is based on interruption of the leakage of hydrosalpinx fluid into the uterine cavity. The individual selection of the surgical method, was proximal obstruction, salpingectomy or salpingostomy, depending on patients' clinical findings, and previous pregnancy outcome. Laparoscopic salpingostomy suits for the patients with mild or moderate hydrosalpinx; pre-IVF laparoscopic salpingectomy or proximal tubal ligation have been shown to restore IVF-ET outcomes in patients with severe hydrosalpinx without tubal funtion. Proximal occlusion of hydrosalpinges with Essure devices before IVF is a useful treatment for patients with a contraindication for salpingectomy. Transvaginal aspiration of the hydrosalpinx fluid is a temporary treatment in patients with newly developed hydrosalpinx in the process of controlled ovarian stimulation. The prefer treatment of hydrosalpinx still awaits more evaluation.

Key words: hydrosalpinx; IVF-ET; treatment; embryo; implantation

子宫内膜异位症患者内膜容受性及“种植窗”的特点

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【摘要】子宫内膜异位症(EMs)通过多个环节影响女性生育能力和不孕的治疗效果。EMs合并不孕的患者其子宫内膜细胞学形态方面: 胞饮突的表达量、内膜腺体数目、基质有丝分裂细胞数较健康对照组均显著减少, 腺体的腺腔分布不规则, 微绒毛少、纤毛再生不全、发育不良; 分子生物学方面: 种植窗期内膜整合素 $\alpha_v\beta_3$ 减少, 基质金属蛋白酶-9(MMP-9)、细胞外基质、激活素 A、细胞黏附分子、芳香化酶 P450、IgG 和 IgA 抗体等多种细胞因子的异常; 基因学方面: *HOXA10*、*HOXA11* 基因呈低水平表达, *MMP-2* 和 *MMP-9* 表达升高; 类固醇激素 17 β -羟基类固醇脱氢酶(17 β -HSD s) 等不表达, 从而降低 EMs 患者的子宫内膜容受性。促性腺激素释放激素激动剂预处理可有效提高 EMs 患者子宫内膜容受性。

关键词: 子宫内膜异位症(EMs); 子宫内膜容受性; 种植窗

中图分类号: R711.74

文献标识码: A

文章编号: 0253-357X(2014)07-0590-05

Characteristic of Endometrial Receptivity and Implantation Window in Women with Endometriosis

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【ABSTRACT】 Endometriosis (EMs) can affect females' ability of fertility and therapeutic effect of infertility through various processes. There are many aspects to exam the differences of endometrium among patients with both EMs and infertility. Firstly, cytologic aspect: expression quantity of pinopodes, quantity of endometrial glands, quantity of mitotic cells in stromata, of whom are significantly fewer compared with healthy controls. Moreover, the distribution of glandular lumens is irregular, the number of microvilli is few, and cilia is incomplete regeneration and dysplasia. Secondly, from molecular biologic aspect, endometrial integrin $\alpha_v\beta_3$ within planting window period decrease with abnormality of multiple cytokines such as matrix metalloproteinase-9 (MMP-9), extracellular matrix, activin-A, cell adhesion molecules, aromatase P450, IgG, IgA, ect. Thirdly, from genetics, the low level expression of *HOXA10* and *HOXA11*, higher expression of *MMP-2* and *MMP-9*, and non-expression of steroid hormones 17β -hydroxy steroid dehydrogenase (17β -HSDs), lower the patients' endometrium receptivity. In addition, the pretreatment of gonadotropin releasing hormone agonist can improve the endometrium receptivity of women with EMs effectively.

Key words: endometriosis (EMs); endometrium receptivity; implantation window

“补肾气, 通胞脉”改善子宫内膜容受性

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【摘要】 体外受精-胚胎移植(IVF-ET)过程中子宫内膜容受性降低是胚胎着床障碍的主要因素之一。现代医学主要对策是补充雌、孕激素或应用抗凝剂, 虽在一定程度上能提高妊娠率, 但亦有一定局限性。很多研究文献表明, 中医药能提高子宫内膜容受性, 并具有整体调节的优势。我们运用“补肾气, 通胞脉”方法, 以骨碎补、补骨脂为主要药物组成方剂, 改善子宫内膜环境, 从而利于孕卵的着床及发育。

关键词: 子宫内膜容受性低; 中医药; 骨碎补; 补骨脂

中图分类号: R711.6

文献标识码: A

文章编号: 0253-357X(2014)07-0595-04

Nourishing the Qi of Kidney with Filling up the Vessels of Uterus to Improve Endometrial Receptivity

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【ABSTRACT】 The endometrial receptivity reduced while IVF-ET is one of the main factors of implantation dysfunction. The main treatment in modern medicine is to complement estrogen and progesterone, or anticoagulants. Although it can improve pregnancy rates to some extent, there are limitations. Many research literatures suggest that Chinese medicine can improve endometrial receptivity, and has the overall regulation advantages. We have used a prescription which contains drynaria and psoralen to nourish the Qi of kidney with fill up the vessels of uterus to improve endometrial receptivity, which is conducive to embryo implantation.

Key words: low endometrial receptivity; Chinese medicine; drynaria and psoralen

• 临床研究 •

有生育需求中老年男性精子参数的评价

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【摘要】 目的: 评价有生育需求中老年男性精子参数的变化。方法: 42例50~58岁有生育需求男性的精液标本, 按照其既往生育史分组, A组: 继发性不育23例, 平均年龄 52.9 ± 2.2 (50~58)岁; B组: 原发性不育19例, 平均年龄 52.7 ± 2.7 (50~58)岁。按世界卫生组织手册(WHO, 2010)方法, 检测患者的精子活动率、前向运动精子率、精子浓度、精子畸形率、畸形精子指数和精子顶体完整率。结果: A组的畸形精子率显著低于B组($P < 0.05$), 其它精子参数组间无统计学差异($P > 0.05$)。与WHO手册(2010)的参考值对照, A、B组的精子活动率均数、前向运动精子率均数和B组的正常形态精子率均数低于参考值下限。A组和B组分别有11例(47.8%)、5例(26.3%)的精子活动率、前向运动精子率、精子浓度和正常形态精子率达到WHO的参考值范围, 但达到WHO参考值的例数比率组间无统计学差异($P > 0.05$)。结论: 50~58岁有生育需求中老年男性的精子参数低下, 但存在明显的个体差异。

关键词: 精子发生; 精子; 顶体; 衰老

中图分类号: R339

文献标识码: A

文章编号: 0253-357X(2014)07-0599-04

Evaluation on Sperm Parameters from Semen of Men Aged 50–58 Years Who Wanted to be Father

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【ABSTRACT】Objective: To investigate sperm parameters from semen of men aged 50–58 years who wanted to be father. **Methods:** Forty-two men aged 50–58 years were enrolled into this study. These men visited the infertility clinic and wanted to be father. Based on their fertility history, 42 men were divided into two groups: group A, 23 cases, 52.9 ± 2.2 (50–58) years, secondary infertility; group B, 19 cases, 52.7 ± 2.7 (50–58) years, primary infertility. According to the WHO manual (2010), sperm parameters including sperm motility, progressive motility, sperm concentration, sperm abnormal form, teratozoospermia index, and acrosome integrity were determined. **Results:** Group B had higher sperm abnormal forms than that of group A ($P < 0.05$), and the rest sperm parameters were not found significant differences between these two groups ($P > 0.05$). According to the WHO reference values, sperm motility and progressive motility in groups A and B did not reach the lower reference limit, and normal morphology in group B did not reach the lower reference limit. In groups A and B, 11 and 5 cases respectively, had normal values on sperm motility, progressive motility, sperm concentration, and sperm normal morphology. **Conclusion:** Men aged 50–58 years would have poor sperm parameters and obvious individual difference for sperm quality.

Key words: spermatogenesis; sperm; acrosome; aging

• 临床报道 •

介入治疗、腹腔镜和经阴道3种途径在剖宫产切口瘢痕妊娠中的应用分析

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【摘要】 目的: 探讨剖宫产切口瘢痕妊娠(CSP)行介入治疗、腹腔镜下病灶切除和经阴道病灶切除术的可行性、疗效和安全性。方法: 回顾性分析113例CSP患者资料, 42例行腹腔镜治疗(A组), 28例行介入治疗(B组), 43例行阴式疤痕妊娠病灶切除(C组), 分析术后hCG下降情况、月经复潮时间和再孕情况。结果: 3组患者在年龄、孕次、术前hCG值、病灶大小、距前次剖宫产时间均无统计学差异($P>0.05$)。A组和C组在术中出血、手术时间、住院时间上无统计学差异($P>0.05$), 两者均优于B组, 差异有统计学意义($P<0.05$), 其中住院费用比较, B组最高, A组其次, C组最少。A组和C组hCG降至正常时间、病灶缩小所需时间、月经复潮时间短于B组, 差异有统计学意义($P<0.01$), C组术后hCG降至正常时间要短于A组。术后再孕C组7例(16.28%, 7/43), A组5例(11.90%, 5/42), 均高于B组(0%, 0/28)。结论: 3种方法各有优缺点, 介入组尤其适合发生大出血的CSP患者, 腹腔镜和阴式2种方法直接清除病灶, 修复瘢痕切口, 术后恢复快, 创伤小, 但腹腔镜手术和介入均需要昂贵的器械, 要具备丰富的手术操作经验, 阴式瘢痕病灶清除相对简单, 并发症少, 不需要昂贵的器械, 有一定阴式手术经验者即可开展, 值得临床推广。

关键词: 剖宫产切口瘢痕妊娠(CSP); 子宫动脉化疗栓塞术; 腹腔镜; 阴式手术

中图分类号: R714.22

文献标识码: A

文章编号: 0253-357X(2014)07-0603-04

Effect of Interventional Therapy, Laparoscope and Transvaginal Therapy on Focus in Patients with Cesarean Scar Pregnancy

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【ABSTRACT】 Objective: To evaluate feasibility, efficacy and safety of interventional therapy, laparoscope and transvaginal therapy on focus in patients with cesarean scar pregnancy (CSP). **Methods:** A total of 113 patients with CSP were recruited and retrospectively analyzed, including 43 patients receiving transvaginal therapy (group A), 28 patients receiving interventional therapy (group B) and 42 patients receiving laparoscope (group C). Post operative hCG, time of menstruation, and re-pregnancy were analyzed. **Results:** There were no significant differences among age, frequency of pregnancy, preoperative hCG, focus size, time of late caesarean among the three groups ($P>0.05$). Blood loss during operation, length of procedure and length of hospitalization did not show significant differences between group C and group A ($P>0.05$), but were significantly lower than those in group B ($P<0.05$). Hospital expenditure was the highest in group B, followed by group C and group A. Time of hCG recovery, days of focus reduction, time of menstruation recovery were significantly shorter in groups A and C than in group B ($P<0.01$). Time of hCG recovery was shorter in group A than in group C. Seven patients (16.28%, 7/43) occurred re-pregnancy in group A and 5 (11.90%, 5/42) in group C, which were higher than that of group B (0%, 0/28). **Conclusions:** Feasibility, efficacy and safety of interventional therapy, laparoscope and transvaginal therapy on focus in patients with CSP were acceptable. Interventional therapy was optional in patients with caesarean due to massive hemorrhage, whereas laparoscope therapy and intervaginal therapy are suitable for debridement, repair of scar due to fast restoration and mini-trauma after operation. Expenditure of interventional therapy and laparoscope are expensive compared with intrevaginal therapy, which is worth being recommend.

Key words: cesarean scar pregnancy (CSP); uterine arterial embolization; laparoscope; intrevaginal therapy

体外受精-胚胎移植后宫内妊娠合并子宫切口妊娠1例治疗分析

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【摘要】 目的: 探讨在宫内合并子宫下段切口瘢痕妊娠(cesarean scar pregnancy, CSP)复合妊娠时治疗CSP同时保存宫内胎儿安全有效的方法。方法: 在本中心行体外受精-胚胎移植(IVF-ET)助孕后妊娠患者1例, 经反复阴道超声检查确诊宫内合并CSP。在患者充分知情同意的前提下, 于移植后35 d行阴道超声引导下经阴道CSP胚胎穿刺减灭术, 术后保胎及定期产检。结果: 孕37周出现宫缩后急诊剖宫产一活婴, 发育正常, 术中下段切口处出血多, 但宫缩正常, 术程共出血1 000 ml, 切口缝合后出血止, 保留子宫, 术后42 d复查子宫复旧好。结论: IVF-ET后出现剖宫产CSP合并宫内妊娠的复合妊娠极为罕见, 早期诊断后通过阴道针刺抽吸妊娠胚囊可以达到终止切口瘢痕妊娠的目的, 而且对宫内正常的妊娠囊无任何影响, 是在保存宫内妊娠的同时治疗CSP切实有效的方法。

关键词: 体外受精-胚胎移植(IVF-ET); 剖宫产切口瘢痕妊娠(CSP); 宫内外复合妊娠; 穿刺减胎

中图分类号: R714.22

文献标识码: A

文章编号: 0253-357X(2014)07-0607-04

Clinical Analysis of A Case of Concurrent Intrauterine and Uterine Caesarean Scar Pregnancy after IVF-ET

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【ABSTRACT】 Objective: To explore safe and effective treatment strategies for intrauterine pregnancy complicated by caesarean scar pregnancy (CSP) that will be able to save the foetus within uterus. **Methods:** Repeated ultrasound scans confirmed concurrent intrauterine pregnancy and CSP in a patient that conceived through IVF-ET at our clinic. Reduction of the foetus that implanted on the caesarean scar by needle aspiration of the embryo was achieved via 35 d after embryo transfer. Anti-miscarriage treatments and regular obstetric check-up ensued. **Results:** Emergency caesarean section was performed when uterine contraction occurred in 37th week of gestation. A live infant was delivered and appeared developmentally normal. Heavy haemorrhage was observed at the caesarean incision in lower uterine segment. However, uterine contraction was normal. Intraoperative bleeding was 1 000 ml. Bleeding was stopped after suture of the caesarean scar and uterus was spared. Follow-up on 42th day after operation showed satisfactory uterine resurrection. **Conclusion:** Intrauterine pregnancy complicated by CSP after IVF-ET is extremely rare. Given early diagnosis, caesarean scar pregnancy can be terminated via by needle aspiration of the embryo while intrauterine pregnancy is effectively preserved.

Key words: IVF-ET; cesarean scar pregnancy (CSP); heterotopic pregnancy; needle aspiration embryo reduction