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编 辑

中华生殖与避孕杂志
编辑委员会
200237,上海市老沪闵路779号
电话:(021)64438169
传真:(021)64438975
Email:rande@sibpt.com
http://zhshzybyzz.yiigle.com

总编辑

乔 杰

编辑部主任

王 健

出 版

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Editing

Editorial Board of Chinese Journal of Reproduction and Contraception
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Tel: 0086-21-64438169
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Editor-in-Chief

Qiao Jie

Managing Director

Wang Jian

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针对生育人群的携带者筛查实验室 和临床实践专家共识

中国妇幼保健协会生育保健分会

通信作者: 黄荷凤, 复旦大学生殖发育研究院, 上海 200001, Email:

huanghefg@fudan.edu.cn, 电话: +86-21-54237800; 徐晨明, 复

旦大学附属妇产科医院妇产科遗传中心, 上海 200001, Email:

chenming_xu2006@163.com, 电话: +86-21-33189900*8412

【摘要】 作为一项孕前/孕早期筛查技术, 携带者筛查已经由最初仅针对特定人群、特定疾病发展为现如今的针对一般人群、多种疾病的筛查, 在防控常染色体隐性或 X 连锁遗传病引起的出生缺陷方面表现出了显著的临床效用, 增加了受检夫妇的生育自主权。为规范携带者筛查的实验室检测和临床实施, 经中国妇幼保健协会生育保健分会专家讨论, 结合我国实际情况, 制定本专家共识, 供临床应用参考。

【关键词】 携带者筛查; 高通量测序技术; 疾病选择; 筛查策略; 检测前遗传咨询; 检测后遗传咨询

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Expert consensus on laboratory and clinical practice of carrier screening for reproductive populations

Reproductive Health Branch of the Chinese Maternal and Child Health Association

Corresponding authors: Huang Hefeng, Institute of Reproduction and Development, Fudan University, Shanghai 200001, China, Email: huanghefg@fudan.edu.cn, Tel: +86-21-54237800; Xu Chenming, Genetics Center of Obstetrics and Gynecology, Obstetrics

and Gynecology Hospital, Fudan University, Shanghai 200001, China, Email: chenming_xu2006@163.com, Tel: +86-21-33189900*8412

【Abstract】 As a pre-pregnancy/early pregnancy screening technology, carrier screening has developed from initially targeting specific populations and diseases to targeting the general population and multiple diseases now. It has shown significant clinical efficacy in preventing and controlling birth defects caused by autosomal recessive or X-linked genetic diseases, and has increased the reproductive autonomy of couples undergoing testing. To standardize laboratory testing and clinical implementation of carrier screening, this expert consensus was developed by experts from the Reproductive Health Branch of the Chinese Maternal and Child Health Association, taking into account the actual situation in China, and is provided for clinical reference.

【Key words】 Carrier screening; High-throughput sequencing technology; Disease selection; Screening strategies; Pre-test genetic consultation; Post-test genetic consultation

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· 微生态与生殖健康专栏 ·

雌激素补充治疗对绝经后高危型 HPV 感染女性阴道菌群及局部免疫的影响

许啸声¹ 赵荣² 冯炜炜¹ 沈健¹

¹上海交通大学医学院附属瑞金医院妇产科, 上海 200025; ²上海市瑞金康复医院妇科, 上海 200023

通信作者: 沈健, Email: sj11002@rjh.com.cn

【摘要】 目的 探讨雌激素补充治疗对绝经后高危型人乳头瘤病毒(human papillomavirus, HPV)感染女性阴道菌群及局部免疫的影响。方法 2018年6月至2023年6月期间在上海市瑞金康复医院妇科招募体检或因妇科疾病就诊的74例绝经后女性为研究对象。根据HPV检测结果分为高危型HPV阴性女性(正常组, $n=14$)和高危型HPV阳性女性($n=60$)。采用随机对照试验, 将高危型HPV阳性女性利用随机数字表法分为试验组(高危型HPV阳性且口服低剂量雌激素治疗, $n=30$)和对照组(高危型HPV阳性且未口服低剂量雌激素, $n=30$)。在入组时(即第0周)、入组后第4周和第8周采用荧光定量PCR仪和酶联免疫吸附实验检测3组的阴道微生物群落结构以及阴道灌洗液中的炎症细胞因子表达情况。结果 入组时3组患者年龄、绝经时间、体质量指数、收缩压、舒张压、心率、pH值和阴道细胞成熟指数(vaginal cell maturation index, VMI)差异均无统计学意义(均 $P>0.05$), 基线可比。经雌激素治疗后, 试验组第4周(5.27 ± 0.13)和第8周(4.84 ± 0.15)的pH值均显著低于第0周(6.59 ± 0.17 , 均 $P<0.001$), 而试验组第4周(41.62 ± 2.62)和第8周的VMI(58.28 ± 2.16)均显著高于第0周(25.97 ± 2.60 , 均 $P<0.001$)。定量结果表明正常组、试验组、对照组3组间及各自组内(即每组不同检测时间点)的大肠杆菌(*Escherichia coli*)丰度差异均无统计学意义(均 $P>0.05$)。试验组第0周加德纳菌(*Gardnerella*)和奇异菌属(*Atopobium*)丰度显著高于第4周和第8周(均 $P<0.001$)。但经雌激素治疗后第4周的试验组阴道*Gardnerella*和*Atopobium*丰度显著低于对照组(均 $P<0.001$), 和正常组相比差异均无统计学意义(均 $P>0.05$)。第0、第4、第8周的正常组、试验组和对照组组间的普雷沃氏菌属(*Prevotella*)、加氏乳酸杆菌(*L. Gasseri*)和惰性乳酸杆菌(*L. Iners*)丰度差异均无统计学意义(均 $P>0.05$)。第0周试验组和对照组卷曲乳酸杆菌(*L. Crispatus*)和詹氏乳酸杆菌(*L. Jensenii*)丰度均显著低于正常组(均 $P<0.001$)。第4周和第8周试验组的*L. Crispatus*丰度均显著高于对照组(均 $P<0.001$), 和正常组比较差异均无统计学意义(均 $P>0.05$)。正常组、试验组和对照组女性阴道灌洗液中的白细胞介素(interleukin, IL)-6、IL-8和干扰素(interferon, IFN)- α 浓度差异均无统计学意义(均 $P>0.05$)。试验组和对照组中IL-1 β 浓度均显著高于正常组(均 $P<0.001$), 试验组和对照组间差异无统计学意义($P>0.05$)。试验组第8周肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)浓度显著低于第0周($P<0.001$), 而第4周后TNF- α 浓度与第0周差异无统计学意义($P>0.05$)。与试验组第0周相比, 经雌激素治疗4周后, 趋化因子C-X-C motif 配体14、IFN- β 浓度差异无统计学意义(均 $P>0.05$), 而治疗8周后这两个因子水平显著下降(均 $P<0.001$)。与正常组相比, 试验组和对照组IFN- γ 诱导蛋白16浓度明显升高(均 $P<0.001$), 试验组和对照组组间差异无统计学意义($P>0.05$)。结论 HPV感染后会增加绝经后妇女阴道中*Gardnerella*和*Atopobium*的丰度并降低*L. Crispatus*和*L. Jensenii*的丰度, 进一步破坏阴道微环境中微生物的稳态。雌激素补充治疗对绝经后高危型HPV感染女性的阴道菌群和局部免疫有一定的改善作用。

【关键词】 人乳头瘤病毒; 绝经; 阴道内微生物群落

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Effect of estrogen supplementation therapy on vaginal microbiota and local immunity in postmenopausal women with high-risk HPV infection

Xu Xiaosheng¹, Zhao Rong², Feng Weiwei¹, Shen Jian¹

¹ Department of Obstetrics and Gynecology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; ² Department of Gynecology, Shanghai Ruijin Rehabilitation Hospital, Shanghai 200023, China

Corresponding author: Shen Jian, Email: sj11002@rjh.com.cn

【 Abstract 】 Objective To investigate the effect of estrogen supplementation therapy on vaginal microbiota and local immunity of postmenopausal high-risk human papillomavirus (HPV) infected women. **Methods** A total of 74 postmenopausal women who underwent gynecological examinations or visits at Department of Gynecology, Shanghai Ruijin Rehabilitation Hospital from June 2018 to June 2023 were included in this study. According to HPV test, they were divided into the high-risk HPV-negative women (normal group, $n=14$) and the high-risk HPV-positive women ($n=60$). A randomized controlled clinical trial was designed. Within the high-risk HPV-positive women, they were further randomly assigned by using the random number table method to the experimental group (high-risk HPV-positive women receiving low-dose estrogen therapy orally, $n=30$) and control group (high-risk HPV-positive women not receiving low-dose estrogen therapy, $n=30$). Vaginal microbiota composition and expression of inflammatory cytokines in vaginal lavage fluid were measured using fluorescence quantitative PCR and enzyme-linked immunosorbent assay at baseline (week 0), 4th week, and 8th week after enrollment. **Results** There were no significant differences in age, menopausal time, body mass index, systolic pressure, diastolic pressure, heart rate, pH value and vaginal cell maturation index (VMI) among the normal group, the experimental group and control group (all $P>0.05$) which indicated the baseline was comparable. After estrogen treatment, the pH value of the experimental group at 4th and 8th weeks (5.27 ± 0.13 , 4.84 ± 0.15) was significantly lower than that at week 0 (6.59 ± 0.17 , all $P<0.001$), while the vaginal cell maturation index (VMI) at 4th and 8th weeks (41.62 ± 2.62 , 58.28 ± 2.16) was significantly higher than that at week 0 (25.97 ± 2.60 , all $P<0.001$). The quantitative results showed no significant differences in the abundance of *Escherichia coli* among the normal group, the experimental group, and control group, and within each group at different time points (all $P>0.05$). The abundance of *Gardnerella* and *Atopobium* in the experimental group was significantly higher at week 0 compared with 4th week and 8th week (all $P<0.001$). However, after estrogen treatment, the abundance of *Gardnerella* and *Atopobium* in the experimental group at 4th week was significantly lower than those in control group (all $P<0.001$), with no significant difference compared with the normal group (all $P>0.05$). There were no significant differences in the abundance of *Prevotella*, *L. Gasseri*, and *L. Iners* among the normal group, the experimental group, and control group at week 0, 4th week and 8th week (all $P>0.05$). The abundance of *L. Crispatus* and *L. Jensenii* in the experimental group and control group at week 0 was significantly lower than that in the normal group (all $P<0.001$). The abundance of *L. Crispatus* in the experimental group at 4th week and 8th week was significantly

higher than that in control group (all $P<0.001$), with no significant difference compared with the normal group ($P>0.05$). There were no significant differences in the concentrations of interleukin (IL)-6, IL-8, and interferon (IFN)- α in vaginal lavage fluid among the normal group, the experimental group, and control group (all $P>0.05$). The concentration of IL-1 β in the experimental group and control group was significantly higher than that in the normal group ($P<0.001$), with no significant difference between the experimental group and control group ($P>0.05$). The concentration of tumor necrosis factor alpha (TNF- α) in the experimental group at 8th week was significantly lower than that at week 0 ($P<0.001$), while there was no significant difference in TNF- α concentration after week 4 compared with week 0 ($P>0.05$). Compared with the experimental group at week 0, the concentration of chemokine C-X-C motif ligand 14 (CXCL14) and IFN- β significantly decreased after 8 weeks of estrogen treatment (all $P<0.001$), with no significant change after 4 weeks of treatment ($P>0.05$). Compared with the normal group, the concentration of IFN- γ inducible protein 16 in the experimental group and control group significantly increased (all $P<0.001$), with no significant difference between the experimental group and control group ($P>0.05$). **Conclusion** HPV infection can increase the abundance of *Gardnerella* and *Atopobium* in the vagina of postmenopausal women and decrease the abundance of *L. Crispatus* and *L. Jensenii*, which further disrupts the homeostasis of microorganisms in the vaginal microenvironment. Estrogen replacement therapy has a certain improvement effect on vaginal flora and local immunity in postmenopausal women with high-risk HPV infection.

【Key words】 Human papillomavirus; Menopause; Vaginal microbial

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· 微生态与生殖健康专栏 ·

男性弱精子症与肠道微生物组关联性研究

李芑 孙龙浩 赵唤 宋世威 许蓬

沈阳菁华医院男科, 沈阳 110000

通信作者: 许蓬, Email: 2285852636@qq.com

【摘要】 目的 探究肠道微生物组与弱精子症之间的关系。方法 本研究为病例对照研究, 共纳入 2021 年 1 月至 2021 年 6 月期间在沈阳菁华医院男科就诊的 32 例轻中度弱精子症男性 (记为弱精子症组) 和 30 名精液正常男性 (记为对

照组)，回顾性收集基础信息，检测精液质量，利用 16S rDNA 全长组装测序技术（16S rDNA full length assembly sequencing technology, 16S-FAST）检测粪便内肠道细菌的丰度。结果 弱精子症患者精子总数 $[112.22 \times 10^6 (79.13 \times 10^6, 179.76 \times 10^6)]$ 、前向运动率 $[22.93\% (16.71\%, 28.02\%)]$ 、非前向运动率 $[5.60\% (3.98\%, 7.62\%)]$ 均显著低于对照组 $[166.76 \times 10^6 (110.17 \times 10^6, 262.79 \times 10^6), P=0.022; 42.37\% (35.21\%, 57.88\%), P<0.001; 8.82\% (6.18\%, 11.14\%), P=0.001]$ ，不动精子率 $[72.19\% (65.27\%, 78.92\%)]$ 显著高于对照组 $[50.88\% (33.33\%, 56.24\%), P<0.001]$ 。两组间年龄与体质指数在组间比较差异均无统计学意义（均 $P>0.05$ ）。参与人群的肠道微生物组可分为肠型 1（拟杆菌肠型）和肠型 2（普氏菌肠型）。在两种肠型的样本中， α 多样性在弱精子症组和对照组中差异均无统计学意义（均 $P>0.05$ ）；在肠型 2 的样本中，弱精子症组与对照组的菌群 β 多样性存在差异，且弱精子症组男性肠道内的变形菌门显著高于对照组，梭状芽孢杆菌（*Clostridium sp.*）、布氏瘤胃球菌（*Ruminococcus bromii*）、*Phocaea massiliensis*、双孢梭菌（*C.disporicum*）、*Tyzzarella sp. Marseille_P3062*、解脲霍华德菌（*Howardella ureilytica*）、产气荚膜梭菌（*C.perfringens*）以及 *C.sp.BG-C151* 等菌种更为丰富（线性判别分析，linear discriminant analysis, $LDA>2$ ）；而在肠型 1 的样本中，菌群 β 多样性组间比较差异未见统计学意义（ $P>0.05$ ）。此外，KEGG 分析显示，在肠型 2 的样本中，与差异菌关联密切的硫胺素代谢通路 PATH ko00730 通路在弱精子症组的富集明显低于对照组（ $LDA>2$ ）。结论 弱精子症男性和精液正常男性的肠道微生物组和 KEGG 功能通路在肠型 2 人群中存在显著差异，而在肠型 1 人群未见差异，肠道微生物组变化可能对特定人群的精子活力存在影响。

【关键词】 弱精子症； 肠道微生物组； 不孕症

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Correlation between male asthenospermia and intestinal microbiome

Li Peng, Sun Longhao, Zhao Huan, Song Shiwei, Xu Peng

Department of Andrology, Jinghua Hospital of Shenyang, Shenyang 110000, China

Corresponding author: Xu Peng, Email: 2285852636@qq.com

【Abstract】 Objective To explore the relationship between intestinal microbiomes and asthenospermia. **Methods** This was a retrospective case control study. A total of 32 men with asthenospermia and 30 normal men (named control group) were included. The subjects were recruited from Department of Andrology of Shenyang Jinghua Hospital from January 2021 to June 2021. Basic information was collected, semen quality was tested, abundance of intestinal bacteria in feces was detected using 16S rDNA full length assembly sequencing technology (16S-FAST). **Results** In patients with asthenospermia, the total sperm count $[112.22 \times 10^6 (79.13 \times 10^6, 179.76 \times 10^6)]$, forward progressive motility rate $[22.93\% (16.71\%, 28.02\%)]$, non-forward progressive motility rate $[5.60\% (3.98\%, 7.62\%)]$ were significantly lower and immobile sperm rate $[72.19\% (65.27\%, 78.92\%)]$ was significantly higher than those of control group $[166.76 \times 10^6 (110.17 \times 10^6, 262.79 \times 10^6), P=0.022; 42.37\% (35.21\%, 57.88\%), P<0.001; 8.82\% (6.18\%, 11.14\%), P=0.001; 50.88\% (33.33\%, 56.24\%), P<0.001]$, and there were no significant

differences in age and body mass index between the two groups (all $P>0.05$). The participating population can be divided into enterotype 1 (*Bacteroides* enterotype) and enterotype 2 (*Prevotella* enterotype). There was no significant difference in α diversity between asthenospermia group and control group in two enterotypes (all $P>0.05$). In the population with enterotype 2, β diversity analysis clearly separated the microbiome of men with asthenospermia and healthy controls, and the abundance of *Proteobacteria* phylum, *Clostridium* sp., *Ruminococcus bromii*, *Phocaea massiensis*, *C. disporicum*, *Tyzzzerella* sp. Marseille_P3062, *Howardella ureilytica*, *C. perfringens*, and *C. sp. BG-C151* species were more abundant in men with asthenospermia compared with control group [linear discriminant analysis (LDA) >2]; while in the population with enterotype 1, β diversity analysis could not separate the microbiome of men with asthenospermia and non-asthenospermia men ($P>0.05$). In addition, KEGG analysis showed that in the population with enterotype 2, thiamine metabolism PATH ko00730 pathway, which was closely related to differential bacteria, was significantly less abundant in asthenospermia group than in control group (LDA >2). **Conclusion** The intestinal microbiome and KEGG functional pathways differed significantly between asthenospermia and normozoospermia in population with enterotype 2, while there was no difference in the enterotype 1 population. Changes in intestinal microbiome may have an impact on sperm motility in specific populations.

【Key words】 Asthenospermia; Intestinal microbiome; Infertility

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• 微生态与生殖健康专栏 •

卷曲乳酸杆菌的分离鉴定及体外益生菌特性评价

陈秀菊¹ 向沙沙² 朱炫³ 孙宁霞¹

¹海军军医大学第二附属医院生殖医学中心, 上海 200003; ²潍坊易北

特健康食品有限公司, 潍坊 261057; ³浙江省食品安全重点实验室

浙江工商大学食品与生物工程学院, 杭州 310018

通信作者: 孙宁霞, Email: suesunchzh@126.com, 电话: +86-21-

81886715

【摘要】 目的 分离并筛选健康女性阴道中的卷曲乳酸杆菌并评估其体外益生特性, 为进一步筛选有效治疗女性生殖系统疾病的微生态制剂提供新型菌株。方法 2023年4月至2023年5月期间采集海军军医大学第二附属医院体检中心10名健康女性阴道分泌物并分离筛选卷曲乳酸杆菌, 通过16S rRNA序列鉴定卷曲乳酸杆菌, 并测定其生长特性、产酸能力、产H₂O₂能力、抑菌能力。结果 从10名健康女性阴道内共分离并鉴定出39株卷曲乳酸杆菌。本实验卷曲乳酸杆菌的生长对数期为10~40 h, 其中卷曲乳酸杆菌4-5及卷曲乳酸杆菌6-7生长速度较快。本实验卷曲乳酸杆菌的pH在8~24 h内下降速度较快, 48 h菌液的pH稳定在3.89~4.05之间, 其中卷曲乳酸杆菌6-6、6-7、6-9、6-11的产酸性能较好。筛选的10株卷曲乳酸杆菌均能产H₂O₂, 其中卷曲乳酸杆菌4-5、4-11、6-5、6-7产H₂O₂性能较好。卷曲乳酸杆菌6-5、6-7和6-9抑制白假丝酵母菌的效果较好, 其抑菌圈直径分别为(20.90±0.31) mm、(20.61±0.70) mm、(21.73±0.37) mm; 卷曲乳酸杆菌4-5、6-5和6-7抑制金黄色葡萄球菌的效果较好, 其抑菌圈直径分别为(20.95±0.07) mm、(23.52±0.49) mm、(23.49±0.34) mm; 卷曲乳酸杆菌6-5、6-6和6-7抑制大肠埃希菌的效果较好, 其抑菌圈直径分别为(19.03±0.23) mm、(18.20±0.18) mm、(18.55±0.29) mm。结论 卷曲乳酸杆菌6-5和卷曲乳杆菌6-7产酸能力、产H₂O₂能力、抑菌活性较好, 具有优良的生物学特性, 有望成为用于治疗女性生殖系统疾病微生态制剂的备选菌株。

【关键词】 卷曲乳酸杆菌; 乳酸菌; 分离; 鉴定

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Isolation and identification of *Lactobacillus crispatus* and evaluation of probiotic properties *in vitro*

Chen Xiuju¹, Xiang Shasha², Zhu Xuan³, Sun Ningxia¹

¹Department of Reproductive Medicine, the Second Affiliated Hospital of Naval Medical University, Shanghai 200003, China; ²Weifang Elbe Health Food Co., Weifang 261057, China; ³Zhejiang Provincial Key Laboratory of Food Safety; School of Food Science and Biotechnology, Zhejiang Gongshang University, Hangzhou 310018, China

Corresponding author: Sun Ningxia, Email: suesunchzh@126.com, Tel: +86-21-81886715

【Abstract】 Objective To isolate and screen *Lactobacillus crispatus* from healthy female vagina and evaluate its probiotic characteristics *in vitro* in order to provide a new strain for further screening and study of microecological agents for effective treatment of female reproductive system diseases. **Methods** The vaginal secretions of 10 healthy women were collected and screened in Department of Reproductive Medicine, the Second Affiliated Hospital of Naval Medical University from April 2023 to May 2023. *Lactobacillus crispatus* was identified by 16S rRNA sequence, and its growth characteristics, acid-producing ability, H₂O₂ producing ability and bacteriostatic ability were detected. **Results** Totally 39 strains of *Lactobacillus crispatus* were isolated and identified from 10 healthy women. The logarithmic growth phase of *Lactobacillus crispatus* was 10–40 h, among which *Lactobacillus crispatus* 4-5 and *Lactobacillus crispatus* 6-7 grew faster. The pH of *Lactobacillus crispatus* decreased rapidly within 8–24 h, and the pH of 48 h was stable between 3.89 and 4.05. Among them, *Lactobacillus crispatus* 6-6, 6-7, 6-9, 6-11 had better acid production. All 10 strains of *Lactobacillus crispatus* could produce H₂O₂, and *Lactobacillus crispatus* 4-5, 4-11, 6-5 and 6-7 had better H₂O₂ production. *Lactobacillus crispatus* 6-5, 6-7 and 6-9 had better inhibitory effect on *Candida albicans*, in which the diameters of bacteriostatic zone were (20.90±0.31) mm, (20.61±0.70) mm and (21.73±0.37) mm, respectively. *Lactobacillus crispatus* 4-5 and 6-7 had better inhibitory effect on *Staphylococcus aureus*. Among them, the diameters of bacteriostatic zone were (20.95±0.07) mm, (23.52±0.49) mm and (23.49±0.34) mm, respectively. *Lactobacillus crispatus* 6-5, 6-6 and 6-7 had better inhibitory effect on *Escherichia coli*, the diameters of bacteriostatic zone were (19.03±0.23) mm, (18.20±0.18) mm and (18.55±0.29) mm, respectively. **Conclusion** *Lactobacillus crispatus* 6-5 and 6-7 have good acid production, hydrogen peroxide production, bacteriostatic activity and excellent biological characteristics, so they are expected to be candidate strains for the treatment of female reproductive system diseases.

【Key words】 *Lactobacillus crispatus*; *Lactobacillus*; Isolation; Identification

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• 微生态与生殖健康专栏 •

肠道微生态与生殖障碍性疾病的相关研究进展

赵敏 庞艳莉

北京大学第三医院妇产科生殖医学中心 女性生育力促进全国重点实验室 国家妇产疾病临床医学研究中心（北京大学第三医院） 辅助生殖教育部重点实验室（北京大学） 生殖内分泌与辅助生殖技术北京市重点实验室，北京 100191

通信作者：庞艳莉，Email: yanlipang@bjmu.edu.cn，电话：+86-10-82266590

【摘要】 当前育龄人群的生殖健康面临前所未有的挑战，不孕不育的患病率和不良妊娠结局的发生率逐年上升。肠道微生态作为人体的关键组成部分，在一系列正常生命活动的进行中发挥着重要作用。肠道微生态的紊乱已被证明参与多种疾病的进程，越来越多的研究表明，肠道微生态的紊乱与生殖障碍性疾病的发生发展有关。因此，本文将总结肠道微生态与女性生殖障碍性疾病的相关研究进展，为其防治提供新的策略，为提升育龄女性的生育力提供新的思路。

【关键词】 生殖健康； 多囊卵巢综合征； 子宫内膜异位症； 先兆子痫； 复发性流产； 早发性卵巢功能不全； 肠道微生态

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Relevant research progress of gut microbiota and reproductive disorders

Zhao Min, Pang Yanli

Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital; State Key Laboratory of Female Fertility Promotion; National Clinical Research Center for Obstetrics and Gynecology (Peking University Third Hospital); Key Laboratory of Assisted Reproduction (Peking University), Ministry of Education; Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproductive Technology, Beijing 100191, China

Corresponding author: Pang Yanli, Email: yanlipang@bjmu.edu.cn, Tel: +86-10-82266590

【 Abstract 】 At present, the reproductive health of childbearing age population is facing unprecedented challenges, with the incidence of infertility and adverse pregnancy outcomes increasing year by year. As a key component of human body, gut microbiota plays an important role in a series of normal life activities. The disturbance of gut microbiota has been proved to be involved in the process of many diseases, and more and more studies have shown that the disturbance of gut microbiota is also related to the occurrence and development of reproductive disorders. Therefore, this paper will summarize the relevant research progress of gut microbiota and female reproductive disorders, to provide new strategies for their prevention and treatment, and new ideas for improving the fertility of women of reproductive age.

【 Key words 】 Reproductive Health; Polycystic ovary syndrome; Endometriosis; Pre-eclampsia; Abortion, spontaneous; Primary ovarian insufficiency; Gut microbiota

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· 临床研究 ·

新鲜周期第 4 天不同移植方案妊娠结局和母婴结局比较

陶林林¹ 戴芳芳¹ 郑波¹ 李国臻¹ 耿亚松¹ 杨志伟¹ 戴豪杨¹

郭钰英¹ 王树松²

¹ 邢台不孕不育专科医院生殖医学中心, 邢台 054000; ² 河北省生殖健

康科学技术研究院 河北省生殖医学重点实验室, 石家庄 050051

通信作者: 戴芳芳, Email: 281379670@qq.com, 电话: +86-319-

3021530

【摘要】 目的 探讨新鲜周期第 4 天不同移植方案对临床结局及母婴结局的影响。方法 回顾性队列研究分析 2019 年 1 月至 2021 年 12 月期间于邢台不孕不育专科医院生殖医学中心行体外受精 (*in vitro* fertilization, IVF) 和卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI) 的 745 个周期的临床资料。所有周期均在受精后第 4 天移植 1~2 枚胚胎, 根据不同胚胎移植方案分为 5 组: 部分融合 1 枚组 (A 组, $n=17$)、部分融合 2 枚组 (B 组, $n=236$)、完全融合以上 1 枚组 (C 组, $n=241$)、部分融合+完全融合以上组 (D 组, $n=72$) 和完全融合以上 2 枚组 (E 组, $n=179$), 比较不同移植方案对临床结局和母婴结局的影响。结果 不同组间的双原核 (two pronuclei, 2PN) 受精率、2PN 卵裂率、内膜厚度、单卵双胞胎率、手术减胎率、流产率、死亡率、剖宫产率、男婴/女婴比例等差异均无统计学意义 (均 $P>0.05$)。D 组和 E 组临床妊娠率 [83.33% (60/72)、

72.63% (130/179)] 显著高于 B 组 [59.32% (140/236), $P<0.001$, $P=0.005$], E 组活产率 [65.36% (117/179)] 显著高于 B 组 [50.00% (118/236), $P=0.002$], C、D、E 组种植率 [64.73% (156/241)、59.72% (86/144)、54.19% (194/358)] 显著高于 B 组 [39.83% (188/472), 均 $P<0.001$], D 组和 E 组的多胎率 [43.33% (26/60), 49.23% (64/130)] 和早产率 [23.33% (14/60), 26.15% (34/130)] 均显著高于 C 组 [0%, 均 $P<0.001$; 7.69% (12/156), $P=0.002$, $P<0.001$], E 组分娩孕周 [38.0 (36.0, 39.0) 周] 显著低于 C 组 [39.0 (38.0, 39.3) 周, $P<0.001$]。与移植 1 枚组 (A 组和 C 组) 比较, 移植 2 枚胚胎组 (B、D、E 组) 出生体质量显著降低 ($P<0.001$), D 组和 E 组的低出生体质量儿率 [20.90% (14/67), 28.40% (48/169)] 显著高于 C 组 [3.85% (5/130), $P<0.001$]。logistic 回归分析显示, 调整混杂因素后, C 组临床妊娠率显著高于 A 组 ($OR=0.353$, 95% CI : 0.125~0.997, $P=0.049$); E 组的活产率显著高于 C 组 ($OR=1.842$, 95% CI : 1.172~2.895, $P=0.008$); B、D、E 组的早产率均显著高于 C 组 ($OR=2.546$, 95% CI : 1.079~6.005, $P=0.033$; $OR=6.737$, 95% CI : 2.566~17.689, $P<0.001$; $OR=5.863$, 95% CI : 2.494~13.785, $P<0.001$)。结论 新鲜周期第 4 天达到完全融合以上胚胎的妊娠率和活产率显著高于部分融合胚胎, 临床工作中推荐优选完全融合及以上胚胎, 其次选择部分融合胚胎, 行单胚胎移植, 以在获得最佳妊娠结局的同时降低多胎率、早产率及低出生体质量儿率。

【关键词】 妊娠结局; 移植方案; 母婴结局

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Comparison of clinical outcomes and maternal and fetal outcomes between different transplantation schemes on day 4 in fresh cycle

Tao Linlin¹, Dai Fangfang¹, Zheng Bo¹, Li Guozhen¹, Geng Yasong¹, Yang Zhiwei¹, Dai Haoyang¹, Guo Yuying¹, Wang Shusong²

¹ Reproductive Medicine Center, Xingtai Infertility Specialist Hospitals, Xingtai 054000, China; ² Hebei Institute for Family Planning Science and Technology; Hebei Key Laboratory of Reproductive Medicine, Shijiazhuang 050051, China

Corresponding author: Dai Fangfang, Email: 281379670@qq.com, Tel: +86-319-3021530

【Abstract】 **Objective** To explore the effect of different transplantation schemes on the clinical outcomes and maternal and fetal outcomes of fresh cycle on day 4. **Methods** The clinical data of 745 cycles of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in Reproductive Medicine Center of Xingtai Infertility Specialist Hospitals from January 2019 to December 2021 were analyzed retrospectively. In all cycles, 1-2 embryos were transferred on day 4 after fertilization. According to different embryo transfer schemes, they were divided into five groups: one partial compaction embryo group (group A, $n=17$), two partial compaction embryos group (group B, $n=236$), one full compaction above embryo group (group C, $n=241$), partial compaction+full compaction above group (group D, $n=72$), and two full compaction above embryos group (group E, $n=179$), the effects of different transfer schemes on clinical outcomes and maternal and fetal outcomes were compared. **Results** There were no significant differences in two pronuclei (2PN) fertilization rate, 2PN cleavage rate, endometrial thickness, monozygotic

twins rate, surgical reduction rate, abortion rate, stillbirth rate, cesarean section rate, male infant/female infant ratio among the five groups (all $P>0.05$). The clinical pregnancy rate in groups D and E [83.33% (60/72), 72.63% (130/179)] was significantly higher than that in group B [59.32% (140/236), $P<0.001$, $P=0.005$]. The live birth rate of group E [65.36% (117/179)] was significantly higher than that of group B [50.00% (118/236), $P=0.002$]. The implantation rate of groups C, D and E [64.73% (156/241), 59.72% (86/144), 54.19% (194/358)] was significantly higher than that of group B [39.83% (188/472), all $P<0.001$]. The multiple birth rate [43.33% (26/60), 49.23% (64/130)] and the premature delivery rate [23.33% (14/60), 26.15% (34/130)] in groups D and E were significantly higher than those in group C [0%, all $P<0.001$; 7.69% (12/156), $P=0.002$, $P<0.001$]. The gestational weeks of delivery in group E [38.0 (36.0,39.0) weeks] was significantly lower than that in group C [39.0 (38.0,39.3) weeks, $P<0.001$]. Compared with the one embryo transfer group (group A, group C), the birth weight of the two embryos transfer group (group B, group D, group E) was significantly lower ($P<0.001$). The low birth weight infants rate in group D [20.90% (14/67)] and group E [28.40% (48/169)] was significantly higher than that in group C [3.85% (5/130), $P<0.001$]. Logistic regression analysis showed that after adjusted, the pregnancy rate in group C was significantly higher than that in group A ($OR=0.353$, 95% CI : 0.125–0.997, $P=0.049$). The live birth rate of group E was significantly higher than that of group C ($OR=1.842$, 95% CI : 1.172–2.895, $P=0.008$), and the premature delivery rate of groups B, D and E was significantly higher than that of group C ($OR=2.546$, 95% CI : 1.079–6.005, $P=0.033$; $OR=6.737$, 95% CI : 2.566–17.689, $P<0.001$; $OR=5.863$, 95% CI : 2.494–13.785, $P<0.001$). **Conclusion** On day 4 of the fresh cycle, the pregnancy rate and the live birth rate of the full compaction or above embryos are significantly higher than those of the partial compaction embryos. In clinical work, it is recommended to select full compaction embryos or above, and then select partially compaction embryos for single embryo transfer to achieve optimal pregnancy outcomes while reducing the multiple pregnancy rate, premature delivery rate, and low birth weight infant rate.

【Key words】 Pregnancy outcome; Transplantation schemes; Maternal and fetal outcomes

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不同次数输卵管妊娠史患者再次妊娠结局分析

林晓龙 姜文清 邹世恩

复旦大学附属妇产科医院妇科, 上海 200001

通信作者: 邹世恩, Email: zoushien@fudan.edu.cn, 电话: +86-21-33189900

【摘要】 目的 探讨不同次数输卵管妊娠史患者再次妊娠结局差异。方法 回顾性队列研究分析 2019 年 1 月至 2023 年 4 月期间复旦大学附属妇产科医院妇科收治的输卵管妊娠史次数 ≥ 1 次的 415 例患者, 根据输卵管妊娠史分为 2 组: A 组为 1 次输卵管妊娠史 ($n=359$), B 组为 2 次输卵管妊娠史 ($n=56$), 收集每组患者基线信息和再次妊娠结局, 比较保留输卵管和切除输卵管后异位妊娠率的差异。B 组患者根据复发部位, 分为同侧复发亚组和对侧复发亚组, 比较两亚组患者再次妊娠时异位妊娠率的差异, 并通过二元 logistic 回归分析与输卵管妊娠复发相关的影响因素。结果 A 组患者再次妊娠时宫内妊娠率 [66.0% (237/359)] 高于 B 组 [48.2% (27/56), $P=0.008$]。A 组采用甲氨蝶呤 (methotexate, MTX) 注射、输卵管切开取胚和输卵管挤压的患者宫内妊娠率 [77.0% (97/126)、78.2% (93/119)、90.0% (9/10)] 均高于采用输卵管切除的患者 [35.7% (35/98)], 均 $P<0.001$; B 组采用期待、MTX 注射、输卵管切开取胚和输卵管切除的宫内妊娠率差异均无统计学意义 (均 $P>0.05$)。B 组同侧复发亚组 24 例, 对侧复发亚组 32 例, 两亚组再次宫内妊娠率、同侧异位妊娠率、对侧异位妊娠率差异均无统计学意义 (均 $P>0.05$)。第二次输卵管妊娠的发生与距前次妊娠时间和受孕方式有关, 距前次妊娠时间 ≥ 36 个月对输卵管妊娠复发有显著影响 ($OR=5.012$, 95% CI : 2.525~9.949, $P<0.001$)。体外受精-胚胎移植 (*in vitro* fertilization and embryo transfer, IVF-ET) 助孕患者宫内妊娠率 [91.4% (53/58)] 高于自然受孕患者 [61.1% (184/301), $P<0.001$], 其对降低第二次输卵管妊娠的发生有显著影响 ($OR=9.666$, 95% CI : 3.303~28.287, $P<0.001$)。第三次输卵管妊娠的发生与受孕方式有关, IVF-ET 助孕患者宫内妊娠率 [76.5% (13/17)] 高于自然受孕患者 [35.9% (14/39), $P<0.001$], 其对降低第三次输卵管妊娠发生有显著影响 ($OR=5.987$, 95% CI : 1.529~23.447, $P=0.010$)。结论 对于首次出现输卵管妊娠的患者, 实施保留输卵管的治疗方法有助于保存患者将来宫内妊娠的机会。对于同侧输卵管妊娠复发的患者, 目前尚无充分证据支持切除患侧输卵管对患者有利。无论是第一次还是第二次输卵管妊娠, 再次妊娠选择 IVF-ET 助孕可获得更高的宫内妊娠率。

【关键词】 妊娠, 输卵管; 复发; 受精, 体外; 胚胎移植; 妊娠结局; 第三次输卵管妊娠

Analysis of the consecutive pregnancy outcomes in women with different times of tubal pregnancy history

Lin Xiaolong, Jiang Wenqing, Zou Shien

Gynecology Department, Obstetrics & Gynecology Hospital of Fudan University, Shanghai 200001, China

Corresponding author: Zou Shien, Email: zoushien@fudan.edu.cn, Tel: +86-21-33189900

【Abstract】 Objective To analyze the consecutive pregnancy outcomes in women with different times of tubal pregnancy (TP) history. **Methods** The data of 415 patients with a history of TP \geq 1 times admitted in Gynecology Department of Obstetrics & Gynecology Hospital of Fudan University from January 2019 to April 2023 were retrospectively analyzed. They were divided into two groups: the first TP group ($n=359$) and the second TP group ($n=56$). Clinical data and consecutive pregnancy outcomes were collected and the differences of TP rate between patients treated by retaining fallopian tubes and those treated by salpingectomy were analyzed. Patients with a second TP were divided into two subgroups: ipsilateral recurrence subgroup and contralateral recurrence subgroup, and difference of TP rate between the two subgroups was assessed. Risk factors for recurrent TP were assayed by binary logistic analysis. **Results** Intrauterine pregnancy rate in the first TP group was higher than that in the second TP group [66.0% (237/359) vs. 48.2% (27/56), $P=0.008$]. Salpingectomy resulted in significantly lower rate of intrauterine pregnancy [35.7% (35/98)] compared with treatment with methotrexate or salpingotomy or extrusion of fallopian tubes in the first TP group, 77.0% (97/126), 78.2% (93/119), 90.0% (9/10), respectively; all $P<0.001$]. There was no difference of intrauterine pregnancy rate among patients treated by expectant management or methotrexate or salpingectomy or salpingotomy in the second TP group (all $P>0.05$). There were 24 cases in the ipsilateral recurrent subgroup and 32 cases in the contralateral recurrent subgroup. The rates of recurrent intrauterine pregnancy, ipsilateral ectopic pregnancy and contralateral ectopic pregnancy were not different between the two subgroups (all $P>0.05$). Logistic regression analysis suggested time interval from prior TP to next pregnancy ≥ 36 months were positively correlated with occurrence of the second TP ($OR=5.012$, 95% CI : 2.525–9.949, $P<0.001$). Patients concept by *in vitro* fertilization and embryo transfer (IVF-ET) after the first TP had higher rate of intrauterine pregnancy compared with natural conception [91.4% (53/58) vs. 61.1% (184/301), $P<0.001$] and IVF-ET significantly decreased the occurrence of the second TP ($OR=9.666$, 95% CI : 3.303–28.287, $P<0.001$). Patients conceived by IVF-ET after the second TP had higher rate of intrauterine pregnancy compared with natural conception [76.5% (13/17) vs. 35.9% (14/39), $P<0.001$] and IVF-ET significantly decreased the occurrence of the third TP ($OR=5.987$, 95% CI : 1.529–23.447, $P=0.010$). **Conclusion** For patients who experience first-time TP, preserving the fallopian tube can help them gain the opportunity for intrauterine pregnancy. For patients with recurrent ipsilateral fallopian TP, there is currently insufficient evidence to support the benefit of

removing the affected fallopian tube. Whether it is the first or the second TP, IVF-ET can help patients achieve a higher intrauterine pregnancy rate.

【Key words】 Pregnancy;tubal; Recurrence; Fertilization *in vitro*; Embryo transfer; Pregnancy outcome; Third tubal pregnancy

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卵巢过度刺激综合征患者胚胎发育及临床妊娠结局研究

王静 程慧茹 杨丹丹 范咏琪 陈蓓丽 章志国 曹云霞
安徽医科大学第一附属医院妇产科 国家卫生健康委配子及生殖道异常研究重点实验室 生殖健康与遗传安徽省重点实验室, 合肥 230032

通信作者: 章志国, Email: zzg_100@163.com, 电话: +86-18155106683

【摘要】 目的 探讨辅助生殖技术中发生卵巢过度刺激综合征 (ovarian hyperstimulation syndrome, OHSS) 患者的胚胎发育及临床妊娠结局。方法 对 2019 年 8 月至 2021 年 8 月期间在安徽医科大学第一附属医院妇产科行体外受精/卵胞质内单精子注射-胚胎移植治疗的 4 080 个周期的病例资料进行回顾性队列研究。按照是否发生 OHSS 分为 OHSS 组 ($n=524$) 与对照组 (未发生 OHSS 患者, $n=3 556$); 524 个 OHSS 周期依据是否合并多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 分为 OHSS 合并 PCOS 亚组 ($n=231$) 和 OHSS 合并非 PCOS 亚组 ($n=293$)。比较各组之间的基础资料、胚胎发育结局及临床结局。结果 ①OHSS 组患者年龄 [(30.7 ± 3.6) 岁] 小于对照组 [(31.5 ± 4.8) 岁, $P<0.001$]、获卵数 [(28.2 ± 5.7) 枚]、优质胚胎率 [52.7% ($4 982/9 463$)]、优质囊胚率 [54.0% ($5 059/9 371$)]、生化妊娠率 [75.0% ($393/524$)]、临床妊娠率 [69.5% ($364/524$)] 和活产率 [58.0% ($304/524$)] 显著高于对照组 [(12.5 ± 6.7) 枚、 49.8% ($14 042/28 204$)、 51.4% ($14 279/27 797$)、 59.5% ($2 115/3 556$)、 54.1% ($1 924/3 556$)、 43.6% ($1 550/3 556$), 均 $P<0.001$]。②OHSS 合并 PCOS 亚组患者年龄 [(30.2 ± 3.1) 岁] 低于 OHSS 合并非 PCOS 亚组 [(31.1 ± 4.0) 岁, $P=0.009$]; 雌二醇 [165.0 ($101.0, 222.5$) pmol/L] 水平显著高于 OHSS 合并非 PCOS 亚组 [141.0 ($81.0, 202.0$) pmol/L,

$P=0.005$]；优质胚胎率 [56.3% (2 413/4 284)]、囊胚形成率 [67.1% (2 846/4 239)] 和优质囊胚率 [57.7% (2 445/4 239)] 均显著高于 OHSS 合并非 PCOS 亚组 [49.6% (2 569/5 179)、60.3% (3 092/5 132)、50.9% (2 614/5 132)，均 $P<0.001$]。结论 OHSS 与年龄呈一定的相关性，其发生不会影响胚胎的发育，不增加不孕症患者的不良妊娠结局，是否合并 PCOS 不影响 OHSS 患者的妊娠结局，但在辅助生殖技术中我们仍要尽量避免 OHSS 等不良事件的发生。

【关键词】 卵巢过度刺激综合征； 生殖技术， 辅助； 多囊卵巢综合征； 胚胎发育； 妊娠结局

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Research on embryo development and clinical pregnancy outcomes in patients with ovarian hyperstimulation syndrome

Wang Jing, Cheng Huiru, Yang Dandan, Fan Yongqi, Chen Beili, Zhang Zhiguo, Cao Yunxia

Department of Obstetrics and Gynecology, the First Affiliated Hospital of Anhui Medical University; NHC Key Laboratory of Study on Abnormal Gametes and Reproductive Tract (Anhui Medical University); Anhui Province Key Laboratory of Reproductive Health and Genetics, Hefei 230032, China

Corresponding author: Zhang Zhiguo, Email: zzg_100@163.com, Tel: +86-18155106683

【Abstract】 **Objective** To investigate the embryo development and clinical pregnancy outcomes in patients with ovarian hyperstimulation syndrome (OHSS) undergoing assisted reproductive technology (ART). **Methods** A retrospective cohort study was conducted on data from 4 080 cycles of *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer treatments performed at the Department of Obstetrics and Gynecology, the First Affiliated Hospital of Anhui Medical University from August 2019 to August 2021. Patients were divided into OHSS group ($n=524$) and non-OHSS group (control group, $n=3 556$) based on whether OHSS occurred, and the OHSS group was further divided into OHSS combined with polycystic ovary syndrome (PCOS) subgroup ($n=231$) and OHSS combined with non-PCOS subgroup ($n=293$) based on the presence of PCOS. General information, embryo developmental data and clinical outcomes were compared between the two groups. **Results** 1) Patients in the OHSS group [(30.7±3.6) years] were younger than those in control group [(31.5±4.8) years, $P<0.001$], and the number of retrieved oocytes (28.2±5.7), rates of high-quality embryos [52.7% (4 982/9 463)], blastocyst formation [54.0% (5 059/9 371)], biochemical pregnancy [75.0% (393/524)], clinical pregnancy [69.5% (364/524)], and live birth [58.0% (304/524)] were significantly higher in the OHSS group than in control group [12.5±6.7, 49.8% (14 042/28 204), 51.4% (14 279/27 797), 59.5% (2 115/3 556), 54.1% (1 924/3 556), 43.6% (1 550/3 556), respectively; all $P<0.001$]. 2) Patients in the OHSS combined with PCOS subgroup [(30.2±3.1) years] were younger than those in the OHSS combined with non-PCOS subgroup [(31.1±4.0) years, $P=0.009$], and the estradiol level [165.0 (101.0, 222.5) pmol/L] was higher than that in the OHSS

combined with non-PCOS subgroup [141.0 (81.0,202.0) pmol/L, $P=0.005$]; rates of high-quality embryos [56.3% (2 413/4 284)], blastocyst formation [67.1% (2 846/4 239)], and high-quality blastocysts [57.7% (2 445/4 239)] were also significantly higher in the OHSS combined with PCOS subgroup than in the OHSS combined with non-PCOS subgroup [49.6% (2 569/5 179), 60.3% (3 092/5 132), 50.9% (2 614/5 132), respectively; all $P<0.001$]. **Conclusion** There is a certain correlation between OHSS and female age. The occurrence of OHSS does not affect embryo development and does not increase adverse pregnancy outcomes in infertile patients. The presence of PCOS does not affect the pregnancy outcomes of OHSS patients. However, in ART, we still strive to avoid the occurrence of adverse events such as OHSS as much as possible.

【 Key words 】 Ovarian hyperstimulation syndrome; Reproductive technology, assisted; Polycystic ovary syndrome; Embryo development; Pregnancy outcome

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卵母细胞玻璃化冷冻对胚胎发育及移植结局的影响

申春艳 张建瑞 杜姗姗 管一春

郑州大学第三附属医院生殖医学科, 郑州 450052

通信作者: 管一春, Email: lisamayguan@163.com, 电话: +86-

13608695579

【摘要】 目的 探讨玻璃化冷冻卵母细胞行卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI) 对胚胎发育及妊娠结局的影响。方法 回顾性队列研究分析郑州大学第三附属医院生殖医学科 2015 年 10 月至 2022 年 12 月期间行 ICSI 助孕周期患者的临床资料。纳入玻璃化冷冻卵母细胞解冻行 ICSI 助孕的周期 95 个 (记为冷冻卵子组) 和同期新鲜卵母细胞行 ICSI 助孕周期 5 830 个 (记为新鲜卵子组), 冷冻卵子组按照冷冻方法分为二步法亚组与桥接法亚组。利用 1:3 倾向性评分匹配 (propensity score matching, PSM) 后得到冷冻卵

子组 94 个周期, 新鲜卵子组 282 个周期, 比较两组 ICSI 后受精、胚胎发育情况及移植后临床妊娠结局。采用多重线性回归分析影响卵子存活率的相关因素。结果 PSM 匹配后, 冷冻卵子组的正常受精率 [69.59% (572/822)]、正常卵裂率 [95.63% (547/572)]、可利用胚胎率 [74.41% (407/547)]、优质胚胎率 [36.38% (199/547)]、可利用囊胚形成率 [37.08% (89/240)] 及卵子利用率 [37.00% (407/1 100)] 均显著低于新鲜卵子组 [74.26% (1 875/2 525), $P=0.009$; 97.97% (1 837/1 875), $P=0.002$; 84.65% (1 555/1 837), $P<0.001$; 50.08% (920/1 837), $P<0.001$; 51.68% (537/1 039), $P<0.001$; 61.58% (1 555/2 525), $P<0.001$], 总受精率、多原核受精率及卵子退化率差异均无统计学意义 (均 $P>0.05$)。冷冻卵子组卵裂期胚胎移植数 [(1.91 ± 0.28) 枚] 和晚期流产率 [10.53% (4/38)] 显著高于新鲜卵子组 [(1.72 ± 0.45) 枚, $P=0.001$; 1.14% (1/88), $P=0.048$], 卵裂期胚胎着床率、生化妊娠率、临床妊娠率及早期流产率差异均无统计学意义 (均 $P>0.05$)。冷冻卵子组中二步法亚组的卵子存活率 [55.95% (188/336)]、卵子退化率 [6.38% (12/188)]、可利用囊胚形成率 [5.08% (13/59)] 及卵子利用率 [26.49% (89/336)] 与桥接法亚组 [82.98% (634/764), $P<0.001$; 3.00% (19/634), $P=0.032$; 41.99% (76/181), $P=0.006$; 41.62% (318/764), $P<0.001$] 相比, 差异均有统计学意义, 两亚组间总受精率、正常受精率、多原核受精率、正常卵裂率、可利用胚胎率及优质胚胎率差异均无统计学意义 (均 $P>0.05$)。多重线性回归分析影响卵子存活率的因素结果显示促排卵方案 ($\beta=-19.730$, $t=-2.06$, $P=0.043$)、卵子冷冻数 ($\beta=-1.417$, $t=-3.10$, $P=0.003$) 及卵子玻璃化冷冻方法 ($\beta=33.872$, $t=5.04$, $P<0.001$) 对卵子存活率的影响差异具有统计学意义。结论 卵母细胞玻璃化冷冻对胚胎发育造成了不利的影响, 胚胎移植后妊娠结局与新鲜卵母细胞相似, 但其围产期结局的安全性仍需要进一步的研究证实。

【关键词】 卵母细胞; 玻璃化冷冻; 胚胎发育; 胚胎移植

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Effects of oocyte vitrification on the outcomes of embryo development and transfer

Shen Chunyan, Zhang Jianrui, Du Shanshan, Guan Yichun

The Reproductive Center of the Third Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

Corresponding author: Guan Yichun, Email: lisamayguan@163.com, Tel: +86-13608695579

【Abstract】 **Objective** To investigate the effect of vitrified oocytes undergoing intracytoplasmic sperm injection (ICSI) on embryo development and transfer outcomes. **Methods** A retrospective cohort study was conducted to analyze the clinical data of patients who underwent ICSI in the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University from October 2015 to December 2022. A total of 95 cycles of vitrified oocytes (named vitrified oocyte group) and 5 830 cycles of fresh oocytes (named fresh oocyte group) in the same

period were included, ICSI was used in both groups for fertilization. The cycles were matched at 1 : 3 with propensity score matching (PSM), then there was 94 cycles in vitrified oocyte group, 282 cycles in fresh oocyte group. The vitrified oocyte group was divided into two-step method subgroup and crossed bridge method subgroup according to vitrification procedures. The fertilization, embryo development and clinical pregnancy outcomes were compared between the two groups. Multiple linear regression was used to analyze the correlates affecting oocyte survival rate.

Results After PSM in vitrified oocyte group, the normal fertilization rate [69.59% (572/822)], the normal cleavage rate [95.63% (547/572)], the available embryo rate [74.41% (407/547)], the high-quality embryo rate [36.38% (199/547)], the available blastocyst rate [37.08% (89/240)] and the oocyte utilization rate [37.00% (407/1 100)] were significantly reduced compared with fresh oocyte group [74.26% (1 875/2 525), $P=0.009$; 97.97% (1 837/1 875), $P=0.002$; 84.65% (1 555/1 837), $P<0.001$; 50.08% (920/1 837), $P<0.001$; 51.68% (537/1 039), $P<0.001$; 61.58% (1 555/2 525), $P<0.001$]. The total fertilization rate, the multiple pronucleus fertilization rate and the oocyte damage rate had no significant differences (all $P>0.05$). The embryo transfer cycles of vitrified oocyte group had similar implantation rate of cleavage embryos, biochemical pregnancy rate, clinical pregnancy rate and early abortion rate compared with fresh oocyte group (all $P>0.05$), however the number of cleavage embryo transfer was significantly increased (1.91 ± 0.28 vs. 1.72 ± 0.45 , $P=0.001$), the late abortion rate was also significantly increased [10.53% (4/38) vs. 1.14% (1/88), $P=0.048$]. Between two-step method and crossed bridge method subgroups, there were significant differences in oocyte survival rate [55.95% (188/336) vs. 82.98% (634/764), $P<0.001$], oocyte damage rate [6.38% (12/188) vs. 3.00% (19/634), $P=0.032$], available blastocyst rate [5.08% (13/59) vs. 41.99% (76/181), $P=0.006$] and oocyte utilization rate [26.49% (89/336) vs. 41.62% (318/764), $P<0.001$], there were no significant differences in total fertilization rate, normal fertilization rate, multiple pronucleus fertilization rate, normal cleavage rate, available embryo rate and high-quality embryo rate (all $P>0.05$). Multiple linear regression analysis showed that controlled ovarian stimulation procedure ($\beta=-19.730$, $t=-2.06$, $P=0.043$), number of vitrified oocytes ($\beta=-1.417$, $t=-3.10$, $P=0.003$) and procedure of oocytes vitrification ($\beta=33.872$, $t=5.04$, $P<0.001$) had a statistical effect on oocyte survival rate.

Conclusion Vitrification of oocytes has a negative effect on embryo development, the pregnancy outcomes after embryo transfer is similar to fresh oocytes, the perinatal safety remains to be confirmed by further studied.

【Key words】 Oocyte; Vitrification; Embryo development; Embryo transfer

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· 实验研究 ·

MiR-146a-5p 对脂多糖诱导的小鼠胚胎吸收和胎鼠发育不良的改善作用及其机制初探

王龙斌¹ 杨龙² 叶舒婷¹ 石燕² 郭艺芬¹ 顾艳¹

¹天津医科大学第二医院计划生育科, 天津 300221; ²国家卫生健康委员会计划生育药具重点实验室 上海生殖健康药具工程技术研究中心 上海市生物医药技术研究院, 上海 200237

通信作者: 顾艳, Email: woshiguyan277@sina.com, 电话: +86-22-88329022

【摘要】 目的 观察外源性 miR-146a-5p 对脂多糖(lipopolysaccharide, LPS)诱导的小鼠胚胎吸收和胎鼠发育不良的改善作用, 并初步探讨其作用机制。方法 ①将 36 只成年雌鼠与雄鼠交配, 分别于交配前(D0/未孕)、孕第 0.5 天(day 0.5, D0.5, 即见栓当日)、孕第 4.5 天(day 4.5, D4.5)、孕第 7.5 天(day 7.5, D7.5)、孕第 9.5 天(day 9.5, D9.5)和孕第 13.5 天(day 13.5, D13.5)收集小鼠子宫组织, 通过实时荧光定量 PCR (quantitative PCR, qPCR) 和 Western blotting 检测不同妊娠期小鼠子宫组织中 miR-146a-5p 及其靶基因 TRAF6 蛋白的表达水平; ②对孕 D7.5 小鼠腹腔分别注射生理盐水(对照, 记为 COL 组)、LPS 250 $\mu\text{g}/\text{kg}$ (记为 LPS250 组)、LPS 合并尾静脉注射 10 nmol miR-146a-5p 无关序列(negative control, NC, 记为 LPS250+NC 组)、LPS 合并尾静脉注射 10 nmol miR-146a-5p 激动剂(miR-146a-5p agomir, 记为 LPS250+miR-146a-5p agomir 组), 孕第 8.5 天(day 8.5, D8.5)对小鼠宫内总胚胎数和吸收胚胎数进行计量分析, 通过 qPCR 和 Western blotting 分别检测子宫组织中肿瘤坏死因子 α (tumor necrosis factor α , TNF α) mRNA 和 TRAF6 蛋白表达水平; ③将 LPS 剂量减为 50 $\mu\text{g}/\text{kg}$ 后, 将孕 D7.5 小鼠分为 2 组, 每组 3 只: 一组腹腔注射 100 μL LPS (50 $\mu\text{g}/\text{kg}$), 同时鼠尾静脉注射 10 nmol 的

无关序列, 记为 LPS50+NC 组; 另一组行腹腔注射 100 μ L LPS (50 μ g/kg), 同时鼠尾静脉注射 10 nmol 的 miR-146a-5p agomir, 记为 LPS50+miR-146a-5p agomir 组, 孕第 16.5 天 (day 16.5, D16.5) 对小鼠宫内总胎数/胚胎数、吸收胚胎数、存活胎数及存活胎鼠重量和胎盘重量进行计量分析; ④分离培养原代小鼠骨髓源性巨噬细胞 (bone marrow-derived macrophages, BMDM), 利用 LPS 刺激诱导其 M1 极化, 再瞬时转染 miR-146a-5p 模拟物 (miR-146a-5p mimics) 或其 NC 片段后, 通过 qPCR 和 Western blotting 分别检测细胞中 *TNF α* mRNA 和 pSTAT1 蛋白表达水平。结果 miR-146a-5p 在孕 D7.5、D9.5 和 D13.5 小鼠子宫植入部位的表达水平显著高于非植入部位 ($P=0.013$ 、 $P=0.012$ 、 $P=0.003$), TRAF6 蛋白在 D13.5 植入部位的表达水平显著低于非植入部位 ($P=0.012$)。对孕 D7.5 小鼠腹腔注射 250 μ g/kg LPS 后, 孕 D8.5 时 LPS250 组的胚胎吸收率为 $43.13\% \pm 3.31\%$, 显著高于 COL 组 (0%, $P=0.002$), 而 LPS250+miR-146a-5p agomir 组的胚胎吸收率 ($13.50\% \pm 0.87\%$) 显著低于 LPS250+NC 组 ($59.33\% \pm 4.04\%$, $P=0.001$)。当对孕 D7.5 小鼠腹腔注射低剂量 LPS (50 μ g/kg) 后, D16.5 时 LPS50+miR-146a-5p agomir 组存活胎鼠重量 [(0.29 ± 0.09) g] 及胎盘重量 [(0.06 ± 0.02) g] 均显著高于 LPS50+NC 组 [(0.46 ± 0.06) g, $P<0.001$; (0.07 ± 0.02) g, $P=0.021$], 两组间吸收胚胎数及胚胎吸收率差异均无统计学意义 (均 $P>0.05$)。与转染 NC 的 BMDM 细胞相比, 转染 miR-146a-5p mimics 的 BMDM 细胞中, pSTAT1 蛋白和 *TNF α* mRNA 的表达水平都显著下调 ($P=0.012$ 、 $P=0.039$)。结论 miR-146a-5p 在小鼠胚胎植入后期及胎盘发育期母-胎界面的表达水平显著增高, 外源性 miR-146a-5p 能有效改善 LPS 诱导的小鼠胚胎吸收和胎鼠发育不良, miR-146a-5p 能抑制小鼠巨噬细胞的 M1 极化活性, 提示 miR-146a-5p 可能通过抑制小鼠母-胎界面巨噬细胞的 M1 极化而保障妊娠的正常建立和维持。

【关键词】 巨噬细胞; 脂多糖; miR-146a-5p; 胚胎吸收; 胎鼠发育不良

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Therapeutic effects of miR-146a-5p on embryo absorption and abnormal fetal development mice induced by LPS

Wang Longbin¹, Yang Long², Ye Shuting¹, Shi Yan², Guo Yifen¹, Gu Yan¹

¹ Department of Family Planning, the Second Hospital of Tianjin Medical University, Tianjin 300221, China; ² NHC Key Lab of Reproduction Regulation, Shanghai Engineering Research Center of Reproductive Health Drug and Devices, Shanghai Institute for Biomedical and Pharmaceutical Technologies, Shanghai 200237, China

Corresponding author: Gu Yan, Email: woshiguyan277@sina.com, Tel: +86-22-88329022

【Abstract】 **Objective** To observe the ameliorative effects of exogenous miR-146a-5p on lipopolysaccharide (LPS)-induced embryonic resorption and fetal mouse dysplasia, and to preliminarily investigate its mechanism of action. **Methods** 1) After 36 healthy adult female mice were mated with male mice, uterine tissues were collected from females on day (D) 0 (D0/not pregnant), D0.5 (the day of embryo observed), D4.5, D7.5, D9.5 and D13.5 of gestation, and the

expression levels of miR-146a-5p and its target gene TRAF6 protein in uterine tissues of mice at different gestation periods were detected by real-time fluorescent quantitative PCR (qPCR) and Western blotting. 2) The mice on D7.5 of pregnancy were treated with intraperitoneal injection of saline (control, COL group), intraperitoneal injection of 250 μ g/kg LPS (named LPS250 group), LPS combined with tail vein injection of 10 nmol miR-146a-5p unrelated sequence (negative control, NC, named LPS250+NC group), or LPS combined with tail vein injection of 10 nmol miR-146a-5p agonist (miR-146a-5p agomir, named LPS250+miR-146a-5p agomir group). The total number of embryos and the number of absorbed embryos in the uterus of pregnant mice were measured and statistically analyzed on D8.5, and the expression levels of *TNF α* mRNA and TRAF6 protein in uterine tissues were detected by qPCR and Western blotting. 3) Then we reduced the dosage of LPS to 50 μ g/kg and treated the same groups, named LPS50+NC group, LPS50+miR-146a-5p agomir group, respectively. The total number of fetal mice/embryos, the number of absorbed embryos, the number of surviving fetal mice, the weight of surviving fetal mice and the weight of the placenta were measured and statistically analyzed on D16.5. 4) Primary mouse bone marrow-derived macrophages (BMDM) were isolated and cultured. Mouse BMDM was induced to M1 polarization by LPS stimulation, and then was transiently transfected with miR-146a-5p mimics or their NC fragments. The expression levels of *TNF α* mRNA and pSTAT1 protein were detected by qPCR and Western blotting. **Results** The expression level of miR-146a-5p was significantly higher in the implantation sites of D7.5, D9.5 and D13.5 pregnant mice than in the non-implantation sites ($P=0.013$, $P=0.012$, $P=0.003$), and the protein expression level of TRAF6 was significantly lower in the implantation site of D13.5 pregnant mice than in the non-implantation site ($P=0.012$). After intraperitoneal injection of 250 μ g/kg of LPS into D7.5 pregnant mice, the embryo absorption rate of the LPS group on D8.5 was $43.13\%\pm3.31\%$, which was significantly higher than that of COL group (0%, $P=0.002$), while the embryo absorption rate of the LPS250+miR-146a-5p agomir group ($13.50\%\pm0.87\%$) was significantly lower than that of the LPS250+NC group ($59.33\%\pm4.04\%$, $P=0.001$). After intraperitoneal injection of 50 μ g/kg of LPS combined with tail vein injection of NC or miR-146a-5p agomir to D7.5 pregnant mice, the fetal mouse weight [(0.29 ± 0.09) g] and placental weight [(0.06 ± 0.02) g] of surviving fetal mice in the LPS50+NC group on D16.5 and the LPS50+miR-146a-5p agomir group were statistically significant [(0.46 ± 0.06) g, $P<0.001$; (0.07 ± 0.02) g, $P=0.021$], and the differences in the number of absorbed embryos and embryo uptake rate between the two groups were not statistically significant (all $P>0.05$). The expression levels of both pSTAT1 protein and *TNF α* mRNA were significantly downregulated in BMDM transfected with miR-146a-5p mimics compared with those transfected with NC ($P=0.012$, $P=0.039$). **Conclusion** miR-146a-5p expression levels were significantly increased at the maternal-fetal interface during the late stage of mouse embryo implantation and placental development. Exogenous miR-146a-5p could effectively improve LPS-induced mouse embryo resorption and fetal mouse dysplasia. miR-146a-5p could inhibit the M1 polarization activity of mouse macrophages, suggesting that miR-146a-5p may

inhibit the M1 polarization activity of mouse macrophages by suppressing M1 polarization of mouse maternal-fetal interface macrophages to safeguard the normal establishment and maintenance of pregnancy.

【Key words】 Macrophages; Lipopolysaccharide; miR-146a-5p; Embryo absorption; Abnormal fetal development

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· 临床报道 ·

IVF/ICSI 助孕宫内合并输卵管妊娠的风险因素及妊娠结局分析

王丁然 杨艳 张佳佳 宋雪凌 马彩虹 杨硕 李蓉

北京大学第三医院妇产科生殖医学中心 国家妇产疾病临床医学研究中心(北京大学第三医院) 辅助生殖教育部重点实验室(北京大学)

北京市生殖内分泌与辅助生殖技术重点实验室, 北京 100191

通信作者: 杨硕, Email: yangshuo@263.net, 电话: +86-10-82265080

【摘要】 目的 探讨体外受精/卵胞质内单精子注射(*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI)助孕发生宫内孕合并输卵管妊娠的风险因素、妊娠结局及其影响因素。方法 本研究为回顾性病例对照研究,收集了2009年1月至2021年12月期间因不孕于北京大学第三医院妇产科生殖医学中心行IVF/ICSI助孕获得妊娠且诊断为宫内孕或宫内孕合并输卵管妊娠患者的临床资料。研究组为IVF/ICSI助孕后诊断为宫内孕合并输卵管妊娠,且手术治疗的患者($n=91$)。对照组按照1:4比例匹配同一时期行IVF/ICSI助孕后诊断宫内早孕的患者($n=364$)。对两组的一般资料、助孕及妊娠相关资料进行分析,通过单因素及logistic分析IVF/ICSI助孕后发生宫内孕合并输卵管妊娠的风险因素。进一步将研究组以不同妊娠结局(即流产、活产)分为两个亚组,分析宫内合并输卵管妊娠患者手术治疗后妊娠结局的影响因素。结果 研究组和对照组的患者年龄、体质量指数、孕产次、基础激素水平、移植前内膜厚度、移植后人绒毛膜促性腺激素水平组间比较差异均无统计学意义(均 $P>0.05$),两组活产率

差异无统计学意义 ($P>0.05$)。既往异位妊娠病史 ($OR=2.605$, 95% CI : 1.352~5.016, $P=0.004$)、输卵管积水 ($OR=26.012$, 95% CI : 2.942~229.974, $P=0.003$) 是 IVF/ICSI 助孕后发生宫内合并输卵管妊娠的危险因素。活产亚组和流产亚组出现腹痛、宫腔积血的比例等差异均无统计学意义 (均 $P>0.05$)，两组间手术时间、手术时孕周及腹腔内出血量差异均无统计学意义 (均 $P>0.05$)。流产亚组中移植后阴道出血 ($OR=3.128$, 95% CI : 1.067~9.172, $P=0.038$) 可能是宫内合并输卵管妊娠发生流产的危险因素。结论 IVF/ICSI 助孕宫内孕合并输卵管妊娠患者手术治疗后与宫内正常妊娠的患者活产率相当，既往异位妊娠史及输卵管积水可能是导致 IVF/ICSI 助孕后发生宫内孕合并输卵管妊娠的风险因素，移植后有阴道出血可能为宫内合并输卵管妊娠患者手术治疗后流产的高危因素。

【关键词】 受精，体外； 胚胎移植； 妊娠，复合； 活产； 输卵管积水

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Risk factors and pregnancy outcomes of intrauterine pregnancy with tubal pregnancy after IVF/ICSI

Wang Dingran, Yang Yan, Zhang Jiajia, Song Xueling, Ma Caihong, Yang Shuo, Li Rong
Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital; National Clinical Research Center for Obstetrics and Gynecology (Peking University Third Hospital); Key Laboratory of Assisted Reproduction (Peking University), Ministry of Education; Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproductive Technology, Beijing 100191, China

Corresponding author: Yang Shuo, Email: yangshuo@263.net, Tel: +86-10-82265080

【 Abstract 】 Objective To investigate the risk factors, pregnancy outcomes of intrauterine pregnancy with tubal pregnancy after *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI). **Methods** The study was a retrospective case-control study that collected clinical data of patients diagnosed with intrauterine combined with tubal pregnancy after IVF/ICSI for infertility at Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital from January 2009 to December 2021. The study group consisted of patients diagnosed with intrauterine combined with tubal pregnancy after IVF/ICSI and treated with surgery ($n=91$). The control group consisted of patients diagnosed with early intrauterine pregnancy after IVF/ICSI in a 1 : 4 ratio during the same period ($n=364$). General information, assisted reproduction and pregnancy-related data of the two groups were analyzed, and risk factors for intrauterine combined with tubal pregnancy after IVF/ICSI were determined through univariate and logistic analyses. Furthermore, the study group was divided into two subgroups according to different pregnancy outcomes, miscarriage and live birth, and risk factors that may affect pregnancy outcomes of patients with intrauterine combined with tubal pregnancy were analyzed between the two subgroups. **Results** There were no significant differences in age, body mass index, gestational times, basal hormone levels, endometrial thickness before

transplantation and human chorionic gonadotropin level after transplantation between the study group and control group (all $P>0.05$). The live birth rate of the two groups was similar ($P>0.05$). A history of ectopic pregnancy ($OR=2.605$, 95% CI : 1.352–5.016, $P=0.004$) and hydrosalpinx ($OR=26.012$, 95% CI : 2.942–229.974, $P=0.003$) were risk factors for intrauterine combined with tubal pregnancy after IVF/ICSI. Patients with intrauterine combined with tubal pregnancy were divided into live birth subgroup and abortion subgroup. There were no significant differences in the proportion of abdominal pain, uterine hemoperitoneum and other symptoms between the two subgroups (all $P>0.05$), and there were no statistical differences in operation time, gestational age and intraperitoneal hemorrhage between the two subgroups (all $P>0.05$). Vaginal bleeding after transplantation ($OR=3.128$, 95% CI : 1.067–9.172, $P=0.038$) in the abortion subgroup may be a risk factor for miscarriage in intrauterine combined with tubal pregnancy. **Conclusion** Live birth rate in intrauterine pregnancy combined with tubal pregnancy patients after surgery was similar with patients with normal intrauterine pregnancy. Ectopic pregnancy history and hydrosalpinx may be risk factors for patients with intrauterine pregnancy combined with tubal pregnancy after IVF/ICSI, and vaginal bleeding after transplantation may be a high risk factor for abortion in those patients.

【Key words】 Fertilization *in vitro*; Embryo transfer; Pregnancy, heterotopic; Live birth; Hydrosalpinx

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· 个案报道 ·

子宫恶性混合生殖细胞肿瘤患者的保留生育功能治疗病例报道

郭路¹ 李斌² 刘晓霞²

¹ 复旦大学附属中山医院 上海市老年医学中心妇科, 上海 201104;

² 复旦大学附属妇产科医院妇科, 上海 200011

通信作者：刘晓霞，Email: lxxzh7@aliyun.com，电话：+86-21-

33189900

【摘要】 目的 总结子宫恶性混合生殖细胞肿瘤患者保留生育功能治疗的经验。方法 报道 1 例子宫恶性混合生殖细胞肿瘤患者的保留生育功能治疗，并分析其临床特点，同时进行相关文献回顾。结果 该患者化疗结束后卵巢功能逐渐恢复，月经周期恢复正常。术后 5 年随访至今无肿瘤复发征象。结论 子宫恶性混合生殖细胞肿瘤临床罕见，其治疗目前尚无定论，保留生育功能治疗需综合评估并密切随访。

【关键词】 生殖细胞肿瘤； 促性腺激素释放激素激动剂； 保留生育功能治疗

A case report of fertility-sparing of patient with uterine malignant mixed germ cell tumor

Guo Lu¹, Li Bin², Liu Xiaoxia²

¹ Department of Gynecology, Zhongshan Hospital of Fudan University, Shanghai Geriatric Medicine Center, Shanghai 201104, China; ² Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai 200011, China

Corresponding author: Liu Xiaoxia, Email: lxxzh7@aliyun.com, Tel: +86-21-33189900

【Abstract】 Objective To summarize the experience in fertility-sparing of a patient with uterine malignant mixed germ cell tumor. **Methods** This article mainly reported a case of fertility preservation in uterine malignant mixed germ cell tumor, it's clinical characteristics and literature review was analyzed. **Results** After the end of chemotherapy, the patient's ovarian function recovered and her menstrual cycle returned to normal. No sign of tumor recurrence after 5 years follow-up was found. **Conclusion** Uterine malignant mixed germ cell tumors were rare, its treatment was still inconclusive and fertility-sparing required comprehensive evaluation and close monitoring.

【Key words】 Germ cell tumor; Gonadotropin-releasing hormone agonist; Fertility preservation therapy

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• 新技术 •

长读长测序技术在胚胎植入前遗传学检测中的应用

万成 丁韬力 马杰良 王兴兴 杨季 陆思嘉

序康医疗科技（苏州）有限公司，苏州 215000

通信作者：陆思嘉，Email: lusijia@yikongenomics.com，电话：+86-

512-68837388

【摘要】 近年来，长读长测序技术发展迅速，在基因组、转录组、表观遗传学等研究方向发挥了重要作用，并显示出在临床检测领域的广阔应用前景。本文介绍了主要的长读长测序平台的基本原理和性能，综述了该技术在胚胎植入前遗传学检测中的研究进展，以及当前面临的主要挑战和未来可能的发展方向。

【关键词】 生殖健康； 胚胎植入前遗传学检测； 长读长测序； 临床应用

Application of long-read sequencing in preimplantation genetic testing

Wan Cheng, Ding Taoli, Ma Jieliang, Wang Xingxing, Yang Ji, Lu Sijia

Xukang Medical (Suzhou) Ltd., Suzhou 215000, China

Corresponding author: Lu Sijia, Email: lusijia@yikongenomics.com, Tel: +86-512-68837388

【Abstract】 In recent years, the long-read sequencing technology has been developing rapidly, playing a crucial role in research fields of genomics, transcriptomics, and epigenetics, and showing broad application prospects in the field of clinical testing. This paper introduces the basic principles and performance of the main long-read sequencing platforms, reviews the research progress of this technology in preimplantation genetic testing, and discusses the major challenges currently faced and possible future directions.

【Key words】 Reproductive health; Preimplantation genetic testing; Long-read sequencing; Clinical application

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· 综述 ·

醋酸烯诺孕酮/炔雌醇避孕阴道环：一种新型 缓释避孕方法

代雨辛 姚晓英

复旦大学附属妇产科医院计划生育科, 上海 200082

通信作者: 姚晓英, Email: 13916738653@139.com, 电话: +86-

13916738653

【摘要】 醋酸烯诺孕酮/炔雌醇避孕阴道环是一种新的长效可逆复方激素避孕方法, 已在国外上市使用数年, 可以由使用者自行控制使用, 具有一定的避孕优势。本文主要对其结构及作用原理、临床应用、安全性和可接受性进行了综述。

【关键词】 阴道避孕环; 女性激素避孕; 临床优势; 安全性

Segesterone acetate/ethinyl estradiol contraceptive vaginal ring: a novel slow-release contraceptive method

Dai Yuxin, Yao Xiaoying

Family Planning Department, Obstetrics and Gynecology Hospital of Fudan University, Shanghai 200082, China

Corresponding author: Yao Xiaoying, Email: 13916738653@139.com, Tel: +86-13916738653

【Abstract】 The segesterone acetate/ethinyl estradiol contraceptive vaginal ring is a new long-acting reversible combination hormonal contraceptive method, which has been in use abroad for several years. It can be used under the control of the user with some contraceptive advantages. We review its structure and principles of action, clinical application, safety and acceptability.

【Key words】 Vaginal rings; Female hormonal contraception; Clinical advantages; Security

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· 综述 ·

体外获得成熟配子的研究进展和难点

马昕芮 冯蕾 孙莹璞 王海松

郑州大学第一附属医院生殖医学中心 河南省生殖与遗传重点实验室,

郑州 450052

通信作者: 王海松, Email: hswang813@zzu.edu.cn, 电话: +86-371-66913635

【摘要】 成熟配子包括来自于父本的精子和来自母本的卵子, 两者发生精卵结合形成受精卵从而发育为成熟个体。体外获得成熟配子的研究目前主要集中在通过体外诱导分化胚胎干细胞 (embryonic stem cells, ESCs) 或诱导性多能干细胞 (induced pluripotent stem cells, iPSCs) 获得成熟配子。因为多能性干细胞 (pluripotent stem cells, PSCs) 在体外特定条件下可以分化形成包括原始生殖细胞在内的三胚层组织, 所以 PSCs 在体外通过诱导分化和减数分裂等过程可以获得成熟配子, 进而获得后代。本文围绕成熟配子的产生过程, 综述体外产生成熟配子的研究进展和需要攻克的难点。

【关键词】 卵母细胞; 精原细胞; 减数分裂; 多能性干细胞; 原始生殖细胞

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Research progress and difficulties on obtaining mature gametes *in vitro*

Ma Xinrui, Feng Lei, Sun Yingpu, Wang Haisong

Reproductive Medicine Center of the First Affiliated Hospital of Zhengzhou University;
Henan Key Laboratory of Reproduction and Genetics, Zhengzhou 450052, China

Corresponding author: Wang Haisong, Email: hswang813@zzu.edu.cn, Tel: +86-371-66913635

【Abstract】 Mature gametes include sperms originating from the male and oocytes originating from the female. The sperm and oocyte combine to form a fertilized oocyte and develop into a mature individual. At present, the research on obtaining gametes *in vitro* mainly focuses on obtaining mature gametes by inducing differentiation of embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) *in vitro*. *In vitro*, under specific conditions, pluripotent stem cells (PSCs) can differentiate into three germ layers tissues which include primordial germ cells. Therefore, by inducing differentiation and meiosis *in vitro* of PSCs, researchers can obtain mature gametes and offspring. Focusing on the production process of mature gametes, this paper summarized the research progress and difficulties to be overcome in the production of mature gametes *in vitro*.

【Key words】 Oocyte; Spermatogonia; Meiosis; Pluripotent stem cells; Primordial germ cells

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· 综述 ·

染色质重塑因子对哺乳动物配子发生及早期胚胎发育进程影响的研究进展

洪仁芸 梁元姣

东南大学附属中大医院生殖医学科, 南京 210009

通信作者: 梁元姣, Email: yuanjiao1965@126.com, 电话: +86-25-83272201

【摘要】 真核生物中染色质重塑因子种类繁多, 根据 ATP 酶和其他组成蛋白亚单位的不同大致可以分为四类: SWI/SNF、ISWI、CHD 和 INO80。不同的染色质重塑因子在不同的层面通过对染色质结构的改变来影响基因转录调控等, 以确保细胞内各种生物学进程的准确运行。目前, 关于染色质重塑因子在哺乳动物配子发生及早期胚胎发育过程中发挥作用的研究尚不普遍。本文将以四类染色质重塑因子为切入点对此进行简单综述, 为深入了解染色质重塑因子在生殖发育等方面的功能提供理论依据。

【关键词】 染色质重塑因子; 配子发生; 早期胚胎发育; 哺乳动物
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Research progress on the effects of chromatin remodeling factors on mammalian gametogenesis and early embryonic development

Hong Renyun, Liang Yuanjiao

Department of Reproductive Medicine, Zhongda Hospital, Southeast University, Nanjing 210009, China

Corresponding author: Liang Yuanjiao, Email: yuanjiao1965@126.com, Tel: +86-25-83272201

【Abstract】 There are various types of chromatin remodeling factors in eukaryotes, which can be divided into four categories: SWI/SNF, ISWI, CHD and INO80, according to the differences of ATPase and other constituent protein subunits. These remodeling factors affect gene transcription regulation through changes in chromatin structure to ensure the accurate operation of various biological processes in cells. At present, the role of chromatin remodeling factors in mammalian gametogenesis and early embryonic development is not widely studied. In this paper, we will make a brief review to provide theoretical basis for further understanding of the functions about the chromatin remodeling factors in reproductive development.

【Key words】 Chromatin remodeling factors; Gametogenesis; Early embryonic development; Mammal

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· 综述 ·

常见组蛋白修饰调控滋养层细胞谱系分化的研究进展

郑丽彬¹ 李珣² 毛晗馨³ 曹彬⁴

¹厦门大学公共卫生学院, 厦门 361002; ²厦门大学附属第一医院检验

科, 厦门 361003; ³厦门大学医学院, 厦门 361002; ⁴厦门大学医学

院妇产科系 厦门大学附属妇女儿童医院 生殖调控与生殖健康研究

福建省高校重点实验室, 厦门 361002

通信作者: 曹彬, Email: caobin19@xmu.edu.cn, 电话: +86-592-

2880503

【摘要】 胎盘是决定妊娠建立及维持胎儿正常生长发育的重要器官, 其介导了母胎间的复杂对话。滋养层细胞是执行胎盘功能的一类重要细胞类型, 在胎盘发育过程中, 滋养层干细胞可分化为多种滋养层细胞亚型, 从而维持胎盘的结构和功能。组蛋白修饰可通过调控染色质的结构及基因转录参与滋养层细胞谱系的建立和维持。本文系统性总结了重要组蛋白甲基化及乙酰化修饰调控滋养层干细胞分化及胎盘发育的复杂作用及机制。

【关键词】 胎盘; 组蛋白修饰; 滋养层干细胞

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Research progress of common histone modification regulating trophoblast cell lineage differentiation

Zheng Libin¹, Li Xun², Mao Hanxin³, Cao Bin⁴

¹ School of Public Health, Xiamen University, Xiamen 361002, China; ² Department of Laboratory, the First Affiliated Hospital of Xiamen University, Xiamen 361003, China; ³ School of Medicine, Xiamen University, Xiamen 361002, China; ⁴ Fujian Provincial Key Laboratory of Reproductive Health Research, Department of Obstetrics and Gynecology,

Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen 361002, China

Corresponding author: Cao Bin, Email: caobin19@xmu.edu.cn, Tel: +86-592-2880503

【Abstract】 Placenta serves as an important organ, which determines the establishment of pregnancy and intrauterine fetal growth, as well as the complex maternal-fetal crosstalk. Different subtypes of trophoblast cells mediate the diverse functions of the placenta. During placental development, the trophoblast-derived trophoblast stem cells differentiate into all subtypes of trophoblasts and thus maintaining the structure and function of the placenta. Histone modifications can regulate chromatin structure and gene transcription, which is involved in the establishment, maintenance and differentiation of trophoblast lineage. In this review, we systemically overview the indispensable roles of histone methylation and acetylation in trophoblast differentiation.

【Key words】 Placenta; Histone modifications; Trophoblast stem cell

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· 综述 ·

多囊卵巢综合征患者生活质量及精神心理状况研究进展

夏雨琪 田甜 杨蕊

北京大学第三医院妇产科生殖医学中心 国家妇产疾病临床医学研究中心 辅助生殖教育部重点实验室 北京市生殖内分泌与辅助生殖技术重点实验室, 北京 100191

通信作者: 杨蕊, Email: yrjeff@126.com, 电话: +86-10-82266625

【摘要】 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 是一种育龄期女性常见的生殖内分泌疾病, 除了生育、排卵、代谢相关异常, 患者往往存在一系列生活质量降低及精神心理问题的高风险。这种精神心理问题风险主要体现在焦虑与抑郁等心境障碍、性功能障碍、进食障碍与睡眠障碍。这些问题会为 PCOS 患者健康状况带来不利影响, 而改善相关状况有利于患者生殖功能的恢复。因此,

PCOS 患者应积极进行精神心理状况的评估与干预。本文对 PCOS 患者生活质量及精神心理情况做出综述，为相关机制探究与临床干预提供依据。

【关键词】 多囊卵巢综合征； 生活质量； 精神心理状况； 焦虑抑郁； 性功能障碍； 进食障碍； 睡眠障碍

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Current research on quality of life and mental-psychological status in patients with polycystic ovary syndrome

Xia Yuqi, Tian Tian, Yang Rui

Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital; National Clinical Research Center for Obstetrics and Gynecology; Key Laboratory of Assisted Reproduction, Ministry of Education; Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproductive Technology, Beijing 100191, China

Corresponding author: Yang Rui, Email: yrjeff@126.com, Tel: +86-10-82266625

【Abstract】 Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder in reproductive age women. In addition to fertility, ovulation and metabolism-related abnormalities, women with PCOS are at increased risk for lower life quality and a range of mental psychological problems. The health risks are primarily manifested in reduced quality of life, mood disorders including depression and anxiety, sexual dysfunction, eating disorders, and sleep disorders, all of which negatively influence the health status of PCOS patients. Also, ameliorating these comorbidities may also help patients restore their reproductive functions. Therefore, patients with PCOS should also be actively involved in the prevention and treatment of the problems. This article aims to provide a review of the quality of life and mental-psychological status of patients with PCOS, while also providing a basis for the exploration of underlying mechanisms and the development of clinical interventions.

【Key words】 Polycystic ovary syndrome; Quality of life; Mental-psychological status; Anxiety and depression; Sexual dysfunction; Eating disorders; Sleeping disorder

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