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# 新冠病毒感染后生殖临床实践快速指南

中国医师协会生殖医学专业委员会

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**【摘要】** 新冠病毒大规模感染后, 生殖健康和母婴安全问题成为临床医护人员和社会大众共同关注的焦点问题。基于当前的最佳证据, 本快速指南针对生殖临床诊疗过程中临床医师和患者关注的热点问题, 按照循证临床实践指南制订的方法和步骤, 使用推荐意见分级的评估、制定及评价 (grading of recommendations assessment, development and evaluation, GRADE) 方法, 结合临床经验并考虑我国患者的偏好与价值观, 形成了 6 大主题、36 条的具体推荐意见。本快速指南的使用人群是生殖医学科医师、妇产科医师及相关专业人员; 目标人群是计划或正在接受辅助生殖治疗的夫妇, 以及计划或已经妊娠的夫妇。

**【关键词】** 新型冠状病毒; 生殖技术, 辅助; 快速指南; 循证

基金项目: 国家重点研发计划项目 (2022YFC2702500)

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## Rapid guideline on reproductive clinical practice after COVID-19 infection

Chinese Association of Reproductive Medicine

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**【Abstract】** After the COVID-19 pandemic, reproductive health and maternal and children's safety is of concerns for both clinical professionals and the public. Based on the current best available evidence, the rapid guideline focused on hot issues from both clinicians and patients during reproductive clinical diagnosis and treatment. We adopted the methods and procedures in developing evidence-based clinical practice guidelines, used the grading of recommendations assessment,

development and evaluation (GRADE) methods, balanced the clinician's experience with the patients' preferences and values, and finally formed 36 pieces of recommendations in 6 themes. The rapid guideline is intended for use by reproductive physicians, obstetricians, gynecologists, and other related professionals. The target population is couples planning or undergoing assisted reproductive treatment, and couples planning or already pregnant.

**【Key words】** COVID-19; Reproductive technology, assisted; Rapid guideline; Evidence-based

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# 多囊卵巢综合征诊治路径专家共识

多囊卵巢综合征诊治路径专家共识编写组

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**【摘要】** 本文以多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 国际指南 2018 版和中国 PCOS 诊治指南 2018 版为基础, 结合中国 PCOS 人群疾病特征, 从临床诊疗全过程进行重点阐述, 如病史询问、体格检查、辅助检查、临床诊断、从需求方面进行个体化治疗等。经专家组共同审定, 形成具有充分循证支持的标准化 PCOS 诊疗流程, 便于临床一线工作者实施, 同时促进 PCOS 患者全生命周期管理。

**【关键词】** 多囊卵巢综合征; 临床路径; 诊治

## Expert consensus on the pathway of diagnosis and management of polycystic ovary syndrome

*Expert Consensus Compilation Group for the Pathway of Diagnosis and Management of Polycystic Ovary Syndrome*

*Corresponding author: Li Rong, Email: roseli001@sina.com, Tel: +86-10-82265080*

**【Abstract】** Under the guidance of international evidence-based guideline for polycystic ovary syndrome (PCOS) and Chinese guideline for PCOS diagnosis and management in 2018, this paper focused on the whole process of clinical diagnosis and treatment by combining the disease characteristics of PCOS in China, such as medical history collection, physical examination, laboratory examination, diagnosis

and treatment at different stages of life. Through the agreement of the expert group, a standardized PCOS diagnosis and treatment protocol with sufficient evidence support has been formed, which is convenient for clinical workers to implement and promotes the life cycle management of PCOS patients.

**【Key words】** Polycystic ovary syndrome; Clinical pathway; Diagnosis and management

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## 子宫内膜癌保留生育功能多学科诊疗中国专家共识

子宫内膜癌保留生育功能多学科诊疗中国专家共识编写组

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**【摘要】** 子宫内膜癌发病率不断上升, 尤其在中国呈明显年轻化趋势。许多年轻子宫内膜癌患者有迫切生育要求, 这使子宫内膜癌保留生育功能治疗成为肿瘤生殖学领域的研究热点。子宫内膜癌保留生育功能治疗涉及妇科肿瘤、生殖内分泌、影像、病理、产科、内分泌等多个学科, 目前尚缺乏成熟的子宫内膜癌保留生育功能多学科诊疗规范。本专家共识旨在通过建立规范的子宫内膜癌保留生育功能诊治多学科体系, 达到提升子宫内膜癌保留生育功能治疗的有效性和安全性的目的。

**【关键词】** 子宫内膜肿瘤; 保留生育能力; 多学科诊疗

基金项目: 国家重点研发计划(2019YFC1005200); 申康临床科技创新项目(SHDC22021219)

**Chinese expert consensus on multiple disciplinary treatment in endometrial cancer desiring fertility preserving treatment**

*Chinese Expert Consensus Compilation Group for Multiple Disciplinary Treatment in Endometrial Cancer Desiring Fertility Preserving Treatment*

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**【Abstract】** The incidence of endometrial cancer is increasing, with the trend of affecting more young women in China. The fact that a large part of young women has not finished childbearing when diagnosed as endometrial cancer makes fertility preserving treatment of endometrial cancer a new challenge in the field of gynecologic oncology and reproductive medicine. Fertility preserving treatment of endometrial cancer involves multiple disciplines including gynecologic oncology, reproductive medicine, radiology, pathology, metabolism and obstetrics, etc. There is no guidance at present for multiple disciplinary treatment (MDT) in fertility preserving treatment of endometrial cancer. The consensus aimed to establish the MDT system and help improve the efficacy and safety in fertility preserving treatment of endometrial cancer.

**【Key words】** Endometrial neoplasms; Fertility preservation; Multiple disciplinary treatment

**Fund program:** National Key Research and Development Program of China(2019YFC1005200); Shen Kang Clinical Technology Innovative Program (SHDC22021219)

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·临床研究·

## 不同剂量克罗米芬在微刺激方案助孕治疗中对卵巢功能减退患者子宫内膜及妊娠结局等因素的影响分析

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**【摘要】** 目的 探讨不同剂量的克罗米芬 (clomiphene citrate, CC) 对卵巢功能减退 (diminished ovarian reserve, DOR) 患者微刺激方案助孕治疗中子宫内膜因素、获卵数、助孕结局以及其他因素的影响。方法 回顾性队列研究分析 2018 年 1 月至 2020 年 1 月期间于南京医科大学第一附属医院生殖医学中心行微刺激方案体外受精/卵胞质内单精子注射-胚胎移植 (*in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer, IVF/ICSI-ET) 助孕周期的临床资料, 根据不



同 CC 剂量方案分为 4 组: A 组从月经第 3 天起 CC 50 mg/d 至扳机日, 共 1 457 个周期; B 组从月经第 3 天起 CC 50 mg/d 仅使用 3 d, 共 1 533 个周期; C 组从月经第 3 天起 CC 25 mg/d 至扳机日, 共 345 个周期; D 组从月经第 3 天起 CC 25 mg/d 仅使用 3 d, 共 319 个周期, 两两比较并分析 4 组患者的临床数据。结果 A 组患者所用的促性腺激素 (gonadotropin, Gn) 使用总量、Gn 使用时间、优势卵泡数、扳机日激素水平、获卵数、获卵率、受精数、可移植胚胎数以及全胚冷冻率均显著高于 B 组 (均  $P < 0.05$ )。B 组的扳机日内膜厚度 [7.10 (5.40, 8.65) mm] 及 A/A-B 型百分比 [70.70% (888/1256)] 显著优于 A 组 [6.00 (4.70, 8.00) mm,  $P < 0.001$ ; 63.62% (649/1020),  $P < 0.001$ ], 其鲜胚移植率 [20.00% (259/1295)] 显著高于 A 组 [42.94% (584/1360),  $P < 0.001$ ], 两组的移植优质胚胎数和无可移植胚胎率差异均无统计学意义 (均  $P > 0.05$ )。与 D 组比较, C 组患者所用的 Gn 使用总量、Gn 使用时间、优势卵泡数、扳机日雌二醇、获卵数、每周期受精数/可移植胚胎数均显著增加 (均  $P < 0.05$ )。D 组患者的扳机日内膜厚度 [7.00 (5.40, 8.60) mm] 显著高于 C 组 [6.10 (5.00, 7.93) mm,  $P < 0.001$ ], 但是两组间内膜 A/A-B 型百分比差异无统计学意义 ( $P = 0.739$ )。此外, C 组的扳机日黄体生成素及孕酮值显著高于 D 组 ( $P = 0.014$ ,  $P = 0.005$ ), 但是两组卵子早排率、全胚冷冻率差异均无统计学意义 (均  $P > 0.05$ ), C 组鲜胚移植率 [26.04% (75/288)] 显著低于 D 组 [38.80% (97/250),  $P < 0.001$ ]。A 组和 B 组、C 组和 D 组间的累积临床妊娠率和鲜胚/冻胚移植结局差异均无统计学意义 (均  $P > 0.05$ )。结论 小剂量、短时间 CC 用于微刺激助孕方案并不改变最终妊娠结局, 同时节约患者的经济和时间成本, 可作为 DOR 患者优选的微刺激助孕方案。

【关键词】 克罗米芬; 生殖技术, 辅助; 卵巢功能减退; 微刺激; 妊娠结局

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# Effect of clomiphene citrate with different dosages on the endometrium and pregnancy outcome in patients with diminished ovarian reserve during minimal stimulation IVF/ICSI-ET

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【Abstract】 **Objective** To explore the effect of clomiphene citrate (CC) with different dosages on the endometrial factor, number of oocytes retrieved, pregnancy outcomes and other factors in diminished ovarian reserve (DOR) patients with minimal stimulation/natural protocol. **Methods** This was a retrospective cohort study. The patients who underwent minimal stimulation protocol of *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) were divided into 4 groups. Group A: the patients had CC 50 mg/d from the third day of menstruation to the trigger day (1 457 cycles); group B: the patients had 50 mg/d from the third day of menstruation for 3 d (1 533 cycles); group C: the patients had CC 25 mg/d from the third day of menstruation to the trigger day (345 cycles); group

D: the patients had CC 25 mg/d for 3 d (319 cycles). The general data, clinical results, pregnancy and delivery outcomes were compared between group A and group B, as well as group C and group D. **Results** In the treatment of IVF/ICSI, the dosage of gonadotropin (Gn) used, number of dominant follicles, estradiol level, luteinizing hormone level, progesterone level, number of oocytes retrieved, rate of oocytes retrieved, number of fertilizations, number of transplantable embryos and whole embryo freezing rate in patients of group A were significantly higher than those in group B (all  $P<0.05$ ). The endometrial thickness [7.10 (5.40,8.65) mm] and the ratio of endometrial type (A/A-B) on trigger day [70.70% (888/1 256)] of group B were significantly better than those of group A [6.00 (4.70,8.00) mm,  $P<0.001$ ; 63.62% (649/1 020),  $P<0.001$ ], and the fresh embryo transfer rate of group B was significantly higher than that of group A [20.00% (259/1 295) vs. 42.94% (584/1 360),  $P<0.001$ ]. There were no statistical differences in the number of high-quality embryos and the rate of no embryo transfer between the two groups (both  $P>0.05$ ). In group C and group D, the Gn used dosage, the number of dominant follicles, the estradiol level on trigger day, number of oocytes retrieved, embryos/cycles were significantly increased (all  $P<0.05$ ), the endometrial thickness on trigger day of group D [7.00 (5.40, 8.60) mm] was significantly higher than that of group C [6.10 (5.00,7.93) mm,  $P<0.001$ ], but there was no statistical difference of the ratio of endometrial type (A/A-B) between the two groups ( $P=0.739$ ). In addition, the luteinizing hormone and progesterone values on the trigger day in group C were significantly higher than those in group D ( $P=0.014$ ,  $P=0.005$ ), but there were no significant differences in pre-ovulation rate and all embryos frozen rate between the two groups (all  $P<0.05$ ), and the rate of fresh embryo transfer in group C [26.04% (75/288)] was significantly lower than that in group D [38.80% (97/250),  $P<0.001$ ]. Finally, there were no significant differences in cumulative clinical pregnancy rate and fresh/frozen embryo transfer outcome between group A and group B as well as group C and group D (all  $P>0.05$ ). **Conclusion** The use of low-dose and short-time CC in minimal stimulation protocol does not change the final pregnancy outcome, while saving patients' economic and time costs, so it could be an appropriate project for DOR patients.

**【Key words】** Clomiphene citrate; Reproductive technology, assisted; Diminished ovarian reserve; Minimal stimulation; Pregnancy outcome

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·临床研究·

# 单卵裂期胚胎移植临床妊娠率影响因素分析

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**【摘要】** 目的 探讨单卵裂期胚胎移植周期中影响临床妊娠的相关因素。方法 采用回顾性队列研究收集河南省人民医院生殖医学中心 2017 年 1 月至 2021 年 10 月期间行单卵裂期胚胎移植的 2 764 例患者的临床资料与周期结局, 采用单因素与多因素 logistic 回归探讨单卵裂期胚胎移植临床妊娠的独立影响因素。结果 多因素 logistic 回归分析显示年龄、促排卵方案、窦卵泡数、胚胎细胞数、碎片率、内膜厚度、选择性移植是临床妊娠率的独立影响因素 (均  $P < 0.05$ ), 其中卵裂期胚胎细胞数对临床妊娠率的影响 ( $OR = 2.92$ , 95%  $CI$ : 1.58~5.39) 大于碎片率 ( $OR = 0.73$ , 95%  $CI$ : 0.55~0.98)。进一步分层分析结果显示,  $< 35$  岁患者不论移植胚胎碎片率是否  $> 10\%$ , 8-细胞胚胎的临床妊娠率均显著增加 ( $OR = 4.78$ , 95%  $CI$ : 3.06~7.47;  $OR = 3.53$ , 95%  $CI$ : 1.85~6.76); 而  $\geq 35$  岁患者, 当移植胚胎碎片率  $\leq 10\%$ , 8-细胞胚胎较 4~6-细胞的临床妊娠率显著增加 ( $OR = 3.58$ , 95%  $CI$ : 1.64~7.84)。结论 胚胎细胞数、碎片率是影响年轻患者单卵裂期胚胎移植临床妊娠率的主要因素, 其中前者与临床妊娠率的关联强度更大。移植胚胎的细胞数减少与临床妊娠率降低相关, 移植时应首选 8-细胞、碎片率  $\leq 10\%$  的卵裂期胚胎。

**【关键词】** 受精, 体外; 单胚胎移植; 临床妊娠率; 卵裂期胚胎

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## Analysis of influencing factors on clinical pregnancy rate of single cleavage embryo transfer

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**【Abstract】** **Objective** To explore the influencing factors of clinical pregnancy rate after single cleavage embryo transfer. **Methods** A total of 2 764 patients who underwent single cleavage embryo transfer in the Reproductive Medicine Center of Henan Provincial People's Hospital from January 2017 to October 2021 were included in a retrospective cohort study. The clinical data and cycle outcomes were analyzed by using univariate and multivariate logistic regression to explore the independent influencing factors of clinical pregnancy. **Results** Multivariate logistic regression analysis showed that age, ovulation stimulation protocol, antral follicle number, blastomere number, fragment ratio, endometrial

thickness, elective single embryo transfer were independent influencing factors of clinical pregnancy rate (all  $P<0.05$ ). The effect of blastomere number on clinical pregnancy rate ( $OR=2.92$ , 95%  $CI$ : 1.58–5.39) was stronger than that of fragment ratio ( $OR=0.73$ , 95%  $CI$ : 0.55–0.98). The results of further stratified analysis showed that when the number of embryo cells was 8, the clinical pregnancy rate of patients less than 35 years old was significantly increased regardless of whether the embryo fragment ratio was more than 10% or not ( $OR=4.78$ , 95%  $CI$ : 3.06–7.47;  $OR=3.53$ , 95%  $CI$ : 1.85–6.76), while in patients  $\geq 35$  years old, when the fragment ratio of transferred embryos was less than 10%, the clinical pregnancy rate of 8-cell embryos was significantly higher than that of 4–6-cell embryos ( $OR=3.58$ , 95%  $CI$ : 1.64–7.84). **Conclusion** The blastomere number and fragment ratio are the main influencing factors of the clinical pregnancy rate of single cleavage embryo transfer in young patients and the former has a stronger correlation with the clinical pregnancy rate. The decrease of blastomere number of transferred embryos is related to the decrease of clinical pregnancy rate. Cleavage embryos with 8 cells and fragment ratio less than 10% should be preferred for transfer.

**【 Key words 】** Fertilization *in vitro*; Single embryo transfer; Clinical pregnancy rate; Cleavage embryo

**Fund program:** National Natural Science Foundation of China (U2004130)

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·实验研究·

## HIF1 $\alpha$ 通过启动 ALKBH5 调控整合素蛋白 $\alpha_v$ 表达的机制研究

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**【摘要】** 目的 探索缺氧诱导因子 1 $\alpha$  (hypoxia inducible factor 1 $\alpha$ , HIF1 $\alpha$ ) 启动 N6-甲基腺苷 (N6-methyladenosine, m6A) 去甲基化酶 ALKBH5 改善子宫内膜容受性分子标志物整合素蛋白  $\alpha$ v (integrin  $\alpha$ v, ITGAV) 表达的内在机制。方法 利用人子宫内膜癌 Ishikawa 细胞, 低氧以及干扰 HIF1 $\alpha$  条件下实时荧光定量 PCR (real time quantity PCR, RT-PCR) 或 Western blotting 检测 ALKBH5 的表达; 过表达或干扰 ALKBH5 表达后, RT-PCR 或 Western blotting 检测对 ITGAV 基因和蛋白表达的影响; 荧光素酶报告基因系统分析 miR-136-5p 靶向 ITGAV mRNA 表达; RNA pull-down 分析及 m6A 甲基化检测 ALKBH5 与 miR-136-5p 竞争性结合 ITGAV mRNA 上甲基化位点序列。结果 低氧条件下 HIF1 $\alpha$  时间依赖性促进 ALKBH5 蛋白在 Ishikawa 细胞中的表达。过表达 ALKBH5 后, ITGAV 的表达水平升高 ( $P<0.001$ ), Ishikawa 细胞增殖能力增强 ( $P<0.001$ ); ALKBH5 敲除后, ITGAV 的表达水平降低 ( $P<0.001$ ), Ishikawa 细胞的增殖能力下降 ( $P=0.019$ )。miR-136-5p 靶向调节 ITGAV mRNA 后, ITGAV mRNA ( $P=0.007$ ) 和蛋白表达水平 ( $P=0.015$ ) 下调。miR-136-5p 靶向调节 ITGAV 的序列与 ALKBH5 所识别的甲基化位点所在序列重叠, 两者在调控 ITGAV mRNA 上存在竞争性。结论 HIF1 $\alpha$  通过调控 ALKBH5, 竞争性地结合 miR-136-5p 所靶向的 ITGAV mRNA 上特定序列, 精细化调节 ITGAV 的表达, 改善子宫内膜容受性。

**【关键词】** 子宫内膜容受性; 缺氧诱导因子 1 $\alpha$ ; ALKBH5; N6-甲基腺苷甲基化; 整合素蛋白  $\alpha$ v

基金项目: 首都医科大学科研培育基金 (PYZ19057); 北京市医院管理局培育计划 (PX2018053)

## Mechanism of HIF1 $\alpha$ regulating integrin protein $\alpha$ v expression by activating ALKBH5

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**【Abstract】 Objective** To explore the intrinsic mechanism of hypoxia inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) initiating N6-methyladenosine (m6A) demethylase ALKBH5 expression to improve the expression of integrin  $\alpha$ v (ITGAV), a molecular marker of endometrial receptivity. **Methods** Human endometrial cells Ishikawa were used in this study. The expression of ALKBH5 was detected by real time quantity PCR (RT-PCR) and Western blotting under hypoxia and HIF1 $\alpha$  interference conditions. After overexpression or interference ALKBH5, RT-PCR and Western blotting were used to detect ITGAV expression; Luciferase reporter gene system was used to detect miR-136-5p targeting ITGAV mRNA expression; RNA pull-down analysis and m6A methylation were used to detect the competitive binding of ALKBH5 and miR-136-5p to the methylation site sequence on ITGAV mRNA. **Results** HIF1 $\alpha$  promoted ALKBH5 protein expression in a time-dependent manner under hypoxic conditions in Ishikawa cells. Overexpression of ALKBH5 enhanced the expression of ITGAV and cell proliferation ( $P<0.001$ ,  $P<0.001$ ), while knockout of

ALKBH5 inhibited the expression of ITGAV and cell proliferation ( $P=0.001, P=0.019$ ). ITGAV mRNA ( $P=0.007$ ) and protein expression level ( $P=0.015$ ) were significantly down-regulated by miR-136-5p. And the location of mRNA sequence by miR-136-5p targeted overlapped with the methylation site recognized by ALKBH5, furthermore competed in regulating ITGAV mRNA. **Conclusion** HIF1 $\alpha$  regulates the expression of ITGAV and improves endometrial receptivity by regulating the expression of ALKBH5 and competitively binding to the specific sequence on ITGAV mRNA targeted by miR-136-5p.

**【 Key words 】** Endometrial receptivity; Hypoxia inducible factor-1 $\alpha$ ; ALKBH5; N6-methyladenosine methylation; Integrin  $\alpha$ v protein

**Fund program:** Capital Medical University Scientific Research Cultivation Fund (PYZ19057); Beijing Municipal Hospital Scientific Research Cultivation Program (PX2018053)

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·实验研究·

# PBMCs 源性外泌体经 miR-1306 改善子宫内膜容受性的机制研究

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**【摘要】** 目的 探讨外周血单个核细胞(peripheral blood mononuclear cells, PBMCs)源性外泌体经 miR-1306 改善子宫内膜容受性的机制。方法 运用皮下注射米非司酮制备着床障碍小鼠模型并分为着床障碍组、PBMCs 干预组, 同时设置正常组, 每组 12 只。PBMCs 干预组给予宫腔注射 PBMCs 源性外泌体干预, 正常组和着床障碍组宫腔注射等体积缓冲液, 比较各组小鼠的妊娠率和着床点数, RT-PCR 法检测子宫内膜组织 miR-1306 表达, 酶联免疫吸附试验检测子宫内膜组织活性氧(reactive oxygen species, ROS)、白细胞介素-6(interleukin-6, IL-6)、单核细胞趋化因子-1(monocyte chemoattractant protein-1, MCP-1)、超氧化物歧化酶(superoxide dismutase, SOD)水平, Western blotting 法检测小鼠子宫内膜组织中妊娠相关蛋白表达。将子宫内膜上皮细胞分为对照组、实验组、阴性对照组、miR-1306 inhibitor 组, 除对照组外余下各组细胞均采取 Transwell 共培养 PBMCs

源性外泌体,使用 MTT 法、Edu 法、Annexin-V/PI 流式法分别检测细胞活性、增殖和凋亡情况,试剂盒检测细胞 ROS 水平,Western blotting 检测相关蛋白表达。结果 着床障碍组小鼠妊娠率 [8.33% (1/12)]、着床点数 [0 (0, 0) 个] 和子宫内膜组织 miR-1306 表达 (0.24±0.05)、SOD 水平 [ (5.66±0.72) U/mL] 均显著低于正常组 [100% (12/12)、16.50 (14.00, 19.00) 个、1.03±0.05、(8.69±1.21) U/mL, 均  $P<0.05$ ]; 子宫内膜组织 ROS 水平 [ (4.87±0.39) U/mL]、IL-6 水平 [ (116.51±5.78) ng/L]、MCP-1 水平 [ (36.84±3.56)  $\mu$ g/L] 和 KIR2DL4 (0.87±0.06)、核因子红细胞 2 相关因子 2 (nuclear factor erythroid-2-related factor 2, Nrf2, 0.76±0.06)、Kelch 样环氧氯丙烷相关蛋白 1 (Kelch-like ECH-associated protein 1, Keap1, 0.79±0.05)、受体相互作用蛋白酶 1 (receptor interacting protein 1, RIP1, 0.94±0.04) 和 RIP3 蛋白 (0.86±0.05) 表达水平均显著高于正常组 [ (2.41±0.19) U/mL、(83.79±6.68) ng/L、(12.32±2.09)  $\mu$ g/L、0.27±0.03、0.31±0.05、0.23±0.04、0.34±0.03、0.31±0.05, 均  $P<0.05$ ]。PBMCs 干预组小鼠妊娠率 [75.00% (9/12)]、着床点数 [13.00 (13.00, 14.75) 个] 和子宫内膜组织 miR-1306 表达 (0.82±0.05)、SOD 水平 [ (7.24±0.84) U/mL] 均显著高于着床障碍组 (均  $P<0.05$ ); 子宫内膜组织 ROS [ (3.43±0.30) U/mL]、IL-6 [ (94.69±3.99) ng/L]、MCP-1 水平 [ (27.03±3.48)  $\mu$ g/L] 和 KIR2DL4 (0.54±0.08)、Nrf2 (0.48±0.05)、Keap1 (0.43±0.05)、RIP1 (0.56±0.05)、RIP3 蛋白表达 (0.49±0.03) 均显著低于着床障碍组 (均  $P<0.05$ )。实验组细胞活性 [ (126.63±1.25)%]、增殖率 [ (53.54±2.82)%] 和 ROS 水平 [ (3.12±0.31) U/mL] 均显著高于对照组 [100%、(23.18±3.07)%、(2.51±0.28) U/mL, 均  $P<0.05$ ]、凋亡率 [ (5.69±0.47)%]、KIR2DL4 (0.36±0.06)、Nrf2 (0.30±0.06)、Keap1 (0.26±0.04)、RIP1 (0.27±0.05) 和 RIP3 蛋白表达 (0.26±0.06) 均低于对照组 [ (27.13±2.97)%、0.84±0.06、0.75±0.05、0.68±0.05、0.80±0.06、0.80±0.07, 均  $P<0.05$ ]。miR-1306 inhibitor 组细胞活性 [ (83.48±5.34)%]、增殖率 [ (38.42±4.28)%] 均显著低于阴性对照组 [ (127.12±4.08)%、(53.57±2.09)%、均  $P<0.05$ ]、细胞凋亡率 [ (13.63±1.77)%]、ROS 水平 [ (6.49±0.62) U/mL]、KIR2DL4 (0.67±0.07)、Nrf2 (0.57±0.05)、Keap1 (0.50±0.05)、RIP1 (0.64±0.06) 和 RIP3 蛋白表达 (0.61±0.08) 均显著高于阴性对照组 [ (5.71±0.78)%、(3.23±0.31) U/mL、0.36±0.07、0.30±0.07、0.27±0.06、0.28±0.07、0.28±0.06, 均  $P<0.05$ ]。结论 PBMCs 源性外泌体可以提高着床障碍小鼠妊娠率,可能是通过促进 miR-1306 表达、抑制 KIR2DL4 表达以改善炎症反应,还与缓解子宫内膜过度氧化应激和细胞凋亡有关。

【关键词】 外泌体; 着床障碍; 外周血单个核细胞; miR-1306; 子宫内膜容受性

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## Mechanism of PBMCs-derived exosomes on improving endometrial receptivity by miR-1306

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【Abstract】 **Objective** To explore the mechanism of peripheral blood mononuclear cells (PBMCs)-derived exosomes on improving endometrial

receptivity by miR-1306. **Methods** The models of mice with implantation disorders were prepared by subcutaneous injection of mifepristone. And they were divided into implantation disorder group and PBMCs intervention group, 12 mice in each group. The normal group was set up. PBMCs intervention group was given intrauterine injection of PBMCs-derived exosomes, while normal group and implantation disorder group were given the same volume of buffer solution. The pregnancy rates and number of embryos implantation in different groups were compared. The expression of miR-1306 in endometrial tissues was detected by RT-PCR. The levels of reactive oxygen species (ROS), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and superoxide dismutase (SOD) in endometrial tissues were detected by enzyme-linked immunosorbent assay. The expressions of pregnancy-related proteins in endometrial tissues were detected by Western blotting. The endometrial epithelial cells were divided into control group, experimental group, negative control group and miR-1306 inhibitor group. Except control group, cells were co-cultured with PBMCs-derived exosomes by Transwell in the other groups. The activity, proliferation and apoptosis of cells were detected by MTT, Edu and Annexin-V/PI flow, respectively. The level of ROS in cells was detected by kits. And expressions of the related proteins were detected by Western blotting.

**Results** The pregnancy rate [8.33% (1/12), number of embryos implantation [0(0, 0)], expression of miR-1306 in endometrial tissue ( $0.24 \pm 0.05$ ) and SOD level [ $(5.66 \pm 0.72)$  U/mL] in implantation disorder group were significantly lower than those in normal group [100% (12/12), 16.50 (14.00, 19.00),  $1.03 \pm 0.05$ , ( $8.69 \pm 1.21$ ) U/mL,  $P < 0.05$ ], while levels of ROS [ $(4.87 \pm 0.39)$  U/mL], IL-6 [ $(116.51 \pm 5.78)$  ng/L] and MCP-1 in endometrial tissues [ $(36.84 \pm 3.56)$  µg/L], and expressions of KIR2DL4 ( $0.87 \pm 0.06$ ), nuclear factor erythroid-2-related factor 2 (Nrf2,  $0.76 \pm 0.06$ ), Kelch-like ECH-associated protein1 (Keap1,  $0.79 \pm 0.05$ ), receptor interacting protein 1 (RIP1,  $0.94 \pm 0.04$ ) and RIP3 ( $0.86 \pm 0.05$ ) were significantly higher than those in normal group [ $(2.41 \pm 0.19)$  U/mL, ( $83.79 \pm 6.68$ ) ng/L, ( $12.32 \pm 2.09$ ) ng/mL,  $0.27 \pm 0.03$ ,  $0.31 \pm 0.05$ ,  $0.23 \pm 0.04$ ,  $0.34 \pm 0.03$ ,  $0.31 \pm 0.05$ , all  $P < 0.05$ ]. The pregnancy rate [75.00% (9/12)], number of embryos implantation [13.00 (13.00, 14.75)], expression of miR-1306 in endometrial tissues ( $0.82 \pm 0.05$ ) and SOD level [ $(7.24 \pm 0.84)$  U/mL] in PBMCs intervention group were significantly higher than those in implantation disorder group (all  $P < 0.05$ ), while levels of ROS [ $(3.43 \pm 0.30)$  U/mL], IL-6 [ $(94.69 \pm 3.99)$  ng/L] and MCP-1 in endometrial tissues [ $(27.03 \pm 3.48)$  µg/L], and expressions of KIR2DL4 ( $0.54 \pm 0.08$ ), Nrf2 ( $0.48 \pm 0.05$ ), Keap1 ( $0.43 \pm 0.05$ ), RIP1 ( $0.56 \pm 0.05$ ) and RIP3 ( $0.49 \pm 0.03$ ) were significantly lower than those in implantation disorder group (all  $P < 0.05$ ). The cells activity [ $(126.63 \pm 1.25)\%$ ], proliferation rate [ $(53.54 \pm 2.82)\%$ ] and ROS level [ $(3.12 \pm 0.31)$  U/mL] in experimental group were significantly higher than those in control group [100%, ( $23.18 \pm 3.07$ )%, ( $2.51 \pm 0.28$ ) U/mL, all  $P < 0.05$ ], while apoptosis rate [ $(5.69 \pm 0.47)\%$ ], expressions of KIR2DL4 ( $0.36 \pm 0.06$ ), Nrf2 ( $0.30 \pm 0.06$ ), Keap1 ( $0.26 \pm 0.04$ ), RIP1 ( $0.27 \pm 0.05$ ) and RIP3 ( $0.26 \pm 0.06$ ) were lower than those in control group [ $(27.13 \pm 2.97)\%$ ,  $0.84 \pm 0.06$ ,  $0.75 \pm 0.05$ ,  $0.68 \pm 0.05$ ,  $0.80 \pm 0.06$ ,  $0.80 \pm 0.07$ , all  $P < 0.05$ ]. The cells activity [ $(83.48 \pm 5.34)\%$ ] and proliferation rate [ $(38.42 \pm 4.28)\%$ ] in miR-1306 inhibitor group were significantly



lower than those in negative control group [(127.12±4.08)%, (53.57±2.09)%, all  $P<0.05$ ], while apoptosis rate [(13.63±1.77)%], ROS level [(6.49±0.62) U/mL], expressions of KIR2DL4 (0.67±0.07), Nrf2 (0.57±0.05), Keap1 (0.50±0.05), RIP1 (0.64±0.06) and RIP3 (0.61±0.08) were significantly higher than those in negative control group [(5.71±0.78)%, (3.23±0.31) U/mL, 0.36±0.07, 0.30±0.07, 0.27±0.06, 0.28±0.07, 0.28±0.06, all  $P<0.05$ ]. **Conclusion** PBMCs-derived exosomes can improve pregnancy rate in mice with implantation disorders, which may improve inflammatory response by promoting miR-1306 expression and inhibiting KIR2DL4 expression, and is also related to relieving excessive oxidative stress and apoptosis of endometrium.

**【 Key words 】** Exosomes; Implantation disorder; Peripheral blood mononuclear cell; miR-1306; Endometrial receptivity

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·临床报道·

## FSH 联合 hCG 双扳机对 IVF-ET 临床结局的影响

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**【摘要】** 目的 研究短效长方案促排卵患者使用卵泡刺激素 (follicle-stimulating hormone, FSH) 联合人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 扳机诱发排卵对体外受精/卵胞质内单精子注射-胚胎移植 (*in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer, IVF/ICSI-ET) 结局的影响。方法 回顾性队列研究分析 2016 年 2 月至 2017 年 4 月期间在厦门大学附属妇女儿童医院生殖医学科行 IVF/ICSI-ET 助孕的 682 例短效长方案促排卵患者的临床资料, 根据扳机方式分为重组 hCG (recombinant hCG, r-hCG) 组 (单纯使用 250 μg r-hCG) 439 例和双扳机组 [300 U 尿源性 FSH (urinary FSH, uFSH) 联合 250 μg r-hCG] 243 例。主要观察指标为临床妊娠率与活产率, 次要

观察指标为优质胚胎率、胚胎植入率、生化妊娠率、流产率等。结果 患者的年龄、不孕年限、体质量指数 (body mass index, BMI)、抗苗勒管激素 (anti-Müllerian hormone, AMH)、促性腺激素 (gonadotropin, Gn) 使用总量、Gn 使用时间和移植胚胎数组间比较, 差异均无统计学意义 (均  $P>0.05$ ); 双扳机组胚胎种植率 [40.47% (191/472)] 及生化妊娠率 [64.20% (156/243)] 显著高于 r-hCG 组 [32.42% (272/893),  $P=0.003$ ; 55.35% (243/439),  $P=0.025$ ], 但两组受精率、卵裂率、胚胎形成率、优质胚胎率、流产率、临床妊娠率、活产率比较差异均无统计学意义 (均  $P>0.05$ )。结论 短效长方案促排卵使用 300 U uFSH 联合 250  $\mu$ g r-hCG 双扳机并不能显著提高短效长方案 IVF/ICSI-ET 的临床妊娠率及活产率, 但可显著提高胚胎种植率及生化妊娠率。

【关键词】 受精, 体外; 卵泡刺激素; 双扳机; 重组人绒毛膜促性腺激素扳机; 胚胎移植

### Effects of oocyte maturation trigger using follicle-stimulating hormone plus human chorionic gonadotropin on clinical outcomes of *in vitro* fertilization and embryo transfer

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【Abstract】 **Objective** To investigate the effects of oocyte maturation trigger using follicle-stimulating hormone (FSH) plus human chorionic gonadotropin (hCG) on clinical outcomes of *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) in gonadotropin-releasing hormone agonist (GnRH-a) cycles. **Methods** The retrospective cohort study included 682 patients aged up to 40 years with normal ovarian response who underwent IVF/ICSI-ET at Department of Reproductive Medicine, Women and Children's Hospital, Xiamen University School of Medicine between February 2016 and April 2017. Patients were grouped by whether oocyte maturation was triggered with 250  $\mu$ g recombinant hCG (r-hCG) plus 300 U urinary FSH (uFSH, dual trigger group,  $n=439$ ) or 250  $\mu$ g r-hCG alone (r-hCG group,  $n=243$ ). The main observation indexes were the clinical pregnancy rate and the live birth rate, and the secondary observation indexes were the high-quality embryo rate, the implantation rate, the biochemical pregnancy rate, the abortion rate, etc. **Results** There were no statistically significant differences between the two groups in age, infertility duration, body mass index (BMI), anti-Müllerian hormone (AMH), total dosage and duration of gonadotropin (Gn) used, number of embryos transferred (all  $P>0.05$ ). The live birth rate, the clinical pregnancy rate, the miscarriage rate, the normal fertilization rate, the cleavage rate, the embryo formation rate and the high-quality embryo rate were not significantly different between the two groups (all  $P>0.05$ ). The implantation rate [40.47% (191/472)] and the biochemical pregnancy rate [64.20% (156/243)] were higher in dual trigger group than in r-hCG group [32.42% (272/893),  $P=0.003$ ; 55.35%

(272/893),  $P=0.025$ ]. **Conclusion** Dual trigger of oocyte maturation with 250  $\mu\text{g}$  r-hCG plus 300 U uFSH has no benefit on the clinical pregnancy rate and the live birth rate, but could improve the implantation rate and the biochemical pregnancy rate in women undergoing short-acting GnRH-a protocol in IVF/ICSI-ET.

**【Key words】** Fertilization *in vitro*; Follicle-stimulating hormone; Dual trigger; Recombination human chorionic gonadotropin trigger; Embryo transfer

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·临床报道·

## IVF/ICSI 助孕双胎妊娠选择性减胎的围产期结局分析

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**【摘要】** 目的 分析体外受精/卵胞质内单精子注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 助孕双胚胎移植后, 双绒毛膜双胎妊娠选择性减胎患者的围产期结局。方法 回顾性队列研究分析 2005 年 9 月 1 日至 2020 年 7 月 31 日期间于郑州大学第三附属医院生殖中心行 IVF/ICSI 助孕移植 2 枚胚胎, 获得单胎活产患者的临床资料。根据是否发生减胎分为 3 组: 双绒毛膜双胎选择性减胎为单胎患者组 (记为 A 组,  $n=80$ )、双绒毛膜双胎自然减胎为单胎患者组 (记为 B 组,  $n=832$ ) 和单胎着床患者组 (记为 C 组,  $n=6\,178$ )。以 A 组为参照组, 分别与 B 组、C 组以 1:4 比例近似倾向性评分匹配 (propensity score matching, PSM) 后, 分析 A 组与 B 组、C 组的基线数据及围产期结局的差异。结果 ①PSM 前, A 与 B 组、C 组间患者年龄、既往生育史、不孕类型、移植胚胎类型差异均存在统计学意义 (均  $P<0.05$ ); PSM 后, B 组为 289 例, C 组为 271 例。A 组与 B 组、C 组间基线数据差异均无统计学意义 (均  $P>0.05$ )。②PSM 后, A 组早产率 [17.5% (14/80)] 高于 B 组 [8.7% (25/289),  $P=0.023$ ], 出生孕周 [(38.18 $\pm$ 1.98) 周] 低于 B 组 [(38.64 $\pm$ 1.83) 周,  $P=0.034$ ]; A 组早产率 [17.5% (14/80)] 和胎膜早破发生率 [5.0% (4/80)] 高于 C 组 [7.7% (21/271),  $P=0.011$ ; 0.4% (1/271),  $P=0.002$ ], 出生孕周 [(38.18 $\pm$ 1.98) 周] 及出生体质

量 $[(3\ 253.07\pm 475.73)\text{ g}]$ 低于C组 $[(38.85\pm 1.47)\text{周}]$ ,  $P=0.002$ ;  $[(3\ 384.89\pm 479.54)\text{ g}]$ ,  $P=0.029$ , 差异均有统计学意义。结论 IVF/ICSI 助孕双胚胎移植后双绒毛膜双胎妊娠选择性减胎的围产期结局较差。多胎妊娠选择性减胎并非最佳补救措施, 应采取选择性单胚胎移植策略, 切实降低多胎妊娠率, 改善母婴结局。

【关键词】 双绒毛膜双胎; 自然减胎; 选择性减胎; 围产期结局; 选择性单胚胎移植

## Perinatal outcome of selective fetal reduction in twin pregnancies assisted by IVF/ICSI

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**【Abstract】 Objective** To investigate the perinatal outcome of selective fetal reduction of dizygotic twins pregnancies after double embryo transferred assisted by *in vitro* fertilization/ intracytoplasmic sperm injection (IVF/ICSI). **Methods** The clinical data of patients with single birth who underwent IVF/ICSI after double embryo transferred from September 1, 2005 to July 31, 2020 in Reproductive Center of the Third Affiliated Hospital of Zhengzhou University were retrospectively analyzed. The patients were divided into three groups according to the occurrence of fetal reduction: 80 cases of dizygotic twins to singleton by selective fetal reduction (group A), 832 cases of dizygotic twins to singleton by spontaneous fetal reduction (group B), and 6 178 cases of singleton (group C). Using group A as the reference, after approximately propensity score matching (PSM) with 1:4 ratio, 289 cases in group B and 271 cases in group C were obtained. The differences in baseline data and perinatal outcomes between group A and group B or group C were analyzed. **Results** 1) Before PSM, there were statistically significant differences in patients' age, previous fertility history, type of infertility, and stage of embryo transferred between group A and group B or group C (all  $P<0.05$ ); after PSM, there were no statistically significant differences in baseline data between group A and group B or group C (all  $P>0.05$ ). 2) After PSM, the premature birth rate was higher in group A than in group B [17.5% (14/80) vs. 8.7% (25/289),  $P=0.023$ ] and the gestational weeks  $[(38.18\pm 1.98)\text{ weeks}]$  vs.  $[(38.64\pm 1.83)\text{ weeks}]$ ,  $P=0.034$  were lower; group A had higher incidence rates of premature birth [17.5% (14/80) vs. 7.7% (21/271),  $P=0.011$ ] and premature rupture of membranes [5.0% (4/80) vs. 0.4% (1/271),  $P=0.002$ ] than those in group C, but gestational weeks  $[(38.18\pm 1.98)\text{ weeks}]$  vs.  $[(38.85\pm 1.47)\text{ weeks}]$ ,  $P=0.002$  and birth weight  $[(3\ 253.07\pm 475.73)\text{ g}]$  vs.  $[(3\ 384.89\pm 479.54)\text{ g}]$ ,  $P=0.029$  were lower. **Conclusion** Perinatal outcomes of selective fetal reduction of dizygotic twins pregnancies after assisted by IVF/ICSI were poor. Selective fetal reduction in multiple pregnancies is not the best remedy. The strategy of selective single embryo transfer should be adopted to effectively reduce the rate of multiple pregnancies and improve maternal and infant outcomes.

**【Key words】** Twins, dizygotic; Spontaneous fetal reduction; Selective fetal reduction; Perinatal outcome; Elective single embryo transfer

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·临床报道·

## 子宫腺肌病合并不孕行 IVF-ET 患者外周血免疫分子与子宫体积的相关性探索

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**【摘要】** 目的 探讨子宫腺肌病合并不孕患者外周血免疫分子与子宫体积的关系。方法 本队列研究纳入了 2014 年 1 月至 2020 年 10 月期间于北京大学第三医院妇产科生殖医学中心就诊的 106 例子宫腺肌病合并不孕患者。根据子宫体积将患者分为两组, A 组: 子宫体积 $\leq 100\text{ cm}^3$  ( $n=85$ ); B 组: 子宫体积 $> 100\text{ cm}^3$  ( $n=21$ ), 比较两组外周血中免疫分子表达的差异。结果 B 组患者外周血中 Th17 细胞占比 ( $1.2\%\pm 0.4\%$ ) 和 Th1 细胞占比 ( $15.5\%\pm 4.1\%$ ) 均低于 A 组患者 ( $1.4\%\pm 0.4\%$ ,  $P=0.048$ ;  $19.2\%\pm 4.8\%$ ,  $P=0.019$ )。Th2 细胞占比 (A 组为  $1.8\%\pm 0.4\%$ , B 组为  $1.4\%\pm 0.7\%$ ) 在两组之间差异无统计学意义 ( $P=0.137$ )。淋巴细胞亚群、血清细胞因子、免疫球蛋白水平、补体水平在两组之间差异均无统计学意义 (均  $P>0.05$ )。结论 不同子宫体积的子宫腺肌病不孕患者具有不同的外周血 Th1/Th17 水平。

**【关键词】** 子宫腺肌病; 不孕; Th1 细胞; Th2 细胞; Th17 细胞

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### Association between uterine volume and immunological molecules of peripheral blood in infertile patients with adenomyosis who treated with IVF-ET

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**【Abstract】 Objective** To investigate the association between uterine volume and immunological molecules of peripheral blood in infertile patients with adenomyosis. **Methods** A total of 106 infertile patients with adenomyosis from

January 2014 to October 2020 were included in this cohort study. The subjects were divided into two groups according to the uterine volume (group A: uterine volume  $\leq 100 \text{ cm}^3$ ,  $n=85$ ; group B: uterine volume  $>100 \text{ cm}^3$ ,  $n=21$ ), and the differences in the expression of immunological molecules in peripheral blood were compared between the two groups. **Results** Th17 proportion ( $1.2\% \pm 0.4\%$ ) and Th1 cell proportion ( $15.5\% \pm 4.1\%$ ) in peripheral blood in group B ( $n=21$ ) were lower than those in group A ( $1.4\% \pm 0.4\%$ ,  $P=0.048$ ;  $19.2\% \pm 4.8\%$ ,  $P=0.019$ ). Th2 cell proportion (group A:  $1.8\% \pm 0.4\%$ , group B:  $1.4\% \pm 0.7\%$ ) showed no significant differences between the two groups ( $P=0.137$ ). Proportion of lymphocyte subsets, serum cytokines, immunoglobulin levels and complement levels were not significantly different between the two groups (all  $P>0.05$ ). **Conclusion** Adenomyosis-associated infertile patients with different uterine volume have different Th1/Th17 levels in peripheral blood.

**【Key words】** Adenomyosis; Infertility; Th1 cell; Th2 cell; Th17 cell

**Fund program:** National Natural Science Foundation of China (81521002)

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·个案报道·

## 体外受精-胚胎移植术后小网膜囊腹腔妊娠 1 例报道

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**【摘要】** 目的 总结体外受精-胚胎移植 (*in vitro* fertilization and embryo transfer, IVF-ET) 术后发生的小网膜囊腹腔妊娠的临床诊治经验。方法 报道 1 例 IVF-ET 术后发生的小网膜囊腹腔妊娠病例, 并分析其临床特点。结果 患者移植 2 枚囊胚后 23 d 突发左上腹痛, 超声示: 宫腔内未见孕囊, 左上腹不均质回声, 腹腔少量积液。阴道后穹窿穿刺不凝血, 有腹腔镜探查指征, 术中清理盆腹腔积血后,

行小网膜囊妊娠物清除术，术后患者恢复好。结论 小网膜囊腹腔妊娠罕见，一旦发现应及时终止妊娠，推荐腹腔镜手术。

【关键词】 受精，体外； 胚胎移植； 小网膜囊； 腹腔妊娠； 早期诊断； 腹腔镜手术

## Abdominal pregnancy in the sac of lesser omentum after *in vitro* fertilization and embryo transfer: a case report

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**【Abstract】 Objective** To summarize the clinical experience in the diagnosis and treatment of abdominal pregnancy in the sac of lesser omentum after *in vitro* fertilization and embryo transfer (IVF-ET). **Methods** A case of abdominal pregnancy in the sac of lesser omentum after IVF-ET was reported in detail and summarized, and its clinical characteristics were analyzed. **Results** After two blastocysts were transplanted 23 d, the patient had a sudden left upper abdominal pain. Ultrasound showed no pregnancy sac in utero, left epigastric dysplasia echo, and a small amount of fluid in the abdominal cavity. Puncture of the posterior vaginal fornix was nonclotting, and there was a clear indication of laparoscopic exploration. After cleaning up the blood in the pelvic and abdominal, the gestational tissue of lesser omentum sac was cleared. The patient recovered well after surgery. **Conclusion** Abdominal pregnancy in the sac of lesser omentum after IVF-ET is extremely rare and should be treated timely. Laparoscopic surgery is recommended to determinate abdominal pregnancy in the first trimester.

**【Key words】** Fertilization *in vitro*; Embryo transfer; Sac of lesser omentum; Abdominal pregnancy; Early diagnosis; Laparoscopic surgery

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·个案报道·

单精子测序结合 PCR-反向点杂交技术在 1 例东南亚缺失型  $\alpha$  地中海贫血患者胚胎植入前遗传学检测中的应用

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**【摘要】** 目的 探讨单精子测序结合 PCR-反向点杂交 (PCR-reverse dot blot, PCR-RDB) 技术在东南亚缺失型  $\alpha$  地中海贫血胚胎植入前遗传学检测中的应用价值。方法 选取 2020 年 4 月 24 日就诊于广州医科大学附属第三医院妇产科的一对东南亚缺失型  $\alpha$  地中海贫血携带者夫妇, 针对男方无法提供家系成员样本的情况, 本案例采用上游法结合显微操作移液管挑选其 5 份单精子样本并进行全基因组扩增, 通过 PCR-RDB 技术确定男方单精子样本的地中海贫血基因分型, 在  $--SEA$  区域的上下游 1 Mb 范围内选择单核苷酸多态性位点 (single nucleotide polymorphism, SNP) 作为遗传标记, 进行二代测序分析构建双亲单体型。对 6 份囊胚活检样本进行全基因组扩增后行二代测序, 通过单体型分析胚胎是否携带致病变异, 并选取非患病囊胚进行移植。孕 20 周抽羊水进行产前诊断, 验证与单基因病胚胎植入前遗传学检测 (preimplantation genetic testing for monogenetic disease, PGT-M) 结果是否一致。结果 女方的致病变异来源于其母亲, 男方 5 份单精子样本的地中海贫血基因分型结果显示有 4 份为野生型。单精子测序筛选出男方有效位点 10 个, 女方家系连锁分析得到女方有效位点 6 个, PGT-M 结果显示 4 枚囊胚为  $\alpha\alpha/--SEA$ , 2 枚为  $--SEA/--SEA$ , 产前诊断结果显示胎儿基因型为  $\alpha\alpha/--SEA$ , 与 PGT-M 结果一致, 并于孕 40 周分娩一健康女婴。结论 对于家系不全的男性东南亚缺失型  $\alpha$  地中海贫血携带者, 可采用单精子测序结合 PCR-RDB 技术筛选 SNP 位点, 通过连锁分析行 PGT-M。

**【关键词】** 遗传连锁; 单核苷酸多态性; 植入前诊断; 单精子测序;  
东南亚缺失型  $\alpha$  地中海贫血

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# **Application of single sperm sequencing combined with PCR-reverse dot blot in preimplantation genetic testing of Southeast Asian deletion type $\alpha$ thalassemia**

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**【 Abstract 】 Objective** To investigate the value of single sperm sequencing combined with PCR-reverse dot blot (PCR-RDB) technology in



preimplantation genetic testing (PGT) of Southeast Asian deletion type  $\alpha$  thalassemia.

**Methods** A couple of Southeast Asian deletion type  $\alpha$  thalassemia carrier was selected in this case, who asked for assisted reproduction in the Department of Obstetrics and Gynecology of the Third Affiliated Hospital of Guangzhou Medical University on April 24, 2020. The male carrier was subjected to single sperm isolation by the swim-up method combined with micropipette due to his incomplete pedigree. Five single sperm samples were isolated and their whole-genome were amplified. The genotype of thalassemia of single sperm samples were determined by PCR-RDB. SNPs were selected as genetic markers in the range of 1 Mb upstream and downstream of  $--SEA$  region to construct chromosomal haplotype. Next, we performed whole-genome amplification on six blastocyst biopsy samples, and then next-generation sequencing was carried out to detect the carrier status of the embryos. Finally, the non-pathogenic blastocysts were selected for transplantation, and the preimplantation genetic testing for monogenic (PGT-M) results were confirmed by the prenatal genetic diagnosis during pregnancy. **Results** The pathogenic variant in the female was inherited from her mother, and four of the five single sperm samples were wild-type. Ten male informative SNP markers were identified by single sperm sequencing, and six female informative SNP markers were identified by linkage analysis of female family. PGT-M results indicated that four blastocysts were  $\alpha\alpha/--SEA$  and two were  $--SEA/--SEA$ . The result of prenatal diagnosis revealed that the fetus was a carrier of  $--SEA$ , which was consistent with PGT-M result, and a healthy girl was delivered at 40 weeks of gestation. **Conclusion** For male carriers of Southeast Asian deletion type  $\alpha$  thalassemia with incomplete pedigree, single sperm sequencing combined with PCR-RDB technology can be used to select SNP sites, and PGT-M can be performed by linkage analysis.

**【 Key words 】** Genetic linkage; Polymorphism, single nucleotide; Preimplantation diagnosis; Single sperm sequencing; Southeast Asian deletion type  $\alpha$  thalassemia

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·综述·

## 多囊卵巢综合征患者子宫内膜容受性异常机制研究

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**【摘要】** 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 是育龄期女性常见的内分泌、代谢紊乱性疾病, 其病因复杂, 临床表现高度异质性。子宫内膜容受性不良是 PCOS 患者促排卵后排卵率高而妊娠失败的重要原因。本文就氧化应激、慢性低度炎症、代谢异常、内分泌紊乱、子宫内膜激素受体等异常机制与子宫内膜容受性的关系进行综述, 为临床工作者对 PCOS 患者在子宫内膜容受性方面的诊治, 提供更多理论参考。

**【关键词】** 多囊卵巢综合征; 子宫内膜容受性; 异常机制

基金项目: 国家杰出青年科学基金 (81925013); 中国博士后科学基金 (2021M690259)

## Research progress on the mechanism of abnormal endometrial receptivity in women with polycystic ovary syndrome

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**【Abstract】** Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in women of childbearing age. Its etiology is complex and its clinical manifestations are highly heterogeneous. Poor endometrial receptivity is an important reason for pregnancy failure after PCOS ovulation induction in spite of high ovulation rate. This paper reviewed the relationship between endometrial receptivity and abnormal mechanisms such as oxidative stress, chronic low-grade inflammation, metabolic abnormalities, endocrine disorders and endometrial hormone receptors in order to provide theoretical reference for clinicians to diagnose and treat PCOS women involving the endometrial receptivity.

**【Key words】** Polycystic ovary syndrome; Endometrial receptivity; Abnormal mechanism

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·综述·

## 单卵双胞胎发生机制及其危险因素的研究进展

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**【摘要】** 单卵双胞胎是双胎妊娠中的一种特殊类型。与双卵双胞胎相比, 单卵双胞胎发生流产、胎儿畸形、胎死宫内、宫内生长受限及早产等风险均明显增加。单卵双胞胎的发生机制目前尚不明确, 目前存在“两个模型”和“一个假说”理论, 即“合子分裂模型”“胚胎膜融合模型”和“过度成熟配子”假说。辅助生殖技术与单卵双胞胎的发生密切相关。辅助生殖技术中的母体年龄、促排卵药物的应用、移植周期类型、胚胎培养时间、透明带操作、培养方式和培养液、遗传等均与单卵双胞胎的发生有关。本文对于单卵双胞胎的发生机制及危险因素新进展进行综述, 以期为临床工作提供指导。

**【关键词】** 单卵双胞胎; 危险因素; 生殖技术, 辅助; 发生机制  
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## Research progress on the pathogenetic mechanism and risk factors of monozygous twins

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**【Abstract】** Monozygous twins (MZT) is a special type of twins. The risks of miscarriage, fetal malformation, intrauterine death, intrauterine growth restriction and preterm birth are significantly increased compared with dizygous twins (DZT). The mechanism of MZT has been still unclear. In recent years, studies have shown the existence of "two models" and "one hypothesis", namely "a fission event" "a fusion event" and "overripe" gametes hypothesis. Assisted reproductive technology (ART) is closely related to the occurrence of MZT. The incidence of MZT after ART is related to maternal age, ovulation induction, type of embryo/blastocyst transfer cycle, days of embryo culture, zona pellucida micromanipulation, culture method and medium, heredity and other unknown factors. This paper reviewed the new progress of the pathogenesis and risk factors of MZT, in order to provide guidance for clinical work.

**【Key words】** Twins, monozygotic; Risk factors; Reproductive techniques, assisted; Pathogenetic mechanism

**Fund program:** National Key Research and Development Program  
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·综述·

## 子宫内膜类器官研究进展

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**【摘要】** 子宫内膜类器官(endometrial organoids, EOs)是子宫内膜细胞自组织的三维聚集物,代表子宫内膜的结构和功能。根据所包含的细胞类型的数量,EOs可分为两类:单种细胞EOs和多种细胞EOs。EOs将加速我们对子宫内膜发育和疾病的分子和细胞机制的理解,将成为从疾病建模到个性化医疗等生物学应用的有前途的工具。本文对EOs的表型(典型的表面标记和结构)、遗传特征、培养基、对激素的反应、模拟的疾病模型、挑战和未来展望逐一综述。

**【关键词】** 类器官; 子宫内膜异位症; 子宫内膜增生; 子宫内膜炎; 多囊卵巢综合征; 子宫内膜; 子宫内膜癌

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### Research advances in endometrial organoids

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**【Abstract】** Endometrial organoids (EOs) are three-dimensional aggregates of endometrial cells, which represent the structure and function of endometrium. According to the number of cell types contained, EOs can be divided into two categories, single-cell EOs and multicellular EOs. EOs will accelerate our understanding of the molecular and cellular mechanisms of endometrial development and diseases, and will become a promising tool for biomedical applications from disease modeling to personalized medicine. This review described the phenotype (typical surface markers and structure), genetic characteristics, culture medium, response to hormones, simulated disease model, challenges and future prospects of EOS.

**【Key words】** Organoids; Endometriosis; Endometrial hyperplasia; Endometritis; Polycystic ovary syndrome; Endometrial; Endometrial cancer

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## 阴道微生态与不孕症的相关性研究进展

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**【摘要】** 阴道微生态是阴道微生物与人体相互作用形成的一个相对平衡的生物环境, 阴道微生物群对于维持宿主的正常生理环境至关重要, 当阴道微生态失衡时, 可引起不孕症的发生。深入探讨阴道微生态在女性不孕症中的作用及机制, 对阴道微生态失衡相关不孕症的诊疗具有一定的临床意义。本文就近年来国内外关于阴道微生态与女性不孕症的相关性研究进展进行综述, 旨在为不孕症的治疗和预防提供更有效的策略及方案。

**【关键词】** 生态失调; 阴道微生态; 阴道菌群; 不孕症

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## Research progress on the relationship between vaginal microecology and infertility

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**【 Abstract 】** Vaginal microecology is a relatively balanced biological environment formed by the interaction between vaginal microorganisms and the human body. The vaginal microbiota is essential for maintaining the normal physiological environment of the host. The vaginal dysbiosis can cause infertility. In-depth discussion of the role and mechanism of vaginal microecology in female infertility has certain clinical significance for the diagnosis and treatment of infertility related to vaginal microecology imbalance. This article reviews the research progress on the relationship between vaginal microecology and infertility at home and abroad in recent years, and aims to provide more effective strategies and solutions for the treatment and prevention of infertility.

**【 Key words 】** Dysbiosis; Vaginal microecology; Vaginal microbiota; Infertility

**Fund program:** Reproductive Obstetrics and Gynecology Clinical Center of Yunnan Province (zx2019-01-01, 2021LCZXXF-SZ07)

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## 蛋白质组学技术在弱精子症中的应用进展

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**【摘要】** 弱精子症是一种精子运动活力不足的病症，约有 27.8%的男性不育由弱精子症导致，其病因复杂，发病机制尚不明确，探讨其发病机制有助于寻找有效预防和治疗策略。近年来，随着蛋白质组学技术（双向电泳、酵母双杂交技术、质谱等技术）的发展，众多研究者将研究重点放在基于蛋白质组学的弱精子症研究上，揭示了弱精子症差异蛋白及所在生物通路，为弱精子症的机制研究提供了众多理论支撑。本文围绕蛋白质组学的相关技术，对弱精子症的差异蛋白表达、病因和发生机制等方面取得的诸多成果进行综述，希望为弱精子症的诊治提供新思路。蛋白质间的相互作用和通路及代谢异常为研究弱精子症的精子运动活力提供了一个很有潜力的方向。

**【关键词】** 弱精子症； 蛋白质组学； 电泳， 凝胶， 双向； 酵母双杂交； 色谱； 质谱； 生物信息学； 发生机制

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### **Advances in proteomic technologies for asthenozoospermia**

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**【Abstract】** Asthenozoospermia is a condition of deficient motility of spermatozoa, and about 27.8% of male infertility results from asthenozoospermia. Its etiology is complex and its pathogenesis is still unclear, and exploring its pathogenesis can help to find effective prevention and treatment strategies. In recent years, with the development of proteomic technologies (two-dimensional electrophoresis, yeast two-hybrid technology, mass spectrum, etc.), many researchers have focused their researches on the study of asthenozoospermia based on proteomics, revealing the differential proteins of asthenozoospermia and the biological pathways that underlie them, providing numerous theoretical support for the mechanistic study of asthenozoospermia. In this review, we focus on the relevant techniques of proteomics and summarize the many achievements made in understanding the differential protein expression, etiology, and mechanism of asthenozoospermia, which will hopefully provide new insights into the diagnosis and treatment of asthenozoospermia. Protein-protein interactions and pathways and metabolic abnormalities provide a promising direction to study sperm motility in asthenozoospermia.

**【Key words】** Asthenozoospermia; Proteomics; Electrophoresis, gel, two-dimensional; Yeast two-hybrid; Chromatography; Mass spectrum; Bioinformatics; Mechanisms of occurrence

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