

中华生殖与避孕杂志[®]

原刊名《生殖与避孕》

CHINESE JOURNAL OF REPRODUCTION AND CONTRACEPTION

月刊 1980年12月创刊 第42卷 第2期 2022年2月25日出版



主 管

中国科学技术协会

主 办

中华医学会
上海市生物医药技术研究院
复旦大学附属妇产科医院

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《中华医学杂志》社有限责任公司
100710,北京市东直门大街42号
电话(传真):(010)51322059
Email:office@cmaph.org

广告发布登记号

京东市监广登字20200006号

印 刷

上海船舶设备研究所

发 行

范围:公开
国内:中国邮政集团公司
上海分公司
国外:中国国际图书贸易集团
责任有限公司
(北京399信箱,100044)
代号 BM 389

订 购

全国各地邮政局
邮发代号4-928

邮 购

中华生殖与避孕杂志编辑部
200237,上海市老沪闵路779号
电话:(021)64438169,64438975
Email:rande@sibpt.com

定 价

每期35.00元,全年420.00元

中国标准连续出版物号

ISSN 2096-2916

CN 10-1441/R

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本期责任编委乔杰	本期责任编辑李天琦
本期责任排版年丽红	

CHINESE JOURNAL OF REPRODUCTION AND CONTRACEPTION

(Original title: *Reproduction and Contraception*)

Monthly Established in December 1980 Volume 42, Number 2 February 25, 2022



Responsible Institution

China Association for Science and Technology

Sponsor

Chinese Medical Association,
Shanghai Institute for Biomedical and Pharmaceutical Technologies,
Obstetrics and Gynecology Hospital of Fudan University

Editing

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779 Laohumin Road, Shanghai 200237, China
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Chinese Medical Journals
Publishing House Co., Ltd.
42 Dongsi Xidajie, Beijing 100710, China
Tel(Fax): 0086-10-51322059
Email: office@cmaph.org

Printing

Shanghai Marine Equipment Research Institute

Overseas Distributor

China International Book
Trading Corporation
P.O. Box 399, Beijing 100044, China
Code No.M389

Mail-Order

Editorial Board of Chinese Journal of Reproduction and Contraception
779 Laohumin Road, Shanghai 200237, China
Tel: 0086-21-64438169
Fax: 0086-21-64438975
Email: rande@sibpt.com

CSSN

ISSN 2096-2916
CN 10-1441/R

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DOI: 10.3760/cmaj.cn101441-20211108-00495

收稿日期 2021-11-09 本文编辑 王李艳

引用本文: 引用格式: 中国女医师协会生殖医学专业委员会专家共识编写组. 辅助生殖领域拮抗剂方案标准化应用专家共识[J]. 中华生殖与避孕杂志, 2022, 42(2): 109-116. DOI: 10.3760/cmaj.cn101441-20211108-00495.

辅助生殖领域拮抗剂方案标准化应用专家共识

中国女医师协会生殖医学专业委员会专家共识编写组

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【摘要】 随着辅助生殖技术的飞速发展, 寻求高效与安全并重的促排卵方案是辅助生殖医生的不断追求。目前, 拮抗剂方案因其诸多优势而受到临床医生的青睐。为促进拮抗剂方案的标准化应用, 本共识全面综述了拮抗剂方案使用节点, 讨论和解决在拮抗剂的应用上存在的主要问题, 为临床医师拮抗剂方案的应用提供指导和建议。

【关键词】 生殖技术, 辅助; 受精, 体外; 单精子显微注射, 卵胞质内; 促排卵; 促性腺激素释放激素拮抗剂

基金项目: 国家重点研发计划 (2016YFC1000302); 北京市科技计划课题 (Z191100006619085)

Expert consensus on standardized application of antagonist protocol in assisted reproductive technology

Expert Consensus Compilation Group of Reproductive Medicine Committee of China Medical Women's Association

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【Abstract】 With the rapid development of assisted reproductive technology, it is the continuous pursuit of assisted reproductive doctors to seek an ovarian stimulation protocol with equal emphasis on efficiency and safety. At present, the antagonist protocol is favored by clinicians because of its many advantages. In order to promote the standardized application of the antagonist protocol, this consensus provides a comprehensive overview of use nodes of the antagonist protocol, discuss and solve the main problems in the application of antagonists, provide guidance and suggestions for clinicians in the use of antagonist protocol.

【Key words】 Reproductive technology, assisted; Fertilization *in vitro*; Sperm injection, intracytoplasmic; Ovarian stimulation; Gonadotropin-releasing hormone antagonist

Fund program: National Key Research and Development Program (2016YFC1000302); Beijing Municipal Science & Technology Commission (Z191100006619085)

DOI: 10.3760/cmaj.cn101441-20200908-00488

收稿日期 2020-10-25 责任编辑 李天琦

引用本文: 张俊韦, 杜明泽, 孙丽君, 等. 三种促排卵方案在波塞冬低预后患者中的累积活产率分析[J]. 中华生殖与避孕杂志, 2022, 42(2): 117-124. DOI: 10.3760/cmaj.cn101441-20200908-00488.

·临床研究·

三种促排卵方案在波塞冬低预后患者中的累积活产率分析

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【摘要】 目的 比较拮抗剂方案、甲羟孕酮(medroxyprogesterone, MPA)方案和克罗米芬(clomiphene citrate, CC)方案在卵巢储备功能下降的低预后人群中的累积活产率(cumulative live birth rate, CLBR)。方法 采用回顾性队列研究, 纳入2015年1月至2018年5月期间在郑州大学第三附属医院生殖医学中心行体外受精(*in vitro* fertilization, IVF)或卵胞质内单精子注射(intracytoplasmic sperm injection, ICSI)助孕的患者, 按波塞冬(POSEIDON)标准分组, 纳入POSEIDON 3组人群和4组人群, 促排卵采用拮抗剂方案、MPA方案或CC方案。分析三种促排卵方案的基础数据和临床结局, 主要观察指标为CLBR, 以拮抗剂组为参照, 计算MPA组和CC组校正后比值比(adjusted odds ratio, aOR)及95%置信区间(confidence interval, CI)。结果 波塞冬3组人群中, 三种促排卵方案的CLBR差异无统计学意义($P>0.05$)。经逻辑回归分析, 促排卵方案并不影响POSEIDON 3组人群的CLBR($P=0.226$, $P=0.468$)。在POSEIDON 4组人群中, MPA组的CLBR高于CC方案组(10.7%比5.4%, $P=0.002$), 采用二元逻辑回归, 以拮抗剂为对照, MPA方案的CLBR高于拮抗剂方案(aOR=2.22, 95% CI=1.17~4.24, $P=0.021$), 而CC方案的CLBR与拮抗剂差异无统计学意义(aOR=0.95, 95% CI=0.48~1.85, $P=0.868$)。结论 对于35岁以下、卵巢储备功能低下的患者, 三种促排卵方案的临床结局相似。对于年龄 ≥ 35 岁、卵巢储备功能低下的患者, MPA方案的CLBR更高。

【关键词】 波塞冬标准; 低预后; 受精, 体外; 胚胎移植; 累积活产率

基金项目：2021 年度河南省医学科技攻关联合共建项目（LHGJ20210451）

Analysis of cumulative live birth rate of three controlled ovarian hyperstimulation protocols in POSEIDON patients with low prognosis

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【Abstract】 Objective To compare the cumulative live birth rate (CLBR) of gonadotropin-releasing hormone (GnRH) antagonist protocol, medroxyprogesterone (MPA) protocol and clomiphene citrate (CC) protocol in low prognosis population with decreased ovarian reserve. **Methods** It was a retrospective cohort study. Patients who underwent *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University from January 2015 to May 2018 were recruited. Including POSEIDON group 3 and group 4, GnRH-antagonist protocol, MPA, and CC protocol were used for ovulation stimulation. The basic data and clinical outcomes of the three protocols were analyzed. The main outcome measure was CLBR. With the GnRH-antagonist group as the reference, the adjusted odds ratio (aOR) and 95% confidence interval (CI) of the MPA group and the CC group were calculated. **Results** In the POSEIDON group 3, the CLBR of the three protocols was not statistically different. After logistic regression analysis, the ovulation stimulation protocols did not affect the CLBR of POSEIDON 3 group ($P=0.226$, $P=0.468$). In the POSEIDON group 4, the CLBR of the MPA group was higher than that of the CC group (10.7% vs. 5.4%, $P=0.002$). Using binary logistic regression and GnRH-antagonist group as the control, the CLBR of the MPA protocol was higher (aOR=2.22, 95% CI=1.17–4.24, $P=0.021$), the CLBR of the CC protocol was not significantly different from the GnRH-antagonist group (aOR=0.95, 95% CI=0.48–1.85, $P=0.868$). **Conclusion** For patients under 35 years old with low ovarian reserve, the clinical outcomes of the three ovulation stimulation protocols were similar. For patients who are 35 years or older with low ovarian reserve, the CLBR of the MPA protocol was higher.

【Key words】 POSEIDON criteria; Low prognosis; Fertilization *in vitro*; Embryo transfer; Cumulative live birth rate

Fund program: 2021 Henan Province Medical Science and Technology Research and Joint Construction Project (LHGJ20210451)

DOI: 10.3760/cma.j.cn101441-20210426-00192

收稿日期 2021-04-30 本文编辑 宋培培

引用本文：栾康, 姜宏, 殷慧群, 等. 拮抗剂方案单胚胎移植临床结局分析[J]. 中华生殖与避孕杂志, 2022, 42(2): 125-131. DOI: 10.3760/cma.j.cn101441-20210426-00192.

拮抗剂方案单胚胎移植临床结局分析

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【摘要】 目的 探讨拮抗剂方案单胚胎移植的临床应用价值。方法 回顾性队列研究分析 2017 年 1 月至 2021 年 3 月期间在中国人民解放军联勤保障部队第 901 医院生殖医学中心行拮抗剂方案体外受精/卵胞质内单精子注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 助孕患者的临床资料, 根据胚胎发育时间和移植胚胎数分为第 3 日 (day 3, D3) 单优质卵裂胚移植组 (单优组), D3 双优质卵裂胚移植组 (双优组) 和单囊胚移植组 (单囊胚组)。其中新鲜周期单优组 301 个周期、双优组 253 个周期、单囊胚组 127 个周期; 冻融胚胎移植 (frozen-thawed embryo transfer, FET) 周期单优组 84 个周期、双优组 136 个周期、单囊胚组 396 个周期; 全胚冷冻首次 FET 单优组 69 个周期、单囊胚组 161 个周期。采用单因素方差分析及卡方检验比较新鲜和 FET 周期单优组、双优组、单囊胚组及首次 FET 周期单优组与单囊胚组的临床妊娠率、种植率、多胎妊娠率、早期流产率、持续妊娠率。结果 各组不孕年限、体质量指数 (body mass index, BMI)、基础卵泡刺激素 (follicle-stimulating hormone, FSH)、基础黄体生成素 (luteinizing hormone, LH)、基础雌二醇、抗苗勒管激素 (anti-Müllerian hormone, AMH)、促性腺激素 (gonadotropin, Gn) 用量、获卵数差异均无统计学意义 (均 $P>0.05$)。新鲜周期中单优组的临床妊娠率、种植率、多胎妊娠率、早期流产率、持续妊娠率与新鲜周期单囊胚组比较差异均无统计学意义 (均 $P>0.05$)。临床妊娠率 [46.18% (139/301)]、持续妊娠率 [40.86% (123/301)]、多胎妊娠率 [0% (0/139)] 显著低于双优组 [58.89% (149/253), $P<0.001$; 52.17% (132/253), $P<0.001$; 30.20% (45/149), $P<0.001$]。种植率与双优组比较差异无统计学意义 ($P>0.0167$)。FET 中单优组的临床妊娠率、种植率、持续妊娠率与双优组比较差异均无统计学意义 (均 $P>0.0167$)。但均显著低于单囊胚组 [62.88% (249/396), $P<0.001$; 63.89% (253/396), $P<0.001$; 55.30% (219/396), $P<0.001$]。多胎妊娠率 [0% (0/27)] 则显著低于双优组 [20.37% (11/54), $P=0.013$]。首次 FET 单优组的持续妊娠率 [27.54% (19/69)] 显著低于新鲜周期单优组 [40.86% (123/301), $P=0.040$]。首次 FET 单囊胚组的临床妊娠率 [63.35% (102/161)]、种植率 [63.98% (103/161)] 显著高于新鲜周期单囊胚组 [50.39% (64/127), $P=0.027$; 51.97% (66/127), $P=0.040$]。结论 拮抗剂方案单胚胎移植能显著降低多胎妊娠率;

新鲜周期移植 D3 单优质卵裂胚可获得与 D5 单囊胚相似的临床结局，而 FET 周期移植单囊胚能获得更好的临床结局。

【关键词】 拮抗剂方案； 单囊胚移植； 单卵裂胚移植； 临床结局

基金项目：安徽省科技攻关计划项目（1604a0802095）

Clinical outcomes of single embryo transfer in gonadotropin-releasing hormone antagonist protocol

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【Abstract】 Objective To investigate the clinical value of single embryo transfer for the patients with gonadotropin-releasing hormone (GnRH) antagonist protocol. **Methods** The clinical data of the patients underwent *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) in Reproductive Medicine Center, the 901th Hospital of the Joint Logistics Support Force of PLA from January 2017 to March 2021 were retrospectively analyzed in this cohort study. According to the days of embryo development and No. of embryos, patients were divided into day 3 (D3) single top-quality cleavage-stage embryo transfer group (single top-quality embryo group), D3 double top-quality cleavage-stage embryo transfer group (double top-quality embryos group), and single blastocyst transfer group. In fresh cycles, there were 301 patients in single top-quality embryo group, 253 patients in double top-quality embryos group and 127 patients in single blastocyst group in frozen-thawed embryo transfer (FET) cycles, there were 84 patients in single top-quality embryo group, 136 patients in double top-quality embryos group and 396 patients in single blastocyst group in first FET cycles after all embryos frozen, there were 69 patients in single top-quality group and 161 patients in single blastocyst group. The rates of clinical pregnancy, implantation, multiple pregnancy, early abortion and ongoing pregnancy in the fresh and FET cycles were compared among single top-quality embryo group, double top-quality embryos group and single blastocyst group. Also, the rates of clinical pregnancy, implantation, multiple pregnancy, early abortion and ongoing pregnancy of single top-quality embryo transfer and single blastocyst transfer were compared between the fresh cycle and the first FET cycle. One-way ANOVA and chi-square test were used in this study. **Results** There were no significant difference in duration of infertility, body mass index (BMI), the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, anti-Müllerian hormone (AMH), gonadotropin (Gn) and the numbers of oocytes retrieved among all the groups (all $P>0.05$). There were no significant differences in the rates of clinical pregnancy, implantation, multiple pregnancy, early abortion and ongoing pregnancy between single top-quality embryo group and single blastocyst group (all $P>0.05$) in fresh cycle, while the clinical pregnancy rate [46.18% (139/301)], the ongoing pregnancy rate [40.86% (123/301)] and the multiple pregnancy rate [0% (0/139)] in single top-quality embryo group were

significantly lower than those in double top-quality embryos group [58.89% (149/253), $P<0.001$; 52.17% (132/253), $P<0.001$; 30.20% (45/149), $P<0.001$], with the similar implantation rate between the two groups ($P>0.0167$). The rates of clinical pregnancy, implantation and ongoing pregnancy were comparable between single top-quality embryo group and double top-quality embryos group in FET cycle ($P>0.0167$), while which were all significantly lower than those in single blastocyst group [62.88% (249/396), $P<0.001$; 63.89% (253/396), $P<0.001$; 55.30% (219/396), $P<0.001$]. The multiple pregnancy rate of double top-quality embryos group [20.37% (11/54)] was significantly higher than that of single top-quality embryo group [0% (0/27), $P=0.013$] in FET cycle. The ongoing pregnancy rate of the single top-quality embryo transfer in first FET cycle [27.54% (19/69)] was significantly lower than that in fresh cycle [40.86% (123/301), $P=0.040$], while the clinical pregnancy rate [63.35% (102/161)] and the implantation rate [63.98% (103/161)] of single blastocyst transfer in first FET cycle were significantly higher than those in fresh cycle [50.39% (64/127), $P=0.027$; 51.97% (66/127), $P=0.040$].

Conclusion The clinical outcomes of D3 single top-quality cleavage-stage embryo transfer were similar to D5 single blastocyst transfer in fresh cycle, while the clinical outcomes of single blastocyst transfer in FET cycle were better compared with fresh cycle for the patients with GnRH antagonist protocol. Single embryo transfer can significantly reduce the multiple pregnancy rate of IVF/ICSI.

【 Key words 】 Antagonist protocol; Single blastocyst transfer; Single cleavage-stage embryo transfer; Clinical outcomes

Fund program: Anhui Provincial Science and Technology Breakthrough Plan (1604a0802095)

DOI: 10.3760/cmaj.cn101441-20200602-00325

收稿日期 2020-06-05 本文编辑 王李艳

引用本文: 张少娣, 尹轶莎, 李秋圆, 等. 冻融周期薄型子宫内膜移植胚胎类型对临床结局的影响[J]. 中华生殖与避孕杂志, 2022, 42(2): 132-141. DOI: 10.3760/cmaj.cn101441-20200602-00325.

·临床研究·

冻融周期薄型子宫内膜移植胚胎类型对临床结局的影响

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【摘要】 目的 探讨可以改善薄型子宫内膜患者助孕结局的胚胎移植策略。方法 采用回顾性队列研究分析 2013 年 1 月至 2019 年 12 月期间于河南省人民医院生殖医学中心行冻融胚胎移植的 1924 例薄型子宫内膜患者共 2452 个周期的临床资料。根据移植胚胎的类型分为移植卵裂期胚胎（卵裂胚组）和移植囊胚期胚胎（囊胚组），通过单因素分析、多因素 logistic 回归分析及曲线拟合对比卵裂胚和囊胚周期的临床结局。结果 卵裂胚组移植 2 枚胚胎周期占比 [87.17% (1298/1489)]、异位妊娠率 [3.35% (16/477)] 及多胎分娩率 [23.32% (73/313)] 高于囊胚组 [40.71% (392/963), $P<0.001$; 0.76% (4/524), $P=0.003$; 16.27% (55/338), $P=0.024$]; 囊胚组临床妊娠率 [54.41% (524/963)] 及活产率 [35.10% (338/963)] 显著高于卵裂胚组 [32.03% (477/1489), $P<0.001$; 21.02% (313/1489), $P<0.001$]; 多因素 logistic 回归分析结果显示，调整混杂因素对临床结局的影响后，囊胚组的临床妊娠率 ($OR=3.42$, 95% $CI=2.71\sim4.31$, $P<0.001$) 及活产率 ($OR=2.35$, 95% $CI=1.84\sim3.00$, $P<0.001$) 高于卵裂胚组；分层分析结果显示，不同内膜厚度分层中囊胚组的临床妊娠率 (<6 mm: $OR=2.94$, 95% $CI=1.32\sim6.51$, $P=0.008$; $6\sim7$ mm: $OR=3.41$, 95% $CI=2.13\sim5.45$, $P<0.001$; >7 mm: $OR=3.56$, 95% $CI=2.67\sim4.74$, $P<0.001$) 和活产率 (<6 mm: $OR=2.50$, 95% $CI=1.01\sim6.22$, $P=0.049$; $6\sim7$ mm: $OR=2.56$, 95% $CI=1.56\sim4.21$, $P<0.001$; >7 mm: $OR=2.30$, 95% $CI=1.71\sim3.10$, $P<0.001$) 均高于卵裂胚组。分层曲线拟合分析结果显示，两组的临床妊娠率和活产率均随子宫内膜厚度的增加而增加，任一子宫内膜厚度下囊胚组的临床妊娠率与活产率均高于卵裂胚组，且与囊胚组相比，卵裂胚组内膜厚度与临床妊娠率曲线拟合的斜率更大。结论 薄型子宫内膜患者冻融胚胎移植周期中囊胚移植周期的临床妊娠率和活产率均高于卵裂胚移植周期。孕酮转化日子宫内膜厚度的增加可以改善薄型子宫内膜患者的临床妊娠率和活产率。

【关键词】 激素替代； 冻融胚胎移植； 子宫内膜厚度； 临床妊娠率； 活产率

Effect of the types of transferred embryo on clinical outcomes of frozen-thawed embryo transfer among patients with thin endometrium

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【Abstract】 **Objective** To explore the clinical strategies to improve the clinical outcomes of patients with thin endometrium. **Methods** A retrospective cohort study was conducted to analyze 1924 frozen-thawed embryo transfer (FET) cycles of 2452 patients with thin endometrium at the Reproductive Medicine Center of Henan Provincial People's Hospital from January 2013 to December 2019. According to the type of embryos transferred, they were divided into the embryo

group at cleavage stage (cleavage embryo group) and embryo group at blastocyst stage (blastocyst group). Univariate analysis, multivariate regression analysis, curve fitting and threshold effect analysis were used to compare the clinical outcomes of the cycles transferring cleavage stage embryo and blastocyst. **Results** The percentage of cycles with two embryos transferred [87.17% (1298/1489)], the rate of ectopic pregnancy [3.35% (16/477)] and the rate of multiple births [23.32% (73/313)] in cleavage embryo transfer cycle were higher than those of blastocyst transfer cycle [40.71% (392/963), $P<0.001$; 0.76% (4/524), $P=0.003$; 16.27% (55/338), $P=0.024$]. The clinical pregnancy rate [54.41% (524/963)] and the live birth rate [35.10% (338/963)] in blastocyst transfer cycle were significantly higher than those of cleavage embryo transfer cycle [32.03% (477/1489), $P<0.001$; 21.02% (313/1489), $P<0.001$]. After adjusting for confounders, the clinical pregnancy rate ($OR=3.42$, 95% $CI=2.71-4.31$, $P<0.001$) and the live birth rate ($OR=2.35$, 95% $CI=1.84-3.00$, $P<0.001$) of blastocyst transfer cycle were higher than those of cleavage stage embryo transfer cycle. The results of stratified analysis showed that the clinical pregnancy rate (<6 mm: $OR=2.94$, 95% $CI=1.32-6.51$, $P=0.008$; 6-7 mm: $OR=3.41$; 95% $CI=2.13-5.45$, $P<0.001$; >7 mm: $OR=3.56$, 95% $CI=2.67-4.74$, $P<0.001$) and the live birth rate (<6 mm: $OR=2.50$, 95% $CI=1.01-6.22$, $P=0.049$; 6-7 mm: $OR=2.56$, 95% $CI=1.56-4.21$, $P<0.001$; >7 mm: $OR=2.30$, 95% $CI=1.71-3.10$, $P<0.001$) of blastocyst transfer cycle in different endometrial thickness stratifications were higher than those of cleavage stage embryo transfer cycle. The results of stratified curve fitting analysis showed that with increasing endometrial thickness among patients with thin endometrium, the clinical pregnancy rate and the live birth rate of both cleavage stage embryo cycle and blastocyst transfer cycle increased, and in all of the different endometrial thickness stratifications, the clinical pregnancy rate and the live birth rate in blastocyst transfer cycle were higher than those of cleavage embryo transfer cycle. Compared with the blastocyst transfer cycle, the slope of curve fitting between endometrial thickness and clinical pregnancy rate was larger in cleavage embryo transfer cycle. **Conclusion** The clinical pregnancy rate and the live birth rate of the blastocyst transfer cycle in FET were higher than those of cleavage stage embryo transfer cycle. The increasement of endometrial thickness on the first day of progesterone administration can improve the clinical pregnancy rate and the live birth rate in patients with thin endometrium.

【Key words】 Hormone replacement; Frozen-thawed embryo transfer; Endometrial thickness; Clinical pregnancy rate; Live birth rate

DOI: 10.3760/cmaj.cn101441-20200715-00395

收稿日期 2020-07-17 本文编辑 王李艳

引用本文: 夏雷震, 伍琼芳, 赵琰, 等. 行体外受精-胚胎移植助孕的多囊卵巢综合征患者发生流产的相关因素分析[J]. 中华生殖与避孕杂志, 2022, 42(2): 142-149. DOI: 10.3760/cmaj.cn101441-20200715-00395.

·临床研究·

行体外受精-胚胎移植助孕的多囊卵巢综合征患者发生流产的相关因素分析

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【摘要】 目的 比较多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 患者与非 PCOS 患者行体外受精/卵胞质内单精子显微注射-胚胎移植 (*in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer, IVF/ICSI-ET) 助孕的流产率并分析其影响因素。方法 回顾性队列研究分析 2014 年 1 月至 2019 年 6 月期间于江西省妇幼保健院辅助生殖中心行 IVF/ICSI-ET 助孕后获临床妊娠的 3556 例患者, 其中 PCOS 患者 889 例 (PCOS 组), 单纯输卵管因素不孕患者 2667 例 (对照组)。比较两组妊娠后临床结局, 并通过单/多因素 logistic 回归分析流产的影响因素, 最后按照单/双胎妊娠、体质量指数 (body mass index, BMI) 进行亚组分析。结果 PCOS 组流产率 [11.81% (105/889)]、晚期流产率 [5.29% (47/889)] 显著高于对照组 [9.19% (245/2667), $P=0.023$; 3.64% (97/2667), $P=0.031$]。单因素 logistic 回归显示 PCOS、双胎妊娠、高 BMI、不孕年限延长是流产的风险因素。多因素 logistics 回归显示影响流产率的主要风险因素是双胎妊娠、PCOS 以及两者的交互作用。亚组分析显示单胎妊娠时两组患者早期、晚期流产率没有区别; 双胎妊娠时 PCOS 组患者早期流产率差异无统计学意义, 晚期流产率 [8.58% (29/338)] 显著高于对照组 [3.11% (37/1188), $P<0.001$]。结论 行 IVF/ICSI-ET 助孕的 PCOS 患者单胎妊娠时流产率与单纯输卵管因素不孕患者相似, 双胎妊娠时早期流产率与单纯输卵管因素不孕患者相似而晚期流产率显著增加。

【关键词】 多囊卵巢综合征; 受精, 体外; 单精子注射, 卵胞质内; 流产, 自然; 双胎妊娠; 交互作用

Analysis of related factors of abortion in patients with polycystic ovary syndrome treated by *in vitro* fertilization and embryo transfer

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【Abstract】 Objective To explore the risk factors of abortion and their interactions in patients with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET). **Methods** A total of 3556 pregnant women who underwent IVF/ICSI-ET in Jiangxi Maternal and Child Health Hospital from January 2014 to June 2019 were analyzed, among which 889 women were diagnosed with PCOS (PCOS group) and 2667 women were diagnosed with infertility due to simple tube factors (control group). The clinical outcomes after pregnancy were compared between the two groups. Single and multiple logistic regression were used to find the influencing factors of abortion. Finally, subgroup analysis was conducted according to single/twin pregnancy and body mass index (BMI). **Results** The abortion rate [11.81% (105/889)] and the late abortion rate [5.29% (47/889)] in PCOS group were significantly higher than those in control group [9.19% (245/2667), $P=0.023$; 3.64% (97/2667), $P=0.031$]. Univariate logistic regression showed that PCOS, twin pregnancy, high BMI, long duration of infertility were the risk factors of abortion. Multivariate logistics regression showed that the main risk factors affecting abortion rate were twin pregnancy, PCOS, and the interaction between the two factors. Subgroup analysis found that there were no differences in the early and late abortion rates between the two groups when women were singleton pregnancy. When women were twin pregnancy, the rate of early abortion was similar between the two groups, while the late abortion rate [8.58% (29/338)] in PCOS group was significantly higher than that in control group [3.11% (37/1188), $P<0.001$]. **Conclusion** The rate of abortion is similar for PCOS women and simple tube factor infertility women when they were singleton pregnancy after IVF/ICSI-ET treatment. PCOS women have a similar rate of early abortion and higher rate of late abortion than simple tube factor infertility women when they were twin pregnancy.

【Key words】 Polycystic ovary syndrome; Fertilization *in vitro*; Sperm injection, intracytoplasmic; Abortion, spontaneous; Twin pregnancy; Interaction

DOI: 10.3760/cma.j.cn101441-20200724-00413

收稿日期 2020-07-28 责任编辑 宋培培

引用本文: 张多多, 甄璟然, 郁琦. 泌乳素血清基础水平及卵巢刺激后增幅对长方案 IVF/ICSI 助孕结局的影响[J]. 中华生殖与避孕杂志, 2022, 42(2): 150-155. DOI: 10.3760/cma.j.cn101441-20200724-00413.

·临床研究·

泌乳素血清基础水平及卵巢刺激后 增幅对长方案 IVF/ICSI 助孕结局的 影响

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【摘要】 目的 探讨外源性促性腺激素促排卵过程中, 血清泌乳素水平高低对体外受精/卵胞质内单精子注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 助孕结局的影响。方法 采用回顾性队列研究, 分析 2014 年 7 月 1 日至 2018 年 3 月 31 日期间在北京协和医院妇科内分泌与生殖中心因输卵管或男方因素行 IVF/ICSI 治疗的 3009 例患者的临床资料。根据纳入患者的基础泌乳素水平的中位值 (16.05 $\mu\text{g/L}$) 进行分组后, 比较患者的辅助生殖结局, 并且根据不同的基础泌乳素水平进行多因素亚组分析。采用重复测量的方差分析方法分析促排卵过程中不同时间点泌乳素的生长趋势与对应周期累积妊娠结局的关系。结果 基础泌乳素水平 $>16.05 \mu\text{g/L}$ 的患者比 $\leq 16.05 \mu\text{g/L}$ 患者有更多的获卵数 [9 (5, 12) 枚比 8 (5, 11) 枚, $P=0.013$] 及胚胎数 [6 (3, 10) 枚比 5 (3, 9) 枚, $P=0.015$]。基础泌乳素 $>30 \mu\text{g/L}$ 有利于累积妊娠 ($OR=1.281$, 95% $CI=1.030\sim 1.764$, $P=0.046$), 而 $>40 \mu\text{g/L}$ 有利于累积活产 ($OR=1.916$, 95% $CI=1.115\sim 3.290$, $P=0.008$)。结论 对于长方案促排卵的 IVF/ICSI 人群, 更高的泌乳素水平与更好的累积妊娠或活产结局相关。

【关键词】 泌乳素; 受精, 体外; 单精子注射, 细胞质内; 临床妊娠率; 活产率

Effects of serum prolactin levels at basal and stimulated status on outcomes of patients undergoing *in vitro* fertilization/intracytoplasmic sperm injection in gonadotropin agonist long protocol

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【Abstract】 Objective To determine whether basal prolactin levels impact pregnancy outcomes of the patients who underwent *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) procedures rely on endogenous gonadotropin. **Methods** This retrospective cohort study finally included 3009 patients from July 1st, 2014 to March 31st, 2018 receiving IVF/ICSI cycles owing to tubal or male factors in Center for Gynecological Endocrinology & Reproductive Medicine, Peking Union Medical College Hospital. We compared assisted reproductive outcomes among patients according to their median prolactin levels (16.05 $\mu\text{g/L}$). Subgroup analyses divided by different prolactin levels were done through multifactor analyses. A repeated analysis of variance was used to illustrate the relationship between the scale of prolactin grows while stimulating and

cumulative pregnancy outcomes. **Results** There were more number of oocytes retrieved [9 (5,12)] and embryos [6 (3,10)] in those with basal prolactin above the median level ($>16.05 \mu\text{g/L}$) compared with patients with basal prolactin $\leq 16.05 \mu\text{g/L}$ [8(5, 11), $P=0.013$; 5(3, 9), $P=0.015$]. Prolactin beyond $30 \mu\text{g/L}$ was beneficial to cumulative clinical pregnancy ($OR=1.281$, 95% $CI=1.030-1.764$, $P=0.046$) and prolactin above $40 \mu\text{g/L}$ was a good indication for cumulative live birth rate ($OR=1.916$, 95% $CI=1.115-3.290$, $P=0.008$). **Conclusion** For patients receiving IVF/ICSI treatment in an agonist long protocol, a higher prolactin level during controlled ovarian stimulation is positively associated with cumulative pregnancy/live birth rates.

【 Key words 】 Prolactin; Fertilization *in vitro*; Sperm injection, intracytoplasmic; Clinical pregnancy rate; Live birth rate

DOI:10.3760/cmaj.cn101441-20200707-00382

收稿日期 2020-07-10 本文编辑 宋培培

引用本文: 李华萍, 邬思雨, 王永年, 等. AMH 对绝经前乳腺癌患者卵巢抑制治疗中卵巢功能的评价作用: 一项队列研究[J]. 中华生殖与避孕杂志, 2022, 42(2): 156-164. DOI: 10.3760/cmaj.cn101441-20200707-00382.

·临床研究·

AMH 对绝经前乳腺癌患者卵巢抑制治疗中卵巢功能的评价作用: 一项队列研究

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【摘要】 目的 探讨抗苗勒管激素 (anti-Müllerian hormone, AMH) 对绝经前激素受体阳性的乳腺癌患者应用不同疗程的卵巢功能抑制治疗 (ovarian function suppression, OFS) 时卵巢功能的评价作用。方法 本研究为双向队列研

究,研究的主要终点事件是 OFS 结束后月经的恢复、激素的变化。选取 2015 年 5 月至 2019 年 5 月期间在复旦大学附属肿瘤医院接受手术、化疗、OFS 治疗 24~60 个月的绝经前激素受体阳性原发性乳腺癌 67 例患者为研究对象,因失访等因素剔除 12 例,最终纳入 55 例患者。根据完成 OFS 疗程的不同分为两组,分别为 OFS 24 个月疗程组(A 组, $n=32$)、OFS 25~60 个月疗程组(B 组, $n=23$)。观察患者治疗后的月经恢复情况,检测完成 OFS 治疗后第 1、第 2、第 3 年患者 AMH、促卵泡激素(follicle-stimulating hormone, FSH)和雌激素水平。结果 两组患者随访时间为(42.0±12.3)个月, B 组有 1 例患者复发转移,余均无复发转移,至随访结束全部患者生存。两组患者的年龄、身高、体质量、体质量指数(body mass index, BMI)、月经初潮年龄、病理类型、雌激素受体(estrogen receptor, ER)和孕激素受体(progesterone receptor, PR)阳性率、人表皮生长因子受体-2(human epidermal growth factor receptor-2, HER-2)阳性率、化疗与 OFS 治疗顺序的组间比较差异均无统计学意义(均 $P>0.05$)。两组患者的孕次、产次、病理分级组间差异有统计学意义($P=0.013$, $P=0.028$, $P=0.025$)。与 B 组比, A 组月经恢复时间略长,复潮率略低,月经规律率略低,但差异均无统计学意义(均 $P>0.05$)。OFS 疗程结束后,第 2 年与第 1 年比较,AMH、FSH 的变化差异有统计学意义($P=0.003$, $P=0.004$),第 3 年与第 2 年比较,AMH、雌激素的变化差异有统计学意义($P=0.045$, $P=0.003$); OFS 疗程结束 2、3 年后 AMH 水平与结束 1 年后相比分别升高 51.5%、72.1%,其中 A 组在疗程结束的第 2、第 3 年的 AMH 水平与结束后第 1 年相比上升率分别是 71.7%、101.9%, B 组在疗程结束的第 2、第 3 年的 AMH 水平与停药后第 1 年相比上升率分别是 36.6%、53.5%; A 组的雌激素水平在 OFS 疗程结束 1、3 年后在数值上均低于 B 组($P=0.238$, $P=0.213$),疗程结束 2 年后差异有统计学意义($P=0.009$); OFS 疗程结束 2、3 年后雌激素水平与结束 1 年后相比分别下降 14.8%和升高 59.1%, A 组在疗程结束的第 2、第 3 年的雌激素水平与结束后第 1 年相比下降 29.4%和升高 67.6%, B 组在疗程结束的第 2、第 3 年的雌激素水平与结束后第 1 年相比下降 4.4%和升高 52.5%。OFS 疗程结束 2、3 年后 FSH 水平与结束 1 年后相比分别上升 44.7%、41.6%, A 组在疗程结束的第 2、第 3 年的 FSH 水平与结束后第 1 年相比上升 41.1%、44.3%, B 组在疗程结束的第 2、第 3 年的 FSH 水平与结束后第 1 年相比上升 48.6%、47.0%。结论 AMH 比雌激素、FSH 更可能成为 OFS 治疗评价卵巢功能的指标;不同疗程的 OFS 对绝经前乳腺癌患者的卵巢功能无影响,戈舍瑞林使用 24 个月比使用 25~60 个月卵巢功能恢复快;在 OFS 期间定期监测雌激素水平是必要的。

【关键词】 抗苗勒管激素; 戈舍瑞林; 乳腺肿瘤; 卵巢功能抑制

基金项目:上海市浦东新区学科带头人培养项目(PWRd2016-15);上海市卫计委面上项目(201740291);上海市浦东新区科学技术委员会民生科研专项基金(PKJ2021-Y30)

Anti-Müllerian hormone as a new marker of the individualized ovarian function suppression treatment for premenopausal breast cancer patients: a cohort study

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【Abstract】 Objective To investigate the role of anti-Müllerian hormone (AMH) on the ovarian function evaluation in premenopausal breast cancer patients with hormone receptor positive after different courses of ovarian function suppression (OFS) treatment. **Methods** This study was a two-way cohort study. The main endpoints of the study were menstrual recovery and hormone changes after OFS treatment. Totally sixty-seven premenopausal breast cancer patients were enrolled, whose estrogen receptor (ER) and progesterone receptor (PR) had been tested positive from May 2015 to May 2019, and who had undergone operations, chemotherapies and OFS treatments for 24–60 months in Fudan University Shanghai Cancer Center. Twelve cases were eliminated because of missing tracking. The enrolled cases were divided into 2 groups according to OFS treatment, group A was treated with goserelin for 24 months ($n=32$), and group B, with goserelin for 25–60 months ($n=23$). Following the OFS treatment, the time points of menstrual recovery were observed and the serum levels of AMH, follicle-stimulating hormone (FSH) and estrogen (E_2) levels were measured in the two groups. **Results** The follow-up period of the two groups was (42.0 ± 12.3) months. All the patients survived their follow-ups, except one who developed recurrence and metastasis in the 25–60 month course of OFS. No significant differences were observed in age, height, weight, body mass index (BMI), menarche age, pathological type, pathological grade, ER, PR positive rate, human epidermal growth factor receptor-2 (HER-2) positive rate, sequence of chemotherapy and OFS treatment between the two groups (all $P>0.05$). The time of menstruation recovery was longer in group A than in group B, the menstruation recovery rate became lower, and the regular rate of menstruation became lower, but there was no significant difference (all $P>0.05$). After the completion of OFS treatment, the change of AMH and FSH levels in the second year was significantly different from that in the first year ($P=0.003$, $P=0.004$), and the change of AMH and E_2 levels was statistically different between the third year and the second year ($P=0.045$, $P=0.003$). Compared with group B, the serum AMH levels of group A showed decrease after 1, 2 and 3 years, respectively [(0.53 ± 0.15) $\mu\text{g/L}$ vs. (1.01 ± 0.4) $\mu\text{g/L}$; (0.91 ± 0.25) $\mu\text{g/L}$ vs. (1.38 ± 0.57) $\mu\text{g/L}$; (1.07 ± 0.23) $\mu\text{g/L}$ vs. (1.55 ± 0.64) $\mu\text{g/L}$]. Compared with the 1-year serum AMH levels, those of 2-year and 3-year increased 51.5% and 72.1%, respectively. In group A, the serum AMH levels increased 71.7% and 101.9%, respectively, after 2 and 3 years. In group B, the serum AMH levels increased 36.6% and 53.5%, respectively, after 2 and 3 years. The serum E_2 , FSH levels were higher or lower in group A than in group B after 1, 2, 3 years, showing no significant difference ($P>0.05$). Additionally, the differences in serum E_2 levels were statistically significant after 2 years of OFS treatment ($U=520.51$, $P=0.009$). Compared with the 1-year serum E_2 levels, those of 2-year and

3-year decreased 14.8% and increased 59.1%, respectively. In group A, the serum E₂ levels decreased 29.4% and increased 67.6%, respectively, after 2 and 3 years. In group B, the serum E₂ levels decreased 4.4% and increased 52.5%, respectively, after 2 and 3 years. Compared with the 1-year serum FSH levels, those of 2-year and 3-year increased 44.7%, 41.6%, respectively. In group A, the serum FSH levels increased 41.1%, 44.3%, respectively, after 2 and 3 years. In group B, the serum FSH levels increased 48.6%, 47.0%, respectively, after 2 and 3 years. **Conclusion** Compared with E₂ and FSH, AMH is more likely to be a used clinically to evaluate the ovarian reserve of breast cancer patients. There is no statistical difference in different OFS courses on the ovarian function of premenstrual breast cancer patients. The ovarian function of patients with the short OFS courses could recover more quickly than those with the long OFS courses. It was necessary to monitor the E₂ levels regularly during OFS treatment.

【 Key words 】 Anti-Müllerian hormone; Goserelin; Breast Neoplasms; Ovarian function suppression

Fund program: Medical Leaders Training Program of Health Bureau of Shanghai Pudong in China (PWRd 2016-15); Health Bureau of Shanghai in China (201740291); Special Fund for People's Livelihood Scientific Research of Science and Technology Committee of Shanghai Pudong New Area(PKJ2021-Y30)

DOI: 10.3760/cmaj.cn101441-20201028-00586

收稿日期 2020-11-03 本文编辑 王李艳

引用本文: 童婧, 宋晓雯, 万安然, 等. 非嵌合型克氏综合征患者通过显微取精获得精子后助孕策略的选择[J]. 中华生殖与避孕杂志, 2022, 42(2): 165-169. DOI: 10.3760/cmaj.cn101441-20201028-00586.

·临床报道·

非嵌合型克氏综合征患者通过显微取精获得精子后助孕策略的选择

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【摘要】 目的 观察非嵌合型克氏综合征(Klinefelter syndrome, KS)夫妇接受冷冻复苏的睾丸显微取精(micro-dissection testicular sperm extraction, micro-TESE)获得的精子进行基于二代测序(next-generation sequencing, NGS)

胚胎植入前遗传学检测 (preimplantation genetic testing, PGT) 的临床效果, 探讨非嵌合型 KS 夫妇最合适的辅助生育助孕方式。方法 回顾性病例系列研究了 2018 年 1 月至 2020 年 12 月期间在上海交通大学医学院附属仁济医院生殖医学中心就诊的 22 对非嵌合型 KS 夫妇所完成的 26 个 PGT 周期的临床资料。在女方进行卵巢刺激前, 所有非嵌合型 KS 患者都进行 micro-TESE 获得精子并冷冻保存。采用 NGS 进行胚胎检测。结果 总共对 55 枚胚胎进行了胚胎活检和 PGT, 其中 33 枚 (60.0%) 被检测为整倍体, 10 枚 (18.2%) 非整倍体和 12 枚 (21.8%) 嵌合体胚。同时, 非整倍体和嵌合体胚胎均未涉及性染色体异常。最终 14 对夫妇获得整倍体胚胎并完成了冻融胚胎移植。目前已有 11 对夫妇获得临床妊娠, 其中 6 对夫妇已经活产了 7 个健康的新生儿。结论 当非嵌合型 KS 男性通过 micro-TESE 获得精子后可以生育健康的后代。对获得的精子进行冷冻保存的策略有助于女方进行最合适的卵巢刺激。此外, 非嵌合型 KS 男性后代性染色体异常的遗传风险极低。除了采用卵胞质内单精子显微注射 (intracytoplasmic sperm injection, ICSI) 联合 PGT 助孕之外, ICSI 同样有效且更经济。ICSI 应该作为一种助孕选择提供给该类夫妇, 受孕后可以通过产前诊断明确胎儿核型。

【关键词】 非嵌合型克氏综合征; 胚胎植入前遗传学检测; 睾丸显微取精; 二代测序

Strategy for non-mosaic Klinefelter syndrome patients after obtaining sperm by micro-dissection testicular sperm extraction

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【Abstract】 **Objective** To demonstrate the clinical outcomes of patients with non-mosaic Klinefelter's syndrome (KS) who underwent preimplantation genetic testing (PGT) with frozen-thawed testicular spermatozoa. **Methods** A retrospective case series was performed in the Center for Reproductive Medicine, Renji Hospital, Shanghai Jiao Tong University School of Medicine from January, 2018 to December 2020. A total of 22 couples were included and 26 oocyte retrieval cycles were completed. Micro-dissection testicular sperm extraction (micro-TESE) was performed for sperm retrieval. Next-generation sequencing (NGS) was conducted for embryo analysis. **Results** Euploidy was detected in 33 of 55 (60.0%) embryos. Meanwhile, the numbers of aneuploid and mosaic embryos detected were 10 (18.2%) and 12 (21.8%), respectively, regardless of the lack of sex chromosome abnormality. Finally, 14 couples with euploid embryos completed frozen-thawed embryo transfer (FET). Totally eleven couples had clinical pregnancies, and 6 of them already delivered 5 healthy babies with 1 monozygotic twin. **Conclusion** For KS patients, when sperm can be obtained by micro-TESE, the cryopreservation strategy makes the ovarian stimulation procedure more favorable for female partners. The paternal genetic risk of sex chromosome abnormality to their offspring is extremely low in men with KS. Besides intracytoplasmic sperm injection (ICSI) combined with PGT,

ICSI procedure is comparable effective but more economical for non-mosaic KS couples. ICSI should be offered as an option for such couples, but monitoring by prenatal genetic diagnosis is recommended.

【Key words】 Non-mosaic Klinefelter's syndrome; Preimplantation genetic testing; Micro-dissection testicular sperm extraction; Next-generation sequencing

DOI: 10.3760/cmaj.cn101441-20200520-00296

收稿日期 2020-05-26 本文编辑 王李艳

引用本文: 叶雅丽, 艾继辉, 李豫峰, 等. 中重度宫腔粘连患者综合治疗的临床疗效分析[J]. 中华生殖与避孕杂志, 2022, 42(2): 170-176. DOI: 10.3760/cmaj.cn101441-20200520-00296.

·临床报道·

中重度宫腔粘连患者综合治疗的临床疗效分析

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【摘要】 目的 评估宫腔粘连的综合治疗对中重度宫腔粘连不孕患者的临床疗效及妊娠结局的影响。方法 回顾性队列研究分析 2017 年 5 月 1 日至 2018 年 5 月 1 日期间在华中科技大学同济医学院附属同济医院生殖医学科住院治疗的 148 例中重度宫腔粘连的不孕患者为研究对象, 根据美国生育协会 (American Fertility Association, AFS) 评分法将其分为两组: 中度组 AFS 评分 5~8 分, 共 79 例; 重度组 AFS 评分 9~12 分, 共 69 例。所有患者均运用宫腔粘连的综合治疗方法, 包括宫腔粘连分解术及术后的辅助治疗, 如雌激素、物理屏障、生物凝胶等。通过病例调查、电话以及门诊随访, 收集其术后复查的宫腔情况、月经及妊娠结局, 随访时间为术后 24~36 个月。结果 ①术后宫腔的恢复情况: 80.41% (119/148) 宫腔粘连的患者宫腔环境较前改善, 其中 79 例中度患者中, 有 65 例患者宫腔环境较前明显改善, 改善率为 82.28% (65/79); 69 例重度患者有 54 例宫腔环境明显改善, 改善率为 78.26% (54/69)。②术后宫腔 AFS 评分的变化情况: 中度宫腔粘连患者术后 AFS 评分降低 (4.10 ± 0.21) 分, 差异具有统计学意义 ($P < 0.001$); 重度宫腔粘连患者术后 AFS 评分降低 (7.12 ± 0.30) 分, 差异具有统计学意义 ($P < 0.001$)。③术后月经改善情况: 术后前 3 个月, 中度宫腔粘连患者共 72 例 (91.14%) 月经较前改善; 重度宫腔粘连患者共 57 例 (82.61%) 月经较前改善。术后 3 个月后, 中度宫腔粘连患者共 52 例 (65.82%) 月经较前改善; 重度宫腔粘连患者共 41 例

(59.42%)月经较前改善。④妊娠结局: 79例中度宫腔粘连患者中有44例妊娠, 37例活产(其中自然妊娠19例, 辅助生殖妊娠18例), 活产率为84.09%。重度宫腔粘连患者中有33例妊娠, 20例活产(其中自然妊娠15例, 辅助生殖妊娠5例), 活产率为60.61%。结论 宫腔粘连的综合治疗可明显改善中重度宫腔粘连患者的宫腔环境, 降低AFS评分, 改善月经, 提高妊娠率, 改善妊娠结局。

【关键词】 宫腔粘连; 治疗; 妊娠结局

Clinical effect analysis of comprehensive treatment for patients with moderate and severe intrauterine adhesions

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【Abstract】 Objective To evaluate the clinical effect and pregnancy outcome of infertile patients with moderate and severe intrauterine adhesions by comprehensive treatment. **Methods** Totally 148 infertile patients with moderate to severe intrauterine adhesions who were hospitalized in the Department of Reproductive Medicine of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology from May 1, 2017 to May 1, 2018 were retrospectively analyzed. They were divided into two groups based on American Fertility Association (AFS) scoring: the moderate group (79 patients) with an AFS score of 5–8 and the severe group (69 patients) with an AFS score of 9–12. All patients received comprehensive treatment for intrauterine adhesions, including intrauterine adhesion decompression and postoperative adjuvant therapy, such as estrogen, physical barrier and biogels. Through case investigation, telephone and outpatient follow-up, the postoperative review of uterine cavity, menstruation and pregnancy outcomes were collected, and the follow-up time was 24–36 months after surgery. **Results** 1) Postoperative recovery of uterine cavity: 80.41% (119 cases of 148) patients with intrauterine adhesions had improved uterine cavity environment, and 65 of 79 moderate patients had significantly improved uterine cavity environment, the improvement rate was 82.28% (65/79). The uterine environment was significantly improved in 54 cases of 69 severe patients, the improvement rate was 78.26% (54/69). 2) Changes of postoperative intrauterine AFS score: postoperative AFS score of patients with moderate intrauterine adhesions decreased (4.10 ± 0.21) points, and the difference was statistically significant ($P < 0.001$). AFS score of patients with severe intrauterine adhesions decreased (7.12 ± 0.30) points after operation, and the difference was statistically significant ($P < 0.001$). 3) Improvement of menstruation after surgery: in the first 3 months after surgery, 72 patients with moderate intrauterine adhesions (91.14%) had improved menstruation. A total of 57 patients (82.61%) with severe intrauterine adhesions had improved menstruation. Three months after surgery, 52 patients (65.82%) with moderate intrauterine adhesions had better menses than before; a total of 41

patients (59.42%) with severe intrauterine adhesions had improved menstruation.

4) Pregnancy outcome: among 79 patients with moderate intrauterine adhesions, 44 cases were pregnant, of which 37 cases delivered live births (19 cases of natural pregnancy, 18 cases of assisted reproductive pregnancy), with a live birth rate of 84.09%. There were 33 pregnancies and 20 live births (15 natural pregnancies and 5 assisted pregnancies) in the patients with severe intrauterine adhesions, with a live birth rate of 60.61%. **Conclusion** The comprehensive treatment of intrauterine adhesions can obviously improve the uterine environment of moderate and severe intrauterine adhesions, reduce AFS score, improve menstruation, increase pregnancy rate and improve pregnancy outcome.

【Key words】 Intrauterine adhesions; Treatment; Pregnancy outcomes

DOI: 10.3760/cma.j.cn101441-20200720-00402

收稿日期 2020-08-11 责任编辑 宋培培

引用本文: 冯战启, 郭梁洁, 苏俊祥, 等. 无精子症因子微缺失拓展检测方法在 2 例性染色体拷贝数异常患者中的应用价值[J]. 中华生殖与避孕杂志, 2022, 42(2): 177-182. DOI: 10.3760/cma.j.cn101441-20200720-00402.

·个案报道·

无精子症因子微缺失拓展检测方法在 2 例性染色体拷贝数异常患者中的应用价值

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冯战启与郭梁洁对本文有同等贡献

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【摘要】 目的 探讨 Y 染色体无精子症因子 (azoospermia factor, AZF) 微缺失拓展检测方法在遗传性不育和性发育异常疾病中的应用价值。方法 本研究分别运用多重聚合酶链反应 (polymerase chain reaction, PCR) 结合琼脂糖凝胶电泳方法、复合荧光多重 PCR 毛细管电泳 DNA 片段分析技术以及染色体核型分析技

术对 2020 年 3 月就诊于河南省人民医院生殖中心的 1 例不育症患者（患者 1）和 2020 年 4 月就诊于河南省人民医院内分泌科的 1 例性腺发育异常儿童（患者 2）进行检测。结果 针对 15 个序列标签位点（sequence tagged site, STS）对这 2 例患者进行检测，结果未提示 Y 染色体 AZF 微缺失；针对 27 个 STS 遗传标记进行拓展检测，结果检测提示患者 1 位于 X 染色体长臂的 STS 位点扩增峰值是 X 染色体短臂扩增峰值的近 3 倍（Xqp），X 染色体长臂的 STR 质控位点扩增峰为 2 个峰，且比值约为 2 : 1（GATA31E08 和 DXS6809），TAF9b 位点在 X 染色体长臂扩增峰值与常染色体扩增峰值的比值约为 3 : 2，该患者 X 染色体长臂可能存在拷贝数异常。患者 2，C03Yp、TAF9b、C01Yq 和 C11Xp 位点在 X 染色体或 Y 染色体的扩增峰值与常染色体扩增峰值比值约为 1 : 1，X 染色体的 STR 质控位点扩增峰为 2 个峰，且比值约为 1 : 1（GATA31E08 和 DXS6795），该患者可能存在 X 和 Y 染色体拷贝数异常；染色体核型分析显示患者 1 染色体核型为 47, XY, i (X) (q10)；患者 2 染色体核型为 48, XXYY，与 AZF 微缺失拓展检测结果相印证。结论 与传统 AZF 检测方法相比，本拓展检测方法不仅可以满足 AZF 检测需要，还可以提示性染色体拷贝数异常，较染色体核型分析技术，具有操作简捷的特点，可减低临床检验成本及工作量。

【关键词】 Y 染色体微缺失； 男性不育； 毛细管电泳； 性染色体异常

基金项目：国家自然科学基金（81501336）；国家卫生健康委员会出生缺陷预防重点实验室开放课题（ZD202006）；河南省科技攻关项目（202102310046）；医学科技攻关项目（SBGJ202003001、LHGJ20200695）

Application value of azoospermia factor microdeletion extended detection method in two special cases with abnormal sex chromosome copy numbers

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【Abstract】 **Objective** To explore the clinical application value of extended detection method for Y chromosome azoospermia factor (AZF) microdeletion in hereditary infertility and sexual development disorders. **Methods** Multiplex polymerase chain reaction (PCR) combined with agarose gel electrophoresis method, combined fluorescence multiplex PCR capillary electrophoresis DNA fragment analysis technique and chromosome karyotype

analysis technique were used to detect an infertility patient who visited the Reproductive Center of Henan Provincial People's Hospital in March 2020 (patient 1) and a child with sexual dysplasia who visited the Endocrinology Department of Henan Provincial People's Hospital in June 2020 (patient 2). **Results** We found no AZF microdeletions on the Y-chromosome of the two patients to detect 15 sequence tagged site (STS) sequences. To detect the 27 genetic markers, it was found that in patient 1 the amplification peak of the STS locus on the long arm of the X chromosome was nearly three times as much as the amplification peak of the short arm of the X chromosome (Xqp), the STR quality control loci on the long arm of the X chromosome had two peaks, and the ratio was about 2 : 1 (GATA31E08 and DXS6809), and the ratio of the amplification peak of the long arm of the X chromosome to that of the autosome at the TAF9b locus was about 3 : 2. Patient 1 might have an abnormal copy number of long arm of X chromosome. In patient 2, the ratio of the amplification peak of C03Yp, TAF9b, C01Yq and C11Xp on the X chromosome or Y chromosome to the amplification peak of autosomes was about 1 : 1, and the amplification peak of the STR quality control site on the X chromosome was two peaks, and the ratio was about 1 : 1 (GATA31E08 and DXS6795). Patient 2 might have abnormal X and Y chromosome copy numbers. The results of karyotype analysis showed that the karyotype of patient 1 was 47, XY, i(X)(q10); the karyotype of patient 2 was 48, XXYY, which was consistent with the results of AZF microdeletion extension test. **Conclusion** Compared with the traditional AZF detection method, this extended detection method can not only meet the needs of AZF detection, but also indicate abnormal copy number of sex chromosomes. Compared with the karyotype analysis technology, it has the characteristics of simple operation and can reduce the cost and workload of clinical testing.

【Key words】 Y chromosome microdeletions; Male infertility; Capillary electrophoresis; Sex chromosome abnormalities

Fund program: National Natural Science Foundation of China (81501336); Opening Foundation of National Health Commission Key Laboratory of Birth Defects Prevention (ZD202006); Science and Technology Research Project of Henan Province (202102310046); Medical Science and Technology Project (SBGJ20203001, LHGJ20200695)

DOI: 10.3760/cmaj.cn101441-20200709-00388

收稿日期 2020-07-18 本文编辑 李天琦

引用本文: 林嘉雨, 方丛, 廖建云, 等. 青春期前重度地中海贫血患者生育力保存病例 1 例并文献复习[J]. 中华生殖与避孕杂志, 2022, 42(2): 183-187. DOI: 10.3760/cmaj.cn101441-20200709-00388.

·个案报道·

青春期前重度地中海贫血患者生育力保存病例 1 例并文献复习

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【摘要】 目的 探讨青春期前重度 β -地中海贫血(thalassemia major, TM)患者进行生育力保存的方法,为青春期前血液疾病患者进行生育力保存提供进一步的数据支持。方法 对1例青春期前拟行造血干细胞移植的TM患者通过卵巢组织冷冻(ovarian tissue cryopreservation, OTC)合并卵子体外成熟(*in vitro* maturation, IVM)行生育力保存进行病例报道,结合文献阐述青春期前地中海贫血患者进行生育力保存的时机、指征及策略。结果 患者卵巢组织获取术后,体外穿刺抽吸共获取24枚卵丘-颗粒细胞复合体(cumulus-oocyte complexes, COCs)及11片卵巢组织皮片。COCs经48 h IVM后共有9枚M_{II}期卵子行玻璃化冷冻。结论 对亟待造血干细胞移植的青春期前女童,OTC结合卵母细胞IVM技术能在短期内最大程度地保存TM患者的生育力,提高其生育力保存的治疗效果。

【关键词】 β -地中海贫血; 造血干细胞移植; 生育力保存; 卵母细胞体外成熟技术; 卵巢组织冷冻

基金项目: 中山大学青年教师培训项目(19ykpy04); 国家重点研发计划(2017YFC1001600); 国家自然科学基金(81871214)

A case of fertility preservation in a prepubertal patient with thalassemia major and review of relevant literature

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【Abstract】 Objective To explore the methods of fertility preservation in prepubertal patients with thalassemia major (TM), and to provide further data support for the fertility preservation in prepubertal patients with hematologic diseases. **Methods** A case of a prepubertal patient with TM who required urgent hematopoietic stem cell transplantation (HSCT) receiving ovarian tissue cryopreservation (OTC) and *in vitro* maturation (IVM) to preserve fertility was reported, and the timing, the indications and strategies of fertility preservation in

prepubertal girls with thalassemia were discussed in combination with related literature. **Results** After ovarian tissue extraction, a total of 24 cumulus-oocyte complexes (COCs) and 11 ovarian cortex pieces were obtained through puncture and aspiration. After IVM for 48 h, a total of 9 M_{II} oocytes were frozen by vitrification. **Conclusion** For the prepubertal girls facing HSCT urgently, cryopreserving ovarian tissue in combination with retrieving immature oocytes followed by IVM can preserve the fertility of patients to the greatest extent in a short period of time, as well as improve the therapeutic effect of fertility preservation in patients.

【Key words】 Beta-thalassemia; Hematopoietic stem cell transplantation; Fertility preservation; *In vitro* oocyte maturation techniques; Ovarian tissue cryopreservation

Fund program: Young Teacher Training Program of Sun Yat-sen University (19ykpy04); National Key Research and Development Plan of China (2017YFC1001600); National Natural Science Foundation of China (81871214)

DOI: 10.3760/cmaj.cn101441-20200702-00374

收稿日期 2020-07-08 本文编辑 王李艳

引用本文: 周文青, 宫晓舒, 王莹, 等. 多囊卵巢综合征患者妊娠期并发症、妊娠结局及子代健康研究进展 [J]. 中华生殖与避孕杂志, 2022, 42(2): 188-191. DOI: 10.3760/cmaj.cn101441-20200702-00374.

·综述·

多囊卵巢综合征患者妊娠期并发症、妊娠结局及子代健康研究进展

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【摘要】 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 是最常见的一种妇科内分泌疾病, 患病率高达 6%~20%, 常表现为高雄激素、稀发排卵或无排卵等。PCOS 患者胰岛素抵抗、2 型糖尿病、超重或肥胖、血脂异常、心血管疾病等风险增高。近年来关于 PCOS 患者诊断治疗等方面取得了显著进展, PCOS 患者妊娠并发症及子代健康逐渐成为大家关注的重点。本文综述了近年来 PCOS 患者

妊娠期并发症、妊娠结局及子代远期状况的研究进展,旨在为临床诊疗策略提供有意义的参考。

【关键词】 多囊卵巢综合征; 妊娠; 并发症; 子代健康

基金项目: 国家重点研发计划项目(2021YFC2700404、2018YFC1003202)

Research progress of pregnancy complications, pregnancy outcomes and offspring health of women with polycystic ovary syndrome

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【Abstract】 Polycystic ovary syndrome (PCOS) is the most common gynecological endocrine disease, with a reported prevalence between 6% and 20%. The disease is characterized by high androgen, sparse ovulation or anovulation. It is reported that the risk of insulin resistance, type 2 diabetes, overweight or obesity, dyslipidemia, and cardiovascular disease increased in PCOS patients. In recent years, significant progress has been made in the diagnosis and treatment of PCOS patients, and pregnancy complications and offspring health in PCOS patients have gradually become the focus of attention. In this article, we reviewed the recent research progress of pregnancy complications, pregnancy outcome and long-term status of offspring in PCOS patients to provide a meaningful reference for clinical diagnosis and treatment strategies.

【Key words】 Polycystic ovary syndrome; Pregnancy; Complications; Offspring health

Fund program: National Key Research and Development Program of China (2021YFC2700404, 2018YFC1003202)

DOI: 10.3760/cmaj.cn101441-20200918-00514

收稿日期 2020-09-23 本文编辑 王李艳

引用本文: 胡玉萍, 孙小燕, 张学红. 早发性卵巢功能不全的遗传学病因研究进展[J]. 中华生殖与避孕杂志, 2022, 42(2): 192-198. DOI: 10.3760/cmaj.cn101441-20200918-00514.

·综述·

早发性卵巢功能不全的遗传学病因研究进展

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【摘要】 随着下一代测序技术及表观遗传修饰相关研究的不断发展, 早发性卵巢功能不全 (premature ovarian insufficiency, POI) 的遗传学发病机制的研究越来越深入。与 DNA 修复和减数分裂重组及细胞转录相关的基因在 POI 中被广泛鉴定, 表观遗传修饰与 POI 的相关性也逐渐被揭示, 这为 POI 的诊断、治疗提供了新的思路。本文旨在综述 POI 相关的遗传学发病机制进展, 为 POI 育龄女性的遗传咨询和 POI 治疗提供思路。

【关键词】 早发性卵巢功能不全; 下一代测序技术; 表观遗传学; 遗传学因素

基金项目: 国家自然科学基金 (81960273)

Research progress of the genetic etiology in premature ovarian insufficiency

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【Abstract】 With the development of next-generation sequencing technology and epigenetic modification, and the genetic pathogenesis of premature ovarian insufficiency (POI) has been studied more and more widely. Genes related to DNA repair, meiotic recombination and transcription have been widely identified in POI, and the correlation between epigenetic modification and POI has gradually been revealed, providing new ideas for the diagnosis and treatment of POI. This article aims to review the genetic pathogenesis and treatment progress of POI, and provide treatment basis and methods for preserving POI patients' fertility, delaying ovarian aging and improving related clinical symptoms.

【Key words】 Premature ovarian insufficiency; Next-generation sequencing technology; Epigenetics; Genetic factors

Fund program: National Natural Science Foundation (81960273)

DOI: 10.3760/cmaj.cn101441-20200624-00355

收稿日期 2020-07-06 本文编辑 王李艳

引用本文: 管凤丽, 张玉倩, 陈静, 等. 连接蛋白参与胚胎植入与子宫内膜蜕膜化作用机制的研究进展[J]. 中华生殖与避孕杂志, 2022, 42(2): 199-203. DOI: 10.3760/cmaj.cn101441-20200624-00355.

连接蛋白参与胚胎植入与子宫内膜蜕膜化作用机制的研究进展

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【摘要】 目前胚胎种植成功率为 30%~40%, 并有研究证实有 50%~75% 的妊娠失败源于胚胎植入的异常。胚胎植入是正常妊娠建立的一个关键环节, 子宫内膜容受性受损与子宫内膜间质蜕膜化失败是导致胚胎植入失败的主要原因。胚胎植入涉及一系列信号分子及细胞因子参与, 许多研究证实缝隙连接蛋白参与胚胎植入及子宫内膜蜕膜化的调控。本文就连接蛋白在胚胎植入前子宫内膜容受性、内膜蜕膜化、血管重塑及植入过程中的作用及其调控机制作一综述, 以期为不孕症、反复植入失败患者的治疗提供理论依据, 为药物研发提供新的研究靶点。

【关键词】 连接蛋白; 胚胎植入; 蜕膜化; 子宫内膜容受性

Progress on the mechanism of connexin in embryo implantation and endometrial decidualization

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【Abstract】 At present, the success rate of embryo implantation is 30%-40%, of which 50%-75% of pregnancy failure originates from abnormal embryo implantation. Embryo implantation is a key link in the establishment of normal pregnancy. The main causes of embryo implantation failure are the damage of endometrial receptivity and the failure of endometrial stromal decidualization. Embryo implantation involves a range of signaling molecules and cytokines, and many studies have shown that connexin proteins are involved in the regulation of embryo implantation and endometrial decidualization. This article reviews the role of connexin in endometrial receptivity, decidualization, vascular remodeling, implantation and its regulatory mechanism, in order to provide theoretical basis for the treatment of infertility and repeated implantation failure patients, and provide new research targets for drug development.

【Key words】 Connexin protein; Embryo implantation; Decidualization; Endometrial receptivity

收稿日期 2020-08-31 本文编辑 李天琦

引用本文: 王换, 杨庆岭, 孙莹璞. 肥胖导致精子表观因子变化影响子代健康的研究进展[J]. 中华生殖与避孕杂志, 2022, 42(2): 204-208. DOI: 10.3760/cmaj.cn101441-20200704-00377.

·综述·

肥胖导致精子表观因子变化影响子代健康的研究进展

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【摘要】 肥胖是一种复杂的多因素疾病。全球超过 19 亿成年人患有不同程度的肥胖, 而男性肥胖患者占到一半左右。随着男性肥胖的比例增加, 精子质量下降和男性不育的比例逐渐上升。最近的研究指出肥胖可通过表观遗传改变影响精子发生, 表观遗传是在不改变核苷酸序列的前提下, 对基因表达变化的研究主要包括三个方面, 即 DNA 甲基化、组蛋白修饰和非编码 RNA(non-coding RNA, ncRNA)。动物模型的研究显示肥胖与精子、子代的体细胞和生殖细胞的表观遗传改变直接相关, 表观遗传通过调控生殖细胞的形成和发育, 在男性不育中发挥至关重要的作用, 表观遗传的改变会导致精子畸形和精子功能异常。肥胖改变表观因子后, 不仅可以改变精子功能, 而且对后代会产生影响, 例如父亲肥胖可通过精子表观遗传重编程影响后代的代谢和生殖表型, 而适当的干预措施会对肥胖者精子和其后代的表观基因有一定的改善。本文将从肥胖引起精子表观遗传改变, 对后代的影响和干预措施对精子表观遗传的影响这三个方面逐一综述。

【关键词】 肥胖; 精子; 表观遗传学; 子代

Research progress on the effect of obesity-induced changes in sperm epigenetic factors on offspring health

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【Abstract】 Obesity is a complex, multifactorial disease. More than 1.9 billion adults worldwide are obese, with men accounting for about half. With the number of obese men increasing, the proportion of sperm quality decline and male infertility

gradually rise. Recent studies have shown that obesity can affect spermatogenesis through epigenetic changes. Epigenetics is the study of changes in gene expression without changing nucleotide sequence, which mainly includes three aspects: DNA methylation, histone modification and non-coding RNA (ncRNA). Animal model studies have shown that obesity is directly related to epigenetic changes in sperm, somatic cells of offspring and germ cells. Epigenetic changes play a crucial role in male infertility by regulating the formation and development of germ cells. Epigenetic changes can lead to sperm abnormalities and sperm function abnormalities. Obesity alters epigenetic factors that can not only alter sperm function, but also affect offspring, for example paternal obesity can affect the metabolism and reproductive phenotype of offspring through sperm epigenetic reprogramming, and appropriate intervention measures can improve the epigenetic genes of sperm and offspring in obese people. This paper will review the epigenetic changes of sperm caused by obesity, the influence on offspring and the influence of intervention measures on sperm epigenetic changes.

【Key words】 Obesity; Spermatozoa; Epigenetics; Offspring

DOI: 10.3760/cma.j.cn101441-20200628-00363

收稿日期 2020-07-01 本文编辑 宋培培

引用本文: 朱琦, 王凯娟, 曹云霞, 等. 基于微流控芯片的胚胎体外培养研究进展[J]. 中华生殖与避孕杂志, 2022, 42(2): 209-212. DOI: 10.3760/cma.j.cn101441-20200628-00363.

·综述·

基于微流控芯片的胚胎体外培养研究进展

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【摘要】 胚胎体外培养是辅助生殖技术的一个关键环节, 胚胎培养过程中理化环境的变化会影响胚胎质量。近年来, 一种基于微流控芯片的胚胎动态培养以其强大的微流体和微小物质控制能力, 可以显著改善胚胎的发育潜能, 成为研究胚胎体外培养的新颖且有效方法, 这是传统静态微液滴培养法所不能企及的。本文就微流控芯片技术应用于胚胎体外培养的最新研究进展进行了综述。

【关键词】 胚胎发育; 微流控芯片; 体外培养

基金项目：国家重大科研仪器研制项目（11627803）

Advancements on *in vitro* culture of embryo based on microfluidic chip

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【Abstract】 *In vitro* culture (IVC) of embryo is the focus of assisted reproductive technology. Changes in the physical and chemical environment during embryo culture will affect the quality of embryo. In recent years, a dynamic IVC method based on microfluidic chips, with the powerful capability in microfluidic and micro-substance control, can significantly ameliorate the developmental potential of embryos, and it has become a novel and effective method for the study on the IVC of embryo, which has obvious advantages compared with the traditional static micro-drop culture method. This article reviews the latest research progress of microfluidic chip technology applied to the IVC of embryo.

【Key words】 Embryonic development; Microfluidic chip; *In vitro* culture

Fund program: National Major Scientific Research Instrument and Equipments Development Project (11627803)

·综述·

DOI: 10.3760/cmaj.cn101441-20200626-00359

收稿日期 2020-06-30 本文编辑 孙敏

引用本文：覃清圆, 刘涛, 曲江雪, 等. 脯氨酸作为细胞冷冻保护剂的研究进展[J]. 中华生殖与避孕杂志, 2022, 42(2): 213-217. DOI: 10.3760/cmaj.cn101441-20200626-00359.

脯氨酸作为细胞冷冻保护剂的研究进展

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【摘要】 细胞冷冻保存应用广泛, 但冷冻会损伤细胞导致代谢紊乱, 而冷冻保护剂可缓解该过程。脯氨酸是一种渗透性冷冻保护剂, 可快速透过细胞膜进入细胞内, 与细胞内水氢键结合抑制低温下冰晶形成, 同时可与细胞内水结合减少细胞

内水流失,保护细胞内蛋白质的结构和功能,保护细胞膜。脯氨酸可提高植物、动物及人类体细胞冷冻复苏后存活率。在生殖细胞冷冻中,研究表明脯氨酸可用于卵母细胞冷冻,可提高小鼠卵母细胞冷冻后存活率及保护线粒体功能,但其对于精子的冷冻效果报道尚不一致。脯氨酸冷冻保护剂涉及多种细胞类型且冷冻效果较强,其未来可能更广泛应用于低温生物学领域。本文总结了脯氨酸作为天然小分子冷冻保护剂的应用研究进展,希望能够帮助人们更好地了解生殖细胞冻存的低温生物学机制,为改良生育力冷冻保存技术提供参考。

【关键词】 脯氨酸; 冷冻保护剂; 卵母细胞

基金项目: 国家重点研发计划(2017YFC1002004)

Research progress of proline as cryoprotectant

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【Abstract】 Though cells are easily damaged and performed metabolic disorders in freezing-thawing process, cryoprotectant can relief the injure, which is widely used in the field of cell frozen biology. As one of osmotic cryoprotectants, in freezing process, proline can penetrate through cell membrane quickly, bind intracellular water hydrogen bonds, inhibit formation of ice crystals at low temperatures, protect structure and function of proteins and cell membranes. It can increase the survival rate in plant cells, animal cells and human somatic cells post freezing-thawing. In germ cell cryopreservation, studies have shown that proline can be used for oocyte cryopreservation, which can improve the survival rate of mouse oocytes after cryopreservation and protect mitochondrial function. However, the reports about the cryopreservation efficiency of proline on sperm are not consistent. By improving the efficiency of cryopreservation in various kinds of cells, proline may be more widely used in the area of cell freezing biology in the future. This paper summarizes the research progress of proline as a natural small molecule cryoprotectant, hoping to help people better understand the cryobiological mechanism of germ cell cryopreservation, and provide a reference for improving fertility cryopreservation technology.

【Key words】 Proline; Cryoprotectant; Oocyte

Fund program: National Key Research and Development Program of China (2017YFC1002004)