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44卷　第6期　2024年6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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中华生殖与避孕杂志
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200237,上海市老沪闵路779号
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Email:randc@sibpt.com
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出　版
《中华医学杂志》社有限责任公司
100710,北京市东四西大街42号
电话(传真):(010)51322059
Email:office@cmaph.org

印　刷
上海界龙中报印务有限公司

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,100048)
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:randc@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**　孙敏　　**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 44, Number 6 June 25, 2024

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

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

Printing
Shanghai Jielong Zhongbao Printing Co., Ltd

Overseas Distributor
China International Book Trading Corporation
P.O. Box 399, Beijing 100048, 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, 0086-21-64438975
Email: randc@sibpt.com

CSSN
ISSN 2096-2916
CN 10-1441/R

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DOI：10.3760/cma.j.cn101441-20240105-00006

收稿日期　2024-01-05　本文编辑　孙敏

引用本文：朱焰，张鑫，傅大煦. 生殖药理学学科发展与挑战[J]. 中华生殖与避孕杂志，2024，44(6)：557-561. DOI：10.3760/cma.j.cn101441-20240105-00006.

·生殖药理专栏·

编者按

环境污染、社会压力和生活方式的改变严重影响了人类的生殖能力和生殖健康，全球生育力下降且生育年龄普遍延后，生殖健康领域面临的问题也逐渐凸显。生殖药理学的研究领域也从单一的避孕节育不断扩展，成为了融合生殖医学、分子遗传学、生殖生物学、生殖内分泌学、生殖毒理学和药剂学等的交叉学科。为了推动国内生殖药理学的学科建设、促进生殖健康药物研发及临床应用相关学科的学术交流，《中华生殖与避孕杂志》与中国药理学会生殖药理专业委员会合作，由该学会现任主任委员朱焰研究员负责，共同策划了本期“生殖药理专栏”，以期反映从基础分子机理研究到临床应用等生殖药理学相关领域的工作进展，推动生殖药理学的发展，助力提升我国生殖健康领域的研究水平。

生殖药理学学科发展与挑战

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【摘要】 当前，生殖药理学的核心内容是发掘和研究生育力保护药物及治疗机制。随着时代的发展，生殖药理学已从早期单一的避孕药研究向生育力保护药物

和治疗拓展，延伸至生殖系统疾病、生殖肿瘤以及辅助生育等交叉学科。一些新技术，如基因组学、转录组学、代谢组学、蛋白组学、类器官培养、干细胞和单细胞测序技术等的应用为生殖药理研究提供了丰富的技术手段，为揭示生育力保护药物新靶点和新机制提供了新的研究方向，极大地促进生殖药理学学科的发展。目前，我国面临着低生育率、高流产率和高龄化并存的社会特点，这给生殖药理学的发展提出了新的挑战，督促我们应更加重视生育力保护，通过发掘新的治疗机制研发适合不同人群的、安全有效的生育力保护药物和治疗方法，减少不必要的人工流产，为有意愿生育人群创造生育机会，提高生育能力，延长生育周期，保护其生育力。此外，对辅助生殖技术及其相关产品对后代健康的可能带来药理学效应和影响应予以更多的关注和研究，更好地为提高我国人口素质和生育质量服务，这既是生殖药理学面临的挑战，也是未来学科的发展方向。

【关键词】 生殖药理；生育力保护；避孕节育；子代健康；学科发展

基金项目：上海张江国家自主创新示范区专项发展资金重大项目计划（ZJ2022-ZD-006）

Development and challenges of reproductive pharmacology

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【Abstract】 Currently, the major task of reproductive pharmacology is fertility preservation. Aside from studying the efficacy of contraceptives, the research area of reproductive pharmacology has been expanded to probe into the pharmacodynamics and the mechanism of action of medications for treatment of reproductive system disease and assisted fertility as well. The development of analysis techniques, including genomics, transcriptomics, metabolomics, proteomics, organoid culture, stem cell technology and single cell sequencing, provide multiple ways to explore therapeutic targets and new mechanisms of the treatment approaches. With the changes of age structure diagram in China population accompanied with coexisting lower fertility, higher abortion rate and increased number of seniors, more attention in the area of reproductive pharmacology should be paid on the research and development of contraceptives suitable for the young and the unmarried girls to avoid unnecessary abortion and preserve their fertility and provide more opportunities for those who willing to have children, extending their the reproductive span. Furthermore, pharmacological effects, especially the impact and outcomes of assisted reproductive technology and pertaining products on the health of the offspring should be paid more investigation and concerned, which belong to a part of the basic national policy of eugenics and are crucial to enhance the population quality of all the nationalities. This is a major challenge for the reproductive pharmacology researchers faced.

【Key words】 Reproductive pharmacology; Fertility protection; Contraceptives; Health of offspring; Discipline progress

Fund program: Special Development Funding for Zhangjiang National Independent Innovation Zone Project (ZJ2022-ZD-006)

DOI: 10.3760/cma.j.cn101441-20230711-00272

收稿日期 2023-07-11 本文编辑 宋培培

引用本文：胡颖怡，倪其承，钟瑞华，等. 连续重复给予含左炔诺孕酮紧急避孕药对雌性大鼠生育力及其子代健康的影响[J]. 中华生殖与避孕杂志，2024，44(6)：562-573. DOI：10.3760/cma.j.cn101441-20230711-00272.

·生殖药理专栏·

连续重复给予含左炔诺孕酮紧急避孕药对雌性大鼠生育力及其子代健康的影响

胡颖怡[1] 倪其承[1] 钟瑞华[2] 杨文捷[2] 李国停[2] 周洁芸[2] 郭湘洁[2] 谢淑武[3] 周佳铃[4] 朱焰[2]

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【摘要】 目的 探讨连续重复给予含左炔诺孕酮（levonorgestrel，LNG）紧急避孕药（emergency contraception pills，ECPs）对雌性大鼠生育力及其F1代仔鼠健康的影响。方法 成年SPF级雌性大鼠于每个动情周期连续给予3次LNG-ECPs，分别给予3个（P-3）、6个（P-6）和12个（P-12）动情周期。雌性大鼠每个给药时程下，采用Excel产生随机数按体质量分层随机分为2组，分别为LNG-ECPs组和溶媒对照组，分别灌胃给予0.12 mg/kg LNG-ECPs和等体积溶媒。各组于末次给药后4 h分别取1/2动物（12~18只）进行解剖（6~9只）和交配（6~9只）；剩余1/2动物（12~18只）于停药恢复3个动情周期后再分别进行解剖（6~9只）和交配（6~9只），计算脏器系数。采用酶联免疫吸附法（enzyme-linked immunosorbent assay，ELISA）检测雌性大鼠血清中卵泡刺激素（follicle-stimulating hormone，FSH）、黄体生成素（lutenizing hormone，LH）、雌激素、孕激素、睾酮、抗苗勒管激素（anti-Müllerian hormone，AMH）

以及游离甲状腺激素3（free thyroid hormone，fT3）的水平。雌性大鼠卵巢组织切片苏木精-伊红（hematoxylin and eosin，HE）染色后进行卵泡计数。记录LNG-ECPs给药结束和停药恢复期雌性大鼠妊娠率及窝仔数，测定F1代仔鼠生长指数以及主动和被动运动能力等指标。取P-12大鼠卵巢组织进行转录组学测序，建立LNG-ECPs致卵巢差异表达基因谱，分析LNG-ECPs致卵巢损伤的差异基因，并进行基因本体（gene ontology，GO）和京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genomes，KEGG）通路富集分析。结果　①连续给予3个和6个动情周期后，LNG-ECPs组雌鼠的血清激素水平和生育力与溶媒对照组相比，差异均无统计学意义（均P>0.05）；F1代仔鼠生长指数和行为学结果与溶媒对照组仔鼠相比差异均无统计学意义（均P>0.05）。②连续给予12个动情周期后，与溶媒对照组相比，LNG-ECPs组大鼠血清中FSH［（0.21±0.17）U/L］、LH［（0.27±0.08）U/L］和孕激素［（0.68±0.23）μg/L］水平显著低于溶媒对照组［（1.00±0.82）U/L，P=0.043；（1.00±0.50）U/L，P=0.006；（1.00±0.20）μg/L，P=0.027］，雌二醇［（2.24±1.03）μg/L］和睾酮［（1.25±0.25）μg/L］水平明显高于溶媒对照组［（1.00±0.35）μg/L，P=0.019；（1.00±0.07）μg/L，P=0.044］；卵巢中原始卵泡数量（4.88±2.36）显著少于溶媒对照组（16.13±9.36，P=0.005），闭锁卵泡数量（24.38±5.01）显著高于溶媒对照组（19.13±2.30，P=0.018）；LNG-ECPs组中F1代仔鼠负重游泳时间［（157.13±32.29）s］明显低于溶媒对照组［（198.06±40.01）s，P=0.003］。停药恢复3个动情周期后，LNG-ECPs可造成大鼠血清中FSH［（2.48±1.18）U/L］、LH［（1.60±0.41）U/L］、睾酮［（1.37±0.23）μg/L］及FSH/LH值（1.61±0.41）显著高于溶媒对照组［（1.00±0.67）U/L，P=0.024；（1.00±0.27）U/L，P=0.014；（1.00±0.18）μg/L，P=0.011；1.00±0.49，P=0.042］，且雌激素水平［（0.49±0.15）μg/L］和AMH水平［（0.79±0.15）μg/L］显著低于溶媒对照组［（1.00±0.37）μg/L，P=0.011；（1.00±0.10）μg/L，P=0.016］，同时，大鼠卵巢中原始卵泡数量（6.25±5.06）仍显著少于溶媒对照组（12.00±5.56，P=0.048）；F1代仔鼠在旷场中的运动总距离［（89.85±36.98）m］以及负重游泳时长［（112.00±29.52）s］均显著低于溶媒对照组［（147.55±23.13）m，P<0.001；（137.69±25.85）s，P=0.014］。③转录组测序结果表明，与溶媒对照组相比，LNG-ECPs组雌性大鼠卵巢组织中存在*Cd5*、*Cxcr1*、*Lexm*、*Fga*、*Mybphl*和*Gstm5*等显著差异表达的基因，参与萜类骨架生物合成、卵巢类固醇生成和皮质醇的合成与分泌等类固醇激素合成相关过程，还涉及碳代谢、丁酸甲酯代谢和半胱氨酸等物质代谢过程，以及细胞因子-细胞因子受体相互作用、病毒蛋白与细胞因子及细胞因子受体的相互作用等免疫调节过程。结论　在雌性大鼠中，短期重复（<12个周期）给予LNG-ECPs对雌鼠生育力及其F1代仔鼠生长发育和行为学未见明显影响；而长期重复（12个周期）给予LNG-ECPs会导致卵巢功能损伤，并会对F1代仔鼠的健康产生负面影响，停药恢复3个动情周期后仍未见明显改善。

【关键词】　左炔诺孕酮；　生育力；　行为学；　卵巢损伤；　转录组学

基金项目：上海市自然科学基金（20ZR1448200）

Effects of consecutively repeated application of emergency contraceptive pills containing levonorgestrel on female fertility and the health of F1 offspring

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【**Abstract**】 **Objective** To explore the effects of consecutively repeated application of emergency contraception pills (ECPs) containing levonorgestrel (LNG) on the female fertility and the health outcomes of F1 generation rats. **Methods** Female SPF rats were intragastric administered with LNG-ECPs consecutively for 3 (P-3), 6 (P-6) and 12 (P-12) estrous cycles (three times in each estrous cycle), respectively. Under each administration schedule, rats were randomly divided into 2 groups according to body weight stratification using random numbers generated in Excel, i.e. LNG-ECPs group and solvent control group, administered with 0.12 mg/kg LNG-ECPs and corresponding volumes of 0.5% CMC-Na, respectively. Four hours after the last dosing, half of the animals (12–18) in each group were allotted randomly for dissection (6–9) and mating (6–9), respectively. The remaining half (12–18) were recovered for 3 estrous cycles, and then were randomly allocated for dissection (6–9) and mating (6–9). Organ coefficients were calculated. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, testosterone, anti-Müllerian hormone (AMH) and free thyroid hormone 3 (fT3) were examined by enzyme linked immunosorbent assay (ELISA). Ovarian tissues were sectioned and stained with hematoxylin and eosin (HE) for follicle counting. In addition, the pregnancy rate and litter size of the female rats were recorded, and the growth indexes and behavioral parameters of the cubs were measured. Moreover, RNA sequencing (RNA-seq) of the ovarian tissues was performed to establish the differential expression gene profile of ovarian injury induced by LNG-ECPs. Then gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment were analyzed. **Results** 1) After consecutive administration for 3 and 6 estrous cycles, LNG-ECPs showed no significant impact on the serum hormone levels and female fertility (all $P>0.05$), and the growth indexes and behavioral parameters of the F1 generation (all $P>0.05$). 2) After consecutive administration for 12 estrous cycles, the serum levels of FSH [(0.21±0.17) U/L], LH [(0.27±0.08) U/L] and progesterone [(0.68±0.23) μg/L] in LNG-ECPs group decreased significantly compared with those in solvent control group [(1.00±0.82) U/L, $P=0.043$; (1.00±0.50) U/L, $P=0.006$; (1.00±0.20) μg/L, $P=0.027$], while the level of estradiol [(2.24±1.03) μg/L] and testosterone [(1.25±0.25) μg/L] increased noticeably compared with those in solvent control group [(1.00±0.35) μg/L, $P=0.019$; (1.00±0.07) μg/L, $P=0.044$]. The number of primordial follicles (4.88±2.36) lost distinctly, while the number of atretic follicles (24.38±5.01) increased markedly in LNG-ECPs group compared with those in solvent control group (16.13±9.36, $P=0.005$; 19.13±2.30, $P=0.018$). In addition, the weight-loaded swimming (WLS) time of the F1 generation rats from the LNG-ECPs group

[(157.13±32.29) s] reduced obviously compared with those from the solvent control group [(198.06±40.01) s, *P*=0.003]. Moreover, after recovering for 3 estrous cycles, LNG-ECPs significantly increased the levels of FSH [(2.48±1.18) U/L], LH [(1.60±0.41) U/L], testosterone [(1.37±0.23) μg/L] and the ratio of FSH/LH (1.61±0.41) compared with those in solvent control group [(1.00±0.67) U/L, *P*=0.024; (1.00±0.27) U/L, *P*=0.014; (1.00±0.18) μg/L, *P*=0.011; 1.00±0.49, *P*=0.042], respectively. Additionally, the serum levels of estradiol [(0.49±0.15) μg/L] and AMH [(0.79±0.15) μg/L] were significantly lower than those in solvent control group [(1.00±0.37) μg/L, *P*=0.011; (1.00±0.10) μg/L, *P*=0.016]. In addition, the number of primordial follicles in rats of LNG-ECPs group (6.25±5.06) were obviously less than that in solvent control group (12.00±5.56, *P*=0.048). Furthermore, the total distance in open field [(89.85±36.98) m] and the swimming time in WLS [(112.00±29.52) s] in rats treated with LNG-ECPs both decreased distinctly compared with those in solvent control group [(147.55±23.13) m, *P*<0.001; (137.69±25.85) s, *P*=0.014]. 3) According to transcriptomic analysis, *Cd*5, *Cxcr*1, *Lexm*, *Fga*, *Mybphl* and *Gstm*5 were the significant differential expressed genes (DEGs) in the ovarian tissues of rats. These DEGs were involved in pathways related to steroid hormone biosynthesis, including terpenoid backbone biosynthesis, ovarian steroidogenesis, cortisol synthesis and secretion. Additionally, these genes were involved in metabolic processes, such as carbon metabolism, butanoate metabolism, cysteine and methionine metabolism. And the genes were also involved in immunoregulatory processes including cytokine-cytokine receptor interaction, viral protein interaction with cytokine and cytokine receptors. **Conclusion** Consecutively repeated administering LNG-ECPs to the female rats in a short-term period (<12 cycles) did not demonstrate significant adverse effects on female fertility and the growth and development and the behaviors of their F1 generation cubs. However, long-term repeated treatment with LNG-ECPs (12 cycles) caused ovarian injury on female rats and showed negative impacts on the health of the F1 generation cubs, and no significant improvement was observed after recovering for 3 estrous cycles.

【 Key words 】 Levonorgestrel; Fertility; Ethology; Ovarian injury; Transcriptomics

Fund program: Shanghai Natural Science Foundation (20ZR1448200)

DOI：10.3760/cma.j.cn101441-20240104-00004

收稿日期 2024-01-04 本文编辑 孙敏

引用本文：潘烨栋，周晟，王严慧，等. 慢性不完全睡眠剥夺对小鼠卵巢储备功能的影响[J]. 中华生殖与避孕杂志，2024，44(6)：574-578. DOI：10.3760/cma.j.cn101441-20240104-00004.

慢性不完全睡眠剥夺对小鼠卵巢储备功能的影响

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【摘要】　目的　探讨慢性不完全睡眠剥夺（sleep deprivation，SD）对小鼠卵巢储备功能的影响及其可能作用机制。方法　16只SPF级7~8周龄雌性C57BL/6小鼠，适应性饲养1周后，简单随机化分为对照组和SD组，每组8只，其中SD组小鼠每天7：00~10：00采用剥夺杆进行慢性不完全SD，共计40 d。在实验开始前与结束前的9 d内每天进行阴道脱落细胞涂片检查，记录动情周期。于第40天通过酶联免疫吸附法（enzyme-linked immunosorbent assay，ELISA）试剂盒检测血清雌二醇、孕酮、卵泡刺激素（follicle-stimulating hormone，FSH）、促黄体生成素（luteinizing hormone，LH）和褪黑素（melatonin，MT）水平。取卵巢，计算卵巢指数，并通过切片苏木精-伊红染色计数原始卵泡数量。免疫组织化学方法检测灌注取脑后小鼠视交叉上核（suprachiasmatic nucleus，SCN）脑区神经元c-Fos表达情况。结果　相比于对照组，SD组小鼠动情周期出现紊乱趋势。SD组小鼠雌二醇［（20.19±3.67）ng/L］、孕酮［（2.88±0.53）μg/L］、FSH［（13.42±2.36）U/L］水平明显低于对照组小鼠［（24.66±2.15）ng/L，*P*=0.010；（3.43±0.49）μg/L，*P*=0.049；（17.01±1.49）U/L，*P*=0.003］。SD组小鼠LH和MT水平低于对照组小鼠，但差异均无统计学意义（均*P*>0.05）。SD组小鼠卵巢原始卵泡数量与对照组小鼠相比，差异无统计学意义（*P*>0.05），但是SD组卵母细胞形态不佳，颗粒细胞排列紊乱，闭锁卵泡数量减少，卵巢纤维化明显。免疫组织化学染色观察到SD组小鼠SCN区神经元c-Fos蛋白表达上调。结论　连续40 d每天进行3 h SD后小鼠卵巢储备功能受损，可能与SCN过度激活有关。

【关键词】　睡眠剥夺；　卵巢储备功能；　动情周期

基金项目：国家自然科学基金面上项目（32371033、32170983）；上海市自然科学基金面上项目（21ZR1408000）；复旦大学上海医学院卿枫学者本科生创新创业项目（QF2134）

Impact of chronic incomplete sleep deprivation on ovarian reserve function in mice

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【**Abstract**】 **Objective** To explore the effect of chronic incomplete sleep deprivation (SD) on ovarian reserve function in mice and its potential mechanisms. **Methods** Sixteen 7–8 week old female C57BL/6 SPF mice were randomly divided into control and SD groups (*n*=8 per group) after one week of acclimatization. The mice in the SD group were treated with SD from 7:00 to 10:00 using a deprivation rod for a total of 40 d. Before the first day and the last day of the experiment, vaginal smears were collected daily for 9 d to record and evaluate the estrous cycle. On the last day of the experiment, serum levels of estradiol, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and melatonin (MT) were measured by enzyme-linked immunosorbent assay (ELISA). The ovaries were dissected to calculate the ovarian index and count the number of primordial follicles by hematoxylin-eosin (HE) staining. Cardiac perfusion was performed to get the brains and the expression of c-Fos protein was observed in the suprachiasmatic nucleus (SCN) by immunohistochemistry. **Results** Compared with control group, SD group had a tendency of estrous cycle disorders. Hormone levels of estradiol [(20.19±3.67) ng/L], progesterone [(2.88±0.53) μg/L], and FSH [(13.42±2.36) U/L] in the SD group were significantly lower than those in control group [(24.66±2.15) ng/L,*P*=0.010; (3.43±0.49) μg/L, *P*=0.049; (17.01±1.49) U/L, *P*=0.003]. Hormone levels of LH and MT in the SD group were lower than those in control group, but without statistical significances (all *P*>0.05). There was no significant change in the number of primordial follicles between the two groups (*P*>0.05). However, the oocyte morphology was poor, the granulosa cells were disorderedly arranged, the number of atretic follicles was decreased, and ovarian fibrosis was obvious in the SD group. Immunohistochemical staining showed an upregulation of c-Fos protein expression in the SCN of the SD group. **Conclusion** Continuous 3 h SD for 40 d impairs ovarian reserve function in mice, possibly related to excessive activation of the SCN.

【**Key words**】 Sleep deprivation; Ovarian reserve; Estrous cycle

Fund program: National Natural Science Foundation of China (32371033, 32170983); Shanghai Natural Science Foundation (21ZR1408000); Innovation and Entrepreneurship of Undergraduate Development Program of Shanghai Medical College, Fudan University (QF2134)

DOI：10.3760/cma.j.cn101441-20231220-00370

收稿日期 2023-12-20 本文编辑 孙敏

引用本文：王圆圆，薛函，李林艳，等. 人脐带间充质干细胞上调 Nrf2 信号改善衰老小鼠睾丸功能[J]. 中华生殖与避孕杂志，2024，44(6)：579-586. DOI：10.3760/cma.j.cn101441-20231220-00370.

人脐带间充质干细胞上调 Nrf2 信号改善衰老小鼠睾丸功能

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王圆圆和薛函对本文有同等贡献

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【摘要】 目的 探讨人脐带间充质干细胞（human umbilical cord mesenchymal stem cells，hUCMSCs）移植对氧化损伤衰老小鼠睾丸功能的影响及分子机制。方法 共纳入 18 只 6~8 周 SPF 级 C57BL/C 雄性小鼠，完全随机分组法分为 3 组，对照组：小鼠注射等量生理盐水；模型组：颈背部皮下注射 D-半乳糖连续 9 周，造模第 4 周末，每只小鼠尾静脉注射生理盐水；hUCMSCs 组：颈背部皮下注射 D-半乳糖连续 9 周，造模第 4 周末，每只小鼠尾静脉注射 hUCMSCs。9 周后，称取小鼠体质量和睾丸重量，计算睾丸指数，酶联免疫吸附试验（enzyme-linked immunosorbent assay，ELISA）法检测小鼠血清睾酮水平、睾丸组织丙二醛（malondialdehyde，MDA）、超氧化物歧化酶（superoxide dismutase，SOD）含量。肉眼观察睾丸外观，苏木精-伊红（hematoxylin-eosin，HE）染色观察睾丸组织病理学变化，实时荧光定量聚合酶链反应和 Western blotting 分别检测核因子 E2 相关因子 2（nuclear factor erythroid 2-related factor 2，Nrf2）信号转导相关基因和蛋白表达。结果 模型组小鼠睾丸指数［（0.64±0.05）%］较对照组［（0.81±0.13）%，*P*=0.006］降低，睾丸体积缩小，生精小管完整性破坏，生精细胞和精子减少，间质稀疏；血清睾水平［（4.10±0.67） μg/L］、睾丸组织 SOD 活性［（48.87±6.40） U/mg Prot］较对照组［（5.71±0.81） μg/L，*P*=0.002；（78.53±9.70） U/mg Prot，*P*=0.001］均降低，而 MDA 含量［（1.11±0.19） nmol/mg Prot］较对照组［（0.77±0.07） nmol/mg Prot，*P*=0.001］增加。*Keap*1 mRNA 和蛋白表达量较对照组均增高（*P*=0.006，*P*=0.043），*Nrf*2、*SOD* 和 *NQO*1 mRNA 表达量较对照组减少（*P*=0.002，*P*<0.001，*P*=0.001），Nrf2、HO-1 蛋白表达量较对照组均明显降低（*P*=0.011，*P*=0.021）。与模型组比较，hUCMSCs 组小鼠睾丸指数［（0.79±0.03）%，*P*=0.010］增高；睾丸组织结构较为清晰、完整，生精小管各级生精细胞和精子及间质细胞较丰富；血清睾酮水平［（5.24±0.21） μg/L，

P=0.028]及睾丸组织 SOD 活性 [（79.47±14.32） U/mg Prot，*P*=0.001]增高，MDA 含量 [（0.77±0.08） nmol/mg Prot，*P*=0.001]降低；*Nrf*2、*SOD*和 *NQO*1 mRNA 表达量均增高（*P*=0.024，*P*=0.037，*P*=0.005），*Keap*1 mRNA 表达量减少（*P*=0.044），Nrf2、HO-1 蛋白表达量均增高(*P*=0.009,*P*=0.012),Keap1 蛋白表达量降低(*P*=0.035)。hUCMSCs 组小鼠睾丸指数、血清睾酮、SOD 活性及 MDA 含量都与对照组差异均无统计学意义（均 *P*>0.05）。结论 hUCMSCs 明显改善氧化损伤所致衰老小鼠睾丸结构和功能损伤，其作用机制与上调 Nrf2 信号转导及其相关下游抗氧化活性 SOD、HO-1 蛋白表达，减少 Keap1 介导的 Nrf2 降解有关。

【关键词】 睾丸； 核因子 E2 相关因子 2； 衰老； 人脐带间充质干细胞； D-半乳糖； 抗氧化

基金项目：国家自然科学基金（82360047）；遵义医科大学附属医院博士后基金（rc220330427）

Human umbilical cord mesenchymal stem cells improve testicular function in aging mice by upregulating Nrf2 signaling

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【**Abstract**】 **Objective** To investigate the effect and mechanism of human umbilical cord mesenchymal stem cells (hUCMSCs) transplantation on testicular function in aging mice with oxidative damage. **Methods** Totally 18 SPF grade C57BL/C male mice aged 6-8 weeks were randomly divided into 3 groups using a complete randomization method. In control group, mice were injected with an equal amount of physiological saline; in model group, mice were subcutaneous injected D-galactose into the neck and back for 9 consecutive weeks, on the 4th weekend of modeling, the mice were injected with physiological saline via the tail vein; in hUCMSCs group: mice were subcutaneous injected D-galactose into the neck and back for 9 consecutive weeks, on the 4th weekend of modeling, the mice were injected with hUCMSCs via the tail vein of each mouse. After 9 weeks, body weight and testicular weight of the three groups mice were measured and testicular index was calculated. The contents of testosterone, malondialdehyde (MDA) and superoxide dismutase (SOD) in serum and testicular tissue were detected by enzyme-linked immunosorbent assay (ELISA) method. Visual observation of testicular appearance, the histopathological changes of testis were observed by hematoxylin-eosin (HE) staining, and the expression of NF-E2-related factor 2 (Nrf2) signal transduction-related genes and proteins were detected by RT-PCR and Western blotting, respectively. **Results** Compared with control group

[(0.81±0.13)%], the testicular index of mice in model group [(0.64±0.05)%, *P*=0.006] was decreased. In model group, the volume of testis was reduced, the integrity of spermatogenic tubules was damaged, spermatogenic cells and sperm were reduced, and the interstitium was sparse. In model group, serum testosterone [(4.10±0.67) μg/L] and SOD [(48.87±6.40) U/mg Prot] were decreased compared with control group [(5.71±0.81) μg/L, *P*=0.002; (78.53±9.70) U/mg Prot, *P*=0.001], MDA [(1.11±0.19) nmol/mg Prot] was increased compared with control group [(0.77±0.07) nmol/mg Prot, *P*=0.001], *Keap*1 mRNA and protein expression were increased (*P*=0.006, *P*=0.043). The expression levels of *Nrf*2, *SOD* and *NQO*1 mRNA were significantly lower than those in control group (*P*=0.002, *P*<0.001, *P*=0.001), and the expression levels of Nrf2 and HO-1 protein were significantly lower than those in control group (*P*=0.011, *P*=0.021). Compared with the model group, the testicular index [(0.79±0.03)%, *P*=0.010] increased in hUCMSCs group, and the tissue structure of testis was clear and complete, spermatogenic cells at all levels of spermatogenic tubules, spermatogenic cells and stromal cells were abundant. Compared with the model group, the content of dihydrotestosterone [(5.24±0.21) μg/L, *P*=0.028] in serum and SOD [(79.47±14.32) U/mg Prot, *P*=0.001] in testicular tissue increased in hUCMSCs group, while the content of MDA [(0.77±0.08) nmol/mg Prot, *P*=0.001] decreased, *Nrf*2, *SOD* and *NQO*1 mRNA expression levels increased (*P*=0.024, *P*=0.037, *P*=0.005), *Keap*1 mRNA expression decreased (*P*=0.044), Nrf2 and HO-1 proteins expression increased (*P*=0.009, *P*=0.012), while Keap1 protein expression decreased (*P*=0.035). There were no statistically significant differences in testicular index, serum testosterone, SOD and MDA between hUCMSCs group and control group (all *P*>0.05). **Conclusion** hUCMSCs significantly improve testicular structure and function damage caused by oxidative damage in aging mice, and the mechanism of action is related to upregulating Nrf2 signaling and downstream antioxidant activity SOD and HO-1 protein expression, reducing Keap1 mediated Nrf2 degradation.

【Key words】 Testis; Nuclear factor erythroid 2-related factor 2; Aging; Human umbilical cord mesenchymal stem cells; D-galactose; Anti-oxidation

Fund program: National Natural Science Foundation of China (82360047); Postdoctoral Foundation of Affiliated Hospital of Zunyi Medical University (rc220330427)

DOI：10.3760/cma.j.cn101441-20240129-00046

收稿日期 2024-01-29 本文编辑 李天琦

引用本文：赖佳嘉，王嫣然，张淑微，等. 影响精子活力的生活方式、环境因素和常用药物[J]. 中华生殖与避孕杂志，2024，44(6)：587-593. DOI：10.3760/cma.j.cn101441-20240129-00046.

影响精子活力的生活方式、环境因素和常用药物

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【摘要】 精子活力即精子的前向运动能力，是精子核心功能之一。在自然生殖过程中，只有具备正常活力的精子才能抵达受精部位并与卵子识别融合。当前向运动精子的百分比低于参考值下限时，可诊断为弱精子症，这是男性不育的主要原因之一。精子活力的维持依赖于尾部结构和信号转导的正常运作。此外，与精子活力相关的胞外环境因素也极为关键。本综述从生活方式、环境因素和常用药物等多角度探讨影响精子活力的外界因素，旨在为弱精子症的预防与诊断提供有益线索，并为预防男性不育症提供科学依据。

【关键词】 精子活力；　年龄；　肥胖；　吸烟；　饮食；　温度；　弱精子症；　药物

基金项目：浙江省自然科学基金（LY22H040011）；浙江省卫生高层次创新人才培养项目（2018）；浙江省人民医院临床基础联合项目（C-2023-YXLH11）

Lifestyles, environmental factors, and commonly used drugs affecting sperm motility

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【Abstract】 Sperm motility, a crucial function of sperm, refers to the ability of sperm to move progressively forward. Only sperm with adequate motility can reach the fertilization site and successfully recognize and fuse with an egg during natural reproduction. Asthenozoospermia, defined by a percentage of progressive sperm below the reference value's lower limit, is one of the most prevalent causes of male infertility. Sperm motility maintenance relies on both a normal flagellar structure and signal transduction pathways. However, extracellular environmental factors related to motility are also of significant importance. This review addresses factors influencing sperm motility, encompassing lifestyles, environmental elements, and commonly used drugs. It offers valuable insights for the prevention and diagnosis of asthenozoospermia and supports the strategies for preventing male infertility.

【Key words】 Sperm motility; Age; Obesity; Smoking; Diet; Temperature; Asthenozoospermia; Drug

Fund program: Zhejiang Provincial Natural Science Foundation (LY22H040011); Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents (2018);Clinic & Basic Joint Research Project of ZJPPH (C-2023-YXLH11)

DOI：10.3760/cma.j.cn101441-20231129-00346

收稿日期 2023-11-29 本文编辑 李天琦

引用本文：温馨，方航萍，刘溢佳，等. 哺乳类卵泡膜细胞及其干细胞的研究进展[J]. 中华生殖与避孕杂志，2024，44(6)：594-601. DOI：10.3760/cma.j.cn101441-20231129-00346.

·生殖药理专栏·

哺乳类卵泡膜细胞及其干细胞的研究进展

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【摘要】 卵泡膜细胞不仅为卵泡的完整性提供支持，还在卵泡发育、闭锁及优势卵泡选择和排卵中发挥至关重要的作用。尽管卵泡膜细胞在女性生殖过程中起到重要作用，但目前针对该类细胞发育、起源及其干细胞的相关研究非常稀少。卵泡膜干细胞的研究不仅能让我们深入了解卵泡膜细胞的募集、生长和分化过程，也能使我们尝试通过卵泡膜干细胞制备高活性的卵泡膜细胞，这对人类卵巢疾病的诊断、预防和治疗以及再生医学都具有重要的临床意义。本文就卵泡膜细胞功能、来源以及卵泡膜干细胞研究进展作一综述，同时也简单介绍单细胞测序技术在卵巢干细胞研究领域中的应用，为进一步探索卵巢卵泡发育机制、病理改变和疾病治疗等方面提供参考。

【关键词】 卵泡发育； 卵泡膜干细胞； 再生医学； 单细胞测序技术

基金项目：浙江省自然科学基金（Z23H040003）；温州市重大科技创新攻关项目（ZY2019002）

Research progress on mammalian theca cells and their stem cells

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【**Abstract**】 Follicular theca cells not only provide support for the integrity of follicles, but also play a crucial role in follicular development, atresia, selection of dominant follicles, and ovulation. Although theca cells play an important role in female reproductive processes, research on their development, origin, and stem cells origin is currently very scarce. The study of theca stem cells not only allows us to gain a deeper understanding of the recruitment, growth, and differentiation of theca cells, but also helps us to make functional theca cells from theca stem cells. These studies will have significance impacts on the diagnosis, prevention, and treatment of human ovarian diseases, as well as regenerative medicine. This article provides a brief review of the functions, sources, and research progress of theca cells, as well as a brief introduction of the application of single-cell RNA-sequencing technology in the field of ovarian stem cell research. It provides a reference for further exploration of the mechanisms of ovarian follicle development, pathological changes, and disease treatment.

【**Key words**】 Follicular development; Theca stem cells; Regenerative medicine; Single-cell sequencing technology

Fund program: Natural Science Foundation of Zhejiang Provience (Z23H040003); Wenzhou Major Scientific and Technological Innovation Project (ZY2019002)

DOI：10.3760/cma.j.cn101441-20231208-00356

收稿日期 2023-12-08 本文编辑 王李艳

引用本文：潘承双，王佩玉，费前进，等. 影响睾丸3β-羟基类固醇脱氢酶的内分泌干扰物及其作用机制进展[J]. 中华生殖与避孕杂志，2024，44(6)：602-609. DOI：10.3760/cma.j.cn101441-20231208-00356.

·生殖药理专栏·

影响睾丸3β-羟基类固醇脱氢酶的内分泌干扰物及其作用机制进展

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【摘要】 睾丸3β-羟基类固醇脱氢酶（3β-hydroxysteroid dehydrogenase，3β-HSD）是一种类固醇生成酶，催化3β-羟基类固醇转化为3-酮类固醇。目前已克隆了人类的两种不同亚型，*HSD*3B1和*HSD*3B2；其中，*HSD*3B2位于睾丸中，表达3β-HSD2。*HSD*3B2是一种双底物酶，可与辅因子NAD^+和3β-类固醇结合。许多内分泌干扰物，包括工业化合物（邻苯二甲酸盐、双酚类、全氟烷基物质和二苯甲酮类）、杀虫剂和杀菌剂（有机氯杀虫剂和有机锡）、食品添加剂（丁基羟基苯甲醚、白藜芦醇、棉酚、黄酮和异黄酮、类姜黄素和查尔酮类）和药物（依托咪酯、甲羟孕酮和酮康唑）可抑制睾丸中3β-HSD的活性，可能干扰雄激素合成。本文总结了3β-HSD的独特睾丸亚型，其基因、化学、亚细胞、位置以及直接抑制睾丸3β-HSD的内分泌干扰物及其抑制模式，期望为临床研究雄激素调控方法及以雄激素为靶点的药物研发提供参考。

【关键词】 3β-羟基类固醇脱氢酶； 睾酮生成； 类固醇生成； 环境内分泌干扰物； 多酚； 邻苯二甲酸盐

基金项目：温州市生殖与遗传学重点实验室资助（22HZSY0051）

Progress on endocrine disruptors affecting testicular 3β-hydroxysteroid dehydrogenase and their mechanism of action

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【Abstract】 3β-hydroxysteroid dehydrogenase (3β-HSD) is a steroidogenic enzyme that catalyzes the conversion of 3β-hydroxysteroids to 3-ketosteroids. Two different subtypes of human 3β-HSD, *HSD*3B1 and *HSD*3B2, have been cloned, with *HSD*3B2 primarily expressed in the testes. *HSD*3B2 exhibits 3β-HSD2 activity and is a dual-substrate enzyme that binds with co-factors NAD^+ and 3β-steroids. Many endocrine disruptors, including industrial compounds (phthalates, bisphenols, perfluoroalkyl substances, and benzophenones), pesticides and fungicides (organochlorine pesticides and organotins), food additives (butylated hydroxyanisole, resveratrol, gossypol, flavonoids and isoflavonoids, curcuminoids, and chalcones), and drugs (etomidate, mifepristone, and ketoconazole) inhibit testicular 3β-HSD, potentially interfering with androgen synthesis. In this review, we summarized the unique testicular subtypes of 3β-HSD, their genes, chemistry, subcellularity, location, and the endocrine disruptors that directly inhibit testicular 3β-HSD and their modes of inhibition, to provide reference for clinical research on androgen regulation methods and the development of androgen-targeted drugs.

【Key words】 3β-hydroxysteroid dehydrogenase; Testosterone synthesis; Steroidogenesis; Environmental endocrine disruptors; Polyphenols; Phthalates

Fund program: Funded by Wenzhou Key Laboratory of Reproduction and Genetics (22HZSY0051)

DOI:10.3760/cma.j.cn101441-20231120-00300

收稿日期　2023-11-20　本文编辑　孙敏
引用本文：吴惠华，朱蕊，李明清，等. 长方案促排卵中 hCG 扳机后 12 h 激素水平的变化对 IVF/ICSI-ET 结局的影响[J]. 中华生殖与避孕杂志，2024，44(6)：610-616. DOI：10.3760/cma.j.cn101441-20231120-00300.

·临床研究·

长方案促排卵中 hCG 扳机后 12 h 激素水平的变化对 IVF/ICSI-ET 结局的影响

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【摘要】　目的　探讨长方案体外受精/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）超促排卵治疗过程中，人绒毛膜促性腺激素（human chorionic gonadotropin，hCG）扳机 12 h 后 hCG、孕酮水平和雌二醇变化对妊娠结局的影响。方法　纳入 2015 年 3 月至 2020 年 6 月期间在南京医科大学附属苏州医院生殖与遗传中心行长方案 IVF/ICSI-ET 助孕治疗的 2 506 例患者，对其控制性超促排卵的相关资料进行回顾性分析。采用 Spearman 秩相关分析和路径分析对 hCG 扳机 12 h 后 hCG 水平、孕酮水平和雌二醇变化的相关影响因素及其对妊娠结局的影响进行分析。结果　hCG 扳机后 hCG 水平与孕酮水平呈正相关（r=0.094，P<0.001），与雌二醇变化率呈负相关（r=-0.093，P<0.001）。hCG 扳机后孕酮水平与雌二醇变化率呈负相关（r=-0.089，P<0.001）。hCG 剂量正向影响 hCG 扳机后 hCG 水平，路径系数（path coefficients，PC）为 0.307（P<0.001）。体质量指数（body mass index，BMI）负向影响 hCG 扳机后 hCG 和孕酮水平（PC=-0.434，P<0.001；PC=-0.154，P<0.001），正向影响雌二醇变化率（PC=0.097，P<0.001）。促性腺激素（gonadotopin，Gn）使用时间和使用总量正向影响 hCG 后孕酮水平（PC=0.102，P<0.001；PC=0.080，P=0.030）。hCG 扳机后 hCG 和孕酮水平正向影响获卵率（PC=0.098，P<0.001；PC=0.080，P<0.001），而雌二醇变化率对获卵率无明显影响（P>0.05）。hCG 扳机日孕酮水平负向影响正常受精率（PC=-0.050，P=0.039）。hCG 扳机后 hCG 水平、

孕酮水平和雌二醇变化率对优质胚胎率、临床妊娠率和活产率无明显影响（均 $P>0.05$）。结论　在长方案促排卵过程中，hCG 扳机后 12 h 的 hCG 水平、孕酮水平正向影响获卵率，而对正常受精率、优质胚胎率、临床妊娠率和活产率无明显影响。因而在长方案 IVF/ICSI-ET 治疗中，需要注意 hCG 扳机后 12 h 的 hCG 水平和孕酮水平。

【关键词】 人绒毛膜促性腺激素； 孕酮； 雌二醇变化率； 获卵率； 受精率

基金项目：苏州市卫生青年骨干人才“全国导师制”培训项目（Qngg2023017）；南京医科大学科技发展基金（NMUB20210280）

Effects of hormone changes 12 h after hCG trigger on the outcomes of IVF/ICSI-ET treatment with GnRH-a protocol

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【 **Abstract** 】 **Objective** To explore the effects of human chorionic gonadotropin (hCG), progesterone as well as the change of estradiol 12 h after hCG trigger on the outcomes of *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET). **Methods** A retrospective study was conducted at the Center for Reproduction and Genetics of the Affiliated Suzhou Hospital of Nanjing Medical University. A total of 2 506 patients received IVF/ICSI-ET treatment with gonadotropin-releasing hormone agonist (GnRH-a) protocol from March 2015 to June 2020 were selected. With Spearman rank correlation analysis and path analysis, we explore the relationship among the changes of these hormones and the baseline characteristic of patients, as well as the relationship among the changes of these hormones and the outcomes of IVF treatment. **Results** The increase of hCG was accompanied by the rise of progesterone and the decline of estradiol change rate (r=0.094, P<0.001; r=−0.093, P<0.001). Meanwhile the rise of progesterone was accompanied by the decline of estradiol change rate (r=−0.089, P<0.001). The dosage of hCG trigger was directly positively correlated to hCG level after hCG trigger, path coefficients (PC) was 0.307 (P<0.001). Body mass index (BMI) was directly negatively correlated to hCG level and progesterone level after hCG trigger (PC=−0.434, P<0.001; PC=−0.154, P<0.001), whereas positively correlated to estradiol change rate (PC=0.097, P<0.001). Meanwhile the duration and dosage of gonadotropin (Gn) used were positively correlated to progesterone level after hCG trigger (PC=0.102, P<0.001; PC=0.080, P=0.030). hCG level and progesterone level after hCG trigger had positive correlation to oocyte retrieved rate (PC=0.098, P<0.001; PC=0.080, P<0.001). While estradiol change rate was not correlated to oocyte retrieved rate (P>0.05). Progesterone level on hCG trigger day negatively related to normal fertilization rate (PC=−0.050, P=0.039). hCG level, progesterone level and estradiol change rate after

hCG trigger had no correlation with high-quality embryo rate, clinical pregnancy rate and live birth rate (all *P*>0.05). **Conclusion** Oocyte retrieved rate was positively affected by hCG level and progesterone level 12 h after hCG trigger. While normal fertilization rate, high-quality embryo rate, clinical pregnancy rate and live birth rate were not affected by the change of hormones level 12 h after hCG trigger. Therefore we should pay attention to hCG level and progesterone level 12 h after hCG trigger.

【**Key words**】 Human chorionic hormone; Progesterone; Estradiol change rate; Oocyte retrieved rate; Fertilization rate

Fund program: The National Mentoring Training Project of Suzhou Key Health Talents (Qngg2023017); The Science and Technology Development Fund of Nanjing Medical University (NMUB20210280)

DOI：10.3760/cma.j.cn101441-20231214-00362

收稿日期 2023-12-14 本文编辑 宋培培

引用本文：郭艺芬，任舒悦，高志贤，等. 基于生物信息学方法筛选复发性流产中巨噬细胞相关的免疫特征基因[J]. 中华生殖与避孕杂志，2024，44(6)：617-627. DOI：10.3760/cma.j.cn101441-20231214-00362.

·临床研究·

基于生物信息学方法筛选复发性流产中巨噬细胞相关的免疫特征基因

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【摘要】 目的 通过生物信息学分析方法，筛选可能导致复发性流产（recurrent miscarriage，RM）的母胎免疫微稳态失衡相关基因，寻找潜在的RM分子标志物。方法 从Gene Expression Omnibus（GEO）数据库下载由24例

RM 患者和 24 例正常对照妇女子宫内膜组织数据所组成的数据集 GSE165004，采用 R 语言的 Limma 包及 CIBERSOR 免疫浸润和加权基因共表达网络分析(weighted gene co-expression network analysis， WGCNA）方法，筛选了差异表达基因（differentially expressed genes， DEGs）和免疫相关模块；通过基因集富集分析（gene set enrichment analysis， GSEA）和基因集变异分析（gene set variation analysis， GSVA），评价了这些核心基因的功能关联性。最后我们使用蜕膜组织的数据集 GSE161969 进一步验证了关键基因的诊断价值。结果 通过差异分析，识别出 580 个差异表达基因，并通过 WGCNA 筛选得到 3 271 个与免疫相关的模块基因；利用机器学习技术，鉴定出 *FGF*2、*ANO*1 和 *LAPTM*5 作为关键基因，并通过 GSVA 分析，发现这些基因在免疫浸润和巨噬细胞途径中发挥重要作用。结论 *FGF*2、*ANO*1 和 *LAPTM*5 可能参与 RM 的免疫致病途径，是潜在的 RM 生物标志分子。

【关键词】 机器学习； 复发性流产； 生物信息学； 免疫浸润； 加权基因共表达网络分析

基金项目：国家卫生健康委员会计划生育药具重点实验室开放课题(2021KF06)

Identification of macrophage-related immune characteristic genes in recurrent miscarriage through bioinformatics approaches

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【**Abstract**】 **Objectives** To screen out genes potentially involved in the dysregulation of immune microhomeostasis at the maternal-fetal interface of recurrent miscarriage (RM) patients, and to identify novel biomarkers of RM by bioinformatic analysis. **Methods** The dataset GSE165004 of endometrial tissues from RM patients (*n*=24) and normal women as the control (*n*=24) was downloaded from the GEO database, and differentially expressed genes (DEGs) and immune-related modules were analyzed by using the R language's Limma package, along with CIBERSORT immune infiltration and Weighted Gene Co-expression Network Analysis (WGCNA). The functional associations of these core genes were evaluated through Gene Set Enrichment Analysis (GSEA) and Gene Set Variation Analysis (GSVA). Finally, we used the decidual tissue dataset GSE161969 to further validate the diagnostic value of these key genes. **Results** Differential analysis identified 580 DEGs, and 3 271 immune-related modular genes were selected by WGCNA analysis. *FGF*2, *ANO*1, and *LAPTM*5 were subsequently identified as key genes through machine learning techniques. GSVA analysis further revealed critical roles of *FGF*2, *ANO*1 and *LAPTM*5 in immune infiltration and macrophage pathways. **Conclusion** *FGF*2, *ANO*1 and *LAPTM*5 might participate in the immuno-related pathogenesis of RM, and present potential biomarkers for the early diagnosis and treatment of RM.

【**Key words**】 Machine learning; Recurrent miscarriage; Bioinformatics; Immune infiltration; Weighted gene co-expression network analysis

Fund program: Open Project Fund from NHC Key Lab of Reproduction Regulation (2021KF06)

DOI: 10.3760/cma.j.cn101441-20231122-00329

收稿日期 2023-11-22 本文编辑 李天琦

引用本文:李梦娜, 郑威, 杨宸, 等. 囊胚形态学评价参数对 IVF/ICSI 助孕后稽留流产绒毛染色体核型异常的影响[J]. 中华生殖与避孕杂志, 2024, 44(6): 628-634. DOI: 10.3760/cma.j.cn101441-20231122-00329.

·临床报道·

囊胚形态学评价参数对 IVF/ICSI 助孕后稽留流产绒毛染色体核型异常的影响

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【摘要】 目的 分析囊胚形态学评价参数包括囊胚发育天数(第5天和第6天)、囊胚扩张程度(4、5、6)、内细胞团和滋养外胚层分级对体外受精/卵胞质内单精子注射(*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI)助孕新鲜或冻融单囊胚移植后稽留流产绒毛染色体核型异常发生的影响。方法 纳入2015年2月至2023年2月期间于郑州大学第三附属医院生殖医学中心行 IVF/ICSI 助孕新鲜或冻融单囊胚移植后稽留流产患者的临床数据及绒毛染色体拷贝数变异(copy number variations, CNVs)的检测结果。采用病例对照研究,根据流产组织绒毛染色体 CNVs 检测结果将数据分为两组:异常染色体核型组(n=139)和正常染色体核型组(n=82),比较两组患者的基线数据。应用单因素 logistic 回归分析囊胚形态学评价参数对流产组织绒毛染色体核型异常发生的影响,同时应用多因素 logistic 回归调整男方年龄、精子正常形态率和女方年龄混杂因素。结果 基线数据中,异常染色体核型组男方年龄[(34.12±6.49)岁]、精子正常形态率[5.00(4.00, 6.00)%]和女方年龄[33.00(30.00, 37.00)岁]高于正常染色体核型组[(32.38±4.69)岁、4.00(2.00, 5.00)%和31.50(29.00, 34.00)岁],差异均具有统计学意义(P=0.022、P=0.020、P=0.009)。单因素和多因素 logistic 回归分析数据显示,囊胚发育天数、扩张程度、内细胞团和滋养外胚层等级均没有增加绒毛染色体核型异常发生的风险(均 P>0.05)。结论 囊

胚形态学评价参数与IVF/ICSI助孕新鲜或冻融单囊胚移植后稽留流产绒毛染色体核型异常无明显相关性。

【关键词】 单囊胚； 胚胎形态学参数； 内细胞团； 滋养外胚层； 稽留流产； 绒毛染色体核型异常

基金项目：国家重点研发计划重点专项（2021YFC2700602）；国家卫生健康委科学研究基金河南省医学科技攻关计划省部共建项目（SBGJ202102180）

Influence of morphological evaluation parameters of blastocysts on chromosomal karyotype abnormalities of chorionic villi in missed abortion after IVF/ICSI treatment

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【 **Abstract** 】 **Objective** Analyzing the influence of morphological evaluation parameters of blastocysts, including days of blastocyst development [day 5 (D5) and day 6 (D6)], degree of blastocyst expansion (4, 5, 6), inner cell mass and trophectoderm grade, on the occurrence of chromosomal karyotype abnormalities of chorionic villi in missed abortion after *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment and fresh/frozen-thawed single blastocyst transfer. **Methods** The clinical data of patients with missed abortion after IVF/ICSI treatment and fresh/frozen-thawed single blastocyst transfer from February 2015 to February 2023 in the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University were included. Using a case-control study, the data were divided into two groups according to the detection results of chromosomal copy number variations (CNVs) in chorionic villi of missed abortion abnormal karyotype group (n=139) and normal karyotype group (n=82). The baseline data between the two groups were compared. Univariate logistic regression was used to investigate the effect of blastocyst morphological rating parameters on the occurrence of chromosomal karyotype abnormalities of chorionic villi in aborted tissues, and multivariate logistic regression was also used to adjust confounding factors. **Results** Male age [(34.12±6.49) years], sperm morphology rate [5.00 (4.00,6.00)%] and female age [33.00 (30.00, 37.00) years] in abnormal karyotype group were higher than those in the normal karyotype group [(32.38±4.69) years, 4.00 (2.00,5.00)% and 31.50 (29.00,34.00) years], and the differences were statistically significant (P=0.022, P=0.020, P=0.009). Univariate and multivariate logistic regression analyses showed that days of blastocyst development, degree of blastocyst expansion, inner cell mass and trophectoderm grade did not increase the risk of chromosomal karyotype abnormalities of chorionic villi (all P>0.05). **Conclusion** There is no significant correlation between blastocyst morphological evaluation parameters

and chromosomal karyotype abnormalities in chorionic villi of missed abortion after fresh/frozen-thawed single blastocyst transfer with IVF/ICSI treatment.

【**Key words**】 Single blastocyst; Embryo morphological parameters; Inner cell mass; Trophectoderm; Missed abortion; Chromosome of chorionic villi

Fund program: National Key R&D Program (2021YFC2700602); National Health Commission Scientific Research Foundation Henan Medical Science and Technology Research Program Provincial Joint Construction Project (SBGJ202102180)

DOI：10.3760/cma.j.cn101441-20231005-00144

收稿日期 2023-10-05 本文编辑 王李艳

引用本文：杨易天，张扬，王磊. IVF-ET 后妊娠并发结核性脑膜炎 3 例并文献复习[J]. 中华生殖与避孕杂志，2024，44(6)：635-638. DOI：10.3760/cma.j.cn101441-20231005-00144.

·个案报道·

IVF-ET 后妊娠并发结核性脑膜炎 3 例并文献复习

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【摘要】 目的 探讨体外受精-胚胎移植（*in vitro* fertilization and embryo transfer，IVF-ET）后妊娠并发结核病的发生规律、临床特点、防治方法。方法 回顾性分析 2020 年 6 月至 2022 年 6 月期间在大连市妇女儿童医疗中心（集团）生殖中心接受 IVF-ET 后妊娠并发结核性脑膜炎的 3 例临床资料，并进行文献复习。结果 3 例 IVF-ET 后妊娠并发结核性脑膜炎患者均为原发性不孕，均有输卵管阻塞病史，首发临床症状均不典型，均存在诊疗延迟，均终止妊娠。结论 对存在输卵管因素的原发性不孕症患者，应重视 IVF-ET 助孕前结核病的筛查，并建议以γ干扰素试验及胸 CT 作为主要筛查手段。

【关键词】 受精，体外； 胚胎移植； 妊娠； 结核； γ干扰素试验

Three cases of pregnancy complicated with tuberculous meningitis after IVF-ET and literature review

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【 **Abstract** 】 **Objective** To investigate the occurrence, clinical characteristics, prevention and treatment of pregnancy complicated with tuberculosis after *in vitro* fertilization-embryo transfer (IVF-ET). **Methods** The clinical data of three cases of pregnancy complicated by tuberculosis meningitis after receiving IVF-ET in Reproductive Center of Dalian Women and Children's Medical Group from June 2020 to June 2022 were retrospectively analyzed, and the literatures were reviewed. **Results** All 3 patients with pregnancy complicated by tuberculosis meningitis after IVF-ET had primary infertility, and had a history of fallopian tube obstruction, atypical first clinical symptoms, delay in diagnosis and treatment, and termination of pregnancy. **Conclusion** For primary infertility patients with tubal factors, attention should be paid to IVF-ET screening before pregnancy tuberculosis, and γ interferon test and thoracic CT should be recommended as the main screening means.

【 **Key words** 】 Fertilization *in vitro*; Embryo transfer; Pregnancy; Tuberculosis; Gamma interferon test

DOI：10.3760/cma.j.cn101441-20231013-00158

收稿日期 2023-10-13 本文编辑 李天琦

引用本文：黄玲玲，陈佳，许定飞，等. 第三代测序技术在 ATR-X 综合征家系胚胎植入前遗传学检测中的应用[J]. 中华生殖与避孕杂志，2024，44(6)：639-645. DOI：10.3760/cma.j.cn101441-20231013-00158.

·个案报道·

第三代测序技术在 ATR-X 综合征家系胚胎植入前遗传学检测中的应用

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【摘要】 目的 探讨第三代测序技术在染色体微重复相关ATR-X综合征家系胚胎植入前遗传学检测中的临床应用价值。方法 2022年10月就诊于江西省妇幼保健院辅助生殖中心的1例生育过疑似ATR-X综合征患儿的家系为研究对象。染色体拷贝数变异测序（copy number variation sequencing, CNV-Seq）检测女方携带Xq21.1区域550 kb临床意义不明确的杂合微重复，该重复累及*ATRX*基因部分序列。采用第三代长读长测序技术对女方基因组序列进行检测，确定上述重复插入基因组的物理位置，明确该重复的致病性，并获得与上述微重复连锁遗传的单核苷酸多态性位点（single nucleotide polymorphism, SNP）单倍型。夫妻双方签署知情同意书后行胚胎植入前遗传学检测(preimplantation genetic testing, PGT)助孕。挑选1枚不携带致病性微重复的整倍体胚胎移植，于孕中期羊水穿刺后进行产前诊断，验证是否与PGT结果一致，跟踪随访胎儿出生后情况。结果 第三代长读长测序及Sanger测序验证结果显示，女方携带的Xq21.1微重复插入至基因组chrX: 76804463-76804464（GRCh37/hg19），为*ATRX*基因内串联重复，预测可能导致ATRX蛋白正常功能受损。该家系经PGT治疗，获得27枚卵子，卵胞质内单精子注射（intracytoplasmic sperm injection, ICSI）受精后成功养成13枚囊胚。囊胚活检细胞经遗传学检测显示,2枚胚胎为不携带上述致病微重复的整倍体胚胎。冻融胚胎移植1枚正常胚胎，成功妊娠，孕17周羊水穿刺检测结果未见异常，2023年11月孕39^{+5}周顺产娩一女活婴，体健。结论 第三代测序技术凭借其长读长的特点，对临床意义不明确微重复进行PGT检测时有显著优势，不仅能够明确微重复插入基因组的位置,判断其致病性,还能够获得与目标变异连锁遗传的SNP单倍型，为后续胚胎检测做准备。

【关键词】 ATR-X综合征； 第三代测序技术； 微重复； 胚胎植入前遗传学检测； 单核苷酸多态性

基金项目：江西省自然科学基金（20224BAB206018、20232BAB21609、20232BAB206028）；江西省自然科学基金（20232BAB206028）；江西省重点研发计划（20203BBGL7359）；江西省卫生健康委科技创新重点项目（2023ZD006）；生殖健康与优生优育江西省重点实验室（2024SSY06211）

Application of third-generation sequencing technology in preimplantation genetic testing of embryos in a family with ATR-X syndrome

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【**Abstract**】 **Objective** To explore the clinical application value of third-generation sequencing technology in preimplantation genetic testing (PGT) of an ATR-X syndrome pedigree with chromosomal microduplication. **Methods** The study selected a pedigree with a suspected ATR-X syndrome child at Assisted Reproductive Center of Jiangxi Maternal and Child Health Hospital in October 2022. After chromosome copy number variation sequencing (CNV Seq) detection, it was found that the female carried a 550 kb heterozygous microrepeat with unclear clinical significance in the Xq21.1 region, which involved partial sequences of the *ATRX* gene. The third generation long read sequencing technology was used to detect the female genome sequence, determine the physical location of the insertion of the above repeat into the genome, clarify the pathogenicity of the repeat, and obtain a single nucleotide polymorphism (SNP) haplotype linked to the above micro repeat inheritance. After the couple's full informed consent, PGT was performed to assist pregnancy. One haploid embryo without pathogenic microduplication was selected for transfer. To verify the consistency with PGT test results, amniocentesis prenatal diagnosis was performed in the second trimester after successful pregnancy, and the fetus was followed up after birth. **Results** The results of the third generation long read sequencing and Sanger sequencing verification showed that the Xq21.1 microrepeat carried by the female was inserted into the genome chrX: 76804463-76804464 (GRCh37/hg19), which is an intra tandem repeat of the *ATRX* gene, and it is predicted that it may cause damage to the normal function of the ATRX protein. After one cycle of PGT treatment, 27 oocytes were obtained and 13 blastocysts were successfully developed after intracytoplasmic sperm injection (ICSI). Through genetic testing, it was found that two blastocysts were haploid embryos without carrying the aforementioned pathogenic microduplication. After thawing and transferring one of the blastocysts, the pregnancy was achieved, and the prenatal diagnosis results of amniocentesis in the second trimester were consistent with the PGT results. In November 2023, at 39^{+5} weeks of pregnancy, a female live baby was delivered by natural delivery, and she is in good health. **Conclusion** The third-generation sequencing technology has significant advantages in PGT detection of clinically ambiguous microreplicates with functional deficiency due to its long read length characteristics. It can not only determine the location of microreplicates inserted into the genome and determine their pathogenicity, but also obtain SNP haplotypes that are linked to the target mutation, thus preparing for subsequent embryo detection.

【**Key words**】 ATR-X syndrome; Third generation sequencing technology; Micro repetition; Preimplantation genetic testing; Single nucleotide polymorphism

Fund program: Jiangxi Provincial Natural Science Foundation Youth Program (20224BAB206018,20232BAB216097,20232BAB206028); Jiangxi Provincial Natural Science Foundation Project (20232BAB206028);Jiangxi Province Key R&D Program Project (20203BBGL7359); Jiangxi Provincial Health Commission Science and Technology Innovation Key Project (2023ZD006); Key Laboratory of Reproductive Health and Eugenics in Jiangxi Province (2024SSY06211)

DOI：10.3760/cma.j.cn101441-20230606-00227

收稿日期　2023-06-06　本文编辑　李天琦

引用本文：徐诗榕，王颖. 抗苗勒管激素在IVF/ICSI女性中预测价值及其影响因素的研究进展[J]. 中华生殖与避孕杂志，2024，44(6)：646-651. DOI：10.3760/cma.j.cn101441-20230606-00227.

·综述·

抗苗勒管激素在IVF/ICSI女性中预测价值及其影响因素的研究进展

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【摘要】 抗苗勒管激素（anti-Müllerian hormone，AMH）作为转化生长因子-β超家族的一员，对接受体外受精-胚胎移植（*in vitro* fertilization and embryo transfer，IVF-ET）女性卵巢储备及卵巢反应性评估、选择合适促排卵方案以及提高临床累积活产率有着重要指导价值。本文通过总结AMH影响卵母细胞发育及卵泡闭锁的可能机制，探讨AMH在卵巢中发挥的生理作用及可能影响AMH在血清及卵泡液中浓度的因素，从而阐明AMH用于预测及改善IVF结局潜在的临床价值，重新全面评估AMH尤其是超生理剂量的AMH在女性生殖、多囊卵巢综合征患者以及IVF/卵胞质内单精子注射中的重要地位，并探讨了AMH在女性生殖中的临床治疗作用。

【关键词】 抗苗勒管激素；　受精，体外；　卵母细胞；　妊娠结局；　卵巢生理

基金项目：国家重点研发项目（2022YFC2702905）；国家自然科学基金（81873833）；北京大学第三医院重点研究项目（SY2018016）

Research progress on the predictive value of anti-Müllerian hormone in IVF/ICSI women and its influencing factors

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【 **Abstract** 】 Anti-Müllerian hormone (AMH) is a member of the transforming growth factor-β superfamily. It has an important guiding value for evaluating ovarian reserve and ovarian responsiveness of women undergoing *in vitro* fertilization and embryo transfer (IVF-ET), selecting the appropriate ovulation regimen for patients, and improving the clinical cumulative live birth rate of women undergoing IVF/intracytoplasmic sperm injection (ICSI). Through literature review, this paper summarized the possible mechanisms of AMH affecting oocyte development and follicular atresia, and explored the physiological roles of AMH in ovaries and the factors that may affect AMH concentration in serum and follicular fluid, to clarify the potential clinical value of AMH in predicting and improving IVF outcomes, re-evaluate the importance of AMH, especially the superphysiological dosage of AMH in female reproduction, polycystic ovary syndrome patients and IVF/ICSI, and explore the clinical therapeutic effect of AMH in female reproduction.

【 **Key words** 】 Anti-Müllerian hormone; Fertilization *in vitro*; Oocytes; Pregnancy outcome; Ovarian physiology

Fund program: National Key R&D Program of China (2022YFC2702905); National Natural Science Foundation of China (81873833); Key Clinical Research Project of Peking University Third Hospital (SY2018016)

DOI：10.3760/cma.j.cn101441-20230606-00226

收稿日期 2023-06-06 本文编辑 李天琦

引用本文：刘佳佳，李虹维，高明霞. 富血小板血浆在卵巢低反应患者中的应用及研究进展[J]. 中华生殖与避孕杂志，2024，44(6)：652-655. DOI：10.3760/cma.j.cn101441-20230606-00226.

·综述·

富血小板血浆在卵巢低反应患者中的应用及研究进展

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【摘要】 卵巢低反应（poor ovarian response，POR）是辅助生殖领域所面临的一大难题。富血小板血浆（platelet-rich plasma，PRP）作为一种新型治疗方法，已被证明在促进血管生成、细胞分化和增殖、卵泡生成等方面发挥着积极的作用，对于 POR 患者的治疗具有巨大的优势。本文就 PRP 的来源及制备、对 POR 患者卵巢功能和妊娠结局的影响以及 PRP 可能的作用机制进行综述。此外，文章还探讨了在 POR 患者治疗过程中 PRP 所面临的挑战以及未来可关注的研究方向，旨在为临床和科研工作者提供参考。

【关键词】 富血小板血浆； 生殖技术，辅助； 卵巢低反应

Application and research progress of platelet-rich plasma in patients with poor ovarian response

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【Abstract】 Poor ovarian response (POR) is a major challenge in the field of assisted reproduction. Platelet-rich plasma (PRP), as a new treatment, has been shown to have significant advantages in promoting angiogenesis, cell differentiation and proliferation, and follicle formation in the treatment of POR patients. This review provides a comprehensive summary of the source and preparation of PRP, the impact of PRP on ovarian reserve and pregnancy outcomes in POR patients, and the possible mechanisms of PRP action. Additionally, it discusses the challenges faced by PRP in the treatment of POR patients and future research directions that can be focused on, aiming to provide valuable insights for clinical and scientific researchers.

【Key words】 Platelet-rich plasma; Reproductive technology, assisted; Poor ovarian response

DOI：10.3760/cma.j.cn101441-20230520-00209

收稿日期 2023-05-20 本文编辑 孙敏

引用本文：徐子宁，王瑶婷，孙娟，等. 应用子宫输卵管超声造影评估输卵管通畅性：在争议与困境中前行[J]. 中华生殖与避孕杂志，2024，44(6)：656-660. DOI：10.3760/cma.j.cn101441-20230520-00209.

·综述·

应用子宫输卵管超声造影评估输卵管通畅性：在争议与困境中前行

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【摘要】 近年来，输卵管性不孕的发病率不断上升。在我国，多数输卵管性不孕女性为了尽可能保留输卵管，会优先考虑接受保守治疗或者输卵管重建手术。为了满足这类患者的生育需求，生殖领域的临床医生就需要综合评价各种不孕危险因素，权衡利弊，探求更符合患者利益的个体化诊疗方案。对于输卵管的影像学评估水准也相应地提出了更高的要求。子宫输卵管超声造影（hysterosalpingo-contrast sonography，HyCoSy）作为评价输卵管通畅性的一线影像学技术，其价值已得到大量临床实践的肯定，但仍面临着众多争议与困境。本文通过文献回顾和经验总结，为 HyCoSy 这项技术的前行提供观点。

【关键词】 子宫输卵管超声造影； 输卵管通畅性； 输卵管性不孕

基金项目：浙江省医药卫生科技计划项目（2024KY688）；浙江省人民医院优秀科研启动基金（ZRY2021B012、 ZRY2020B016）

Evaluation of tubal patency by hysterosalpingo-contrast sonography: moving forward in controversies and dilemmas

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【Abstract】 In recent years, the incidence rate of tubal infertility has been rising. In China, most patients with tubal infertility prioritize conservative management or tubal reconstruction surgery in order to preserve fallopian tubes as far as possible. In order to meet the reproductive needs of tubal infertile patients, clinicians in the reproductive field need to evaluate various infertility risk factors comprehensively, weigh the pros and cons, and explore individualized reproductive programs which are more in line with the interests of patients. Correspondingly, higher requirements for the imaging evaluation efficiency of the fallopian tubes have been put forward. Hysterosalpingo-contrast sonography (HyCoSy), as a first-line imaging technique for evaluating tubal patency, still faces many controversies and dilemmas despite its value being widely recognized in

clinical practice. This paper aims to provide viewpoints for the advancement of HyCoSy by reviewing literature and summarizing experiences.

【**Key words**】 Hysterosalpingo-contrast sonography; Tubal patency; Tubal infertility

Fund program: Medical and Health Technology Project in Zhejiang Province of China (2024KY688); Excellent Scientific Research Foundation of Zhejiang Provincial People's Hospital (ZRY2021B012, ZRY2020B016)

DOI：10.3760/cma.j.cn101441-20230410-00148

收稿日期 2023-04-10 本文编辑 李天琦

引用本文：孙理兰，孙平平，赵文杰，等. 左旋肉碱在卵母细胞成熟和早期胚胎发育中的生物学作用[J]. 中华生殖与避孕杂志，2024，44(6)：661-665. DOI：10.3760/cma.j.cn101441-20230410-00148.

·综述·

左旋肉碱在卵母细胞成熟和早期胚胎发育中的生物学作用

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【摘要】 卵母细胞质量差是导致女性不孕的主要原因之一，寻找改善卵母细胞质量的调节剂越来越受到重视。目前已有大量研究表明左旋肉碱在调节女性生殖能力方面具有重要功能。鉴于此，本文综述了左旋肉碱在卵母细胞成熟和早期胚胎发育中的关键作用及其调控机制，包括活化脂肪酸进行β-氧化来调节能量代谢、抗氧化防止氧化损伤和抑制细胞凋亡等，及左旋肉碱在改善卵母细胞质量和早期胚胎发育中的研究进展。。

【关键词】 左旋肉碱； 卵母细胞； 脂质代谢； 抗氧化； 凋亡； 胚胎

Biological function of L-carnitine in oocyte maturation and early embryo development

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【**Abstract**】 Poor oocyte quality is responsible for female infertility. The search for supplements to improve oocyte quality is receiving increasing attention. Many studies have shown that L-carnitine plays a variety of roles in regulating female fertility. This article reviews the key roles and regulatory mechanisms of L-carnitine in oocyte maturation and early embryonic development, including activating fatty acids for β-oxidation to regulate energy metabolism, antioxidation to prevent oxidative damage, and inhibition of cell apoptosis, and the research progress of LC in improving oocyte quality and early embryo development.

【**Key words**】 L-carnitine; Oocyte; Lipid metabolism; Antioxidants; Apoptosis; Embryo