

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41卷 第12期 2021年12月25日出版

主 管

中国科学技术协会

主 办

中华医学会
上海市计划生育科学研究所
复旦大学附属妇产科医院

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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

广告发布登记号

京东市监广登字20200006号

印 刷

上海商务联西印刷有限公司

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,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30.00元,全年360.00元

中国标准连续出版物号

ISSN 2096-2916

CN 10-1441/R

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《中华生殖与避孕杂志》稿约 封二

本期责任编辑 李劲松 杨蕊 本期责任编辑 孙敏 本期责任编辑 年利红

CHINESE JOURNAL OF REPRODUCTION AND CONTRACEPTION

(Original title: *Reproduction and Contraception*)

Monthly

Established in December 1980

Volume 41, Number 12

December 25, 2021



Responsible Institution

China Association for Science and Technology

Sponsor

Chinese Medical Association, Shanghai Institute of Planned Parenthood Research, Obstetrics and Gynecology Hospital of Fudan University

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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

Business Book Printing Shop Shanghai Printing Co., LTD

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: randc@sibpt.com

CSSN

ISSN 2096-2916
CN 10-1441/R

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DOI: 10.3760/cma.j.cn101441-20210608-00260

收稿日期 2021-06-08 本文编辑 孙敏

引用本文: 刘芯宇, 李劲松. 孤雄单倍体胚胎干细胞的建立及其应用[J]. 中华生殖与避孕杂志, 2021, 41(12): 1053-1061. DOI: 10.3760/cma.j.cn101441-20210608-00260.

·干细胞专栏·

孤雄单倍体胚胎干细胞的建立及其应用

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【摘要】 小鼠孤雄单倍体胚胎干细胞携带一套来源于精子的遗传物质，与二倍体胚胎干细胞相似，拥有干细胞的自我更新和多向分化等特性，能够在体外长期稳定地培养。重要的是，该细胞能够代替精子在注入到卵母细胞中后，产生半克隆小鼠。因其兼具干细胞和精子特性，故又被称为“人造精子”细胞或者类精子干细胞。将孤雄单倍体胚胎干细胞与 CRISPR-Cas9（clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9）等新型基因编辑技术结合起来，能够在细胞水平和动物个体水平进行精准、复杂和高通量的遗传改造，为基因的功能研究提供了强有力的工具。本文综述了孤雄单倍体胚胎干细胞的建立，及其在印记基因功能研究、遗传筛选、人类疾病模拟和蛋白质标签打靶等方面的应用。

【关键词】 单倍体胚胎干细胞； CRISPR-Cas9； 基因编辑； 遗传筛选； 类精子干细胞

Generation and application of androgenetic haploid embryonic stem cells

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【Abstract】 Mouse androgenetic haploid embryonic stem cells (AG-haESCs) only have one set of chromosomes originated from sperm. Same as diploid embryonic stem cell, AG-haESCs have the ability to self-renew and differentiate into different cell types from three embryonic layers. Also, they can be cultured stably *in vitro* for a long time. They are able to be used to replace spermatids for injecting into oocytes to produce semi-cloned mice. Because they have both characters of stem cells and sperm, they are also known as "artificial sperm" or sperm-like stem cells.

Combining with new gene editing technologies such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9), AG-haESCs can be used to edit gene at both cellular and organismal levels with high efficiency, accuracy, and throughput, providing powerful tools for the study of gene functions. Here, we review the establishment of AG-haESCs and their applications in imprinted gene function research, genetic screening, human disease modeling and genome tagging project.

【Key words】 Androgenetic haploid embryonic stem cells; CRISPR-Cas9; Gene editing; Genetic screening; Sperm-like stem cells

DOI: 10.3760/cma.j.cn101441-20201219-00682

收稿日期 2020-12-22 责任编辑 宋培培

引用本文: 李林艳, 刘荣霞, 彭淋坤, 等. 人羊膜间充质干细胞改善小鼠自身免疫性卵巢功能不全及子宫内膜容受性[J]. 中华生殖与避孕杂志, 2021, 41(12): 1062-1070. DOI: 10.3760/cma.j.cn101441-20201219-00682.

·干细胞专栏·

人羊膜间充质干细胞改善小鼠自身免疫性卵巢功能不全及子宫内膜容受性

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【摘要】 目的 探索人羊膜间充质干细胞(human amniotic mesenchymal stem cells, hAMSCs)对自身免疫性早发性卵巢功能不全(premature ovarian insufficiency, POI)小鼠卵巢功能和子宫内膜容受性的影响。方法 使用透明带3多肽-弗氏免疫佐剂诱导小鼠自身免疫性POI, 一次性尾静脉注射移植hAMSCs 1×10^6 细胞/只, 将动物分为正常组($n=10$)、模型组($n=15$)、hAMSCs组($n=15$), 阴道涂片监测动情周期, 酶联免疫法检测血清卵泡刺激素(follicle-stimulating hormone, FSH)、雌二醇与抗苗勒管激素(anti-Müllerian hormone, AMH)含量, HE染色观察卵巢和子宫病理组织学变化, 免疫组织化学检测子宫同源框A10(homeobox A10, HOXA10)、肿瘤坏死因子- α (tumor necrosis factor- α ,

TNF- α) 和 FSH 受体 (FSH receptor, FSHR) 蛋白表达, 综合评价子宫内膜容受性。结果 hAMSCs 移植 6 周, hAMSCs 组动情周期异常率 [40.00% (6/15)] 低于模型组 [86.67% (13/15), $P=0.021$]。与模型组血清 FSH [(10.239 \pm 1.091) $\mu\text{g/L}$]、雌二醇 [(103.325 \pm 4.952) ng/L] 和 AMH [(1.133 \pm 0.494) $\mu\text{g/L}$] 水平相比, hAMSCs 组 FSH 水平 [(7.664 \pm 0.735) $\mu\text{g/L}$] 明显降低 ($P<0.001$), 雌二醇 [(126.883 \pm 23.370) ng/L] 和 AMH [(2.204 \pm 0.453) $\mu\text{g/L}$] 水平均明显升高 ($P=0.015$, $P<0.001$)。与模型组不同, hAMSCs 组卵巢指数、子宫指数增高; 卵巢组织不同发育阶段的卵泡数增加, 间质纤维化和闭锁卵泡少见, 子宫壁与子宫内膜增厚, 腺体数量和体积增加。HOXA10 吸光度 (absorbance, A) 值 hAMSCs 组 (5.90 \pm 1.94) 高于模型组 (2.79 \pm 1.27, $P=0.029$), TNF- α A 值 hAMSCs 组 (3.83 \pm 1.23) 低于模型组 (6.26 \pm 0.96, $P=0.002$); FSHR A 值 hAMSCs 组 (3.61 \pm 1.66) 与模型组 (2.74 \pm 0.22) 差异无统计学意义 ($P>0.05$), 但模型组低于正常组 (4.13 \pm 0.54, $P=0.006$)。结论 移植 hAMSCs 在恢复自身免疫性 POI 小鼠卵巢功能的同时, 可明显改善子宫内膜容受性, 有助于提高生育能力。

【关键词】 原发性卵巢功能不全; 人羊膜间充质干细胞; 子宫内膜容受性; 同源框 A10; 肿瘤坏死因子- α ; 卵泡刺激素受体

Human amniotic mesenchymal stem cells improve ovarian function and endometrial receptivity in mice with autoimmune premature ovarian insufficiency

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【Abstract】 **Objective** To investigate the effect of human amniotic mesenchymal stem cells (hAMSCs) on ovarian function and endometrial receptivity in mice with autoimmune premature ovarian insufficiency (POI). **Methods** POI mouse was induced by treatment with zona pellucida 3 polypeptide fragment-Freund immune adjuvant. The animals were divided into normal group ($n=10$), model group ($n=15$) and hAMSCs group ($n=15$). hAMSCs (1×10^6 cells/mouse) were transplanted by tail vein single injection. The oestrus cycles were evaluated by vaginal smears. The levels of follicle-stimulating hormone (FSH), estrogen and anti-Müllerian hormone (AMH) in serum were detected by enzyme-linked immunosorbent assay methods. Morphological changes of ovarian and uterus tissues were observed after HE staining. The expressions of homeobox A10 (HOXA10), tumor necrosis factor- α (TNF- α) and FSH receptor (FSHR) proteins in uterine were measured by immunohistochemistry. The endometrial receptivity was comprehensively assessed. **Results** After hAMSCs transplanting 6 weeks, the rate of abnormal oestrus cycles in hAMSCs group [40.0% (6/15)] was lower than that in model group [86.7% (13/15), $P=0.021$]. Compared with the levels of serum FSH [(10.239 \pm 1.091) $\mu\text{g/L}$], estradiol [(103.325 \pm 4.952) ng/L] and AMH [(1.133 \pm 0.494) $\mu\text{g/L}$] in model group, the level of FSH in hAMSCs group [(7.664 \pm 0.735) $\mu\text{g/L}$] was significantly decreased ($P<0.001$), the levels of estradiol [(126.883 \pm 23.370) ng/L]

and AMH [(2.204±0.453) µg/L] were significantly increased in hAMSCs group ($P=0.015$, $P<0.001$). Different from model group, the ovarian and uterine index were increased. A large number of healthy follicles at all stages were highly increased, but it was rare to find interstitial fibrosis and atresia follicles. The uterine wall and endometrium were thickened, and the number and volume of the glands were increased. The absorbance (A) of HOXA10 in hAMSCs group (5.90±1.94) was higher than that in model group (2.79±1.27, $P=0.029$). The TNF- α A value of hAMSCs (3.83±1.23) group was significantly lower than that of model group (6.26±0.96, $P=0.002$). Although there was no significant difference on FSHR A value between hAMSCs group (3.61±1.66) and model group (2.74±0.22, $P>0.05$), the FSHR A value of model group was lower than that of normal group (4.13±0.54, $P=0.006$).

Conclusion hAMSCs transplantation could restore ovarian function of autoimmune POI mice meanwhile significantly improve uterine receptivity and fertility.

【 Key words 】 Premature ovarian insufficiency; Human amniotic mesenchymal stem cells; Endometrial receptivity; Homeobox A10; Tumor necrosis factor- α ; Follicle-stimulating hormone receptor

·干细胞专栏·

DOI: 10.3760/cmaj.cn101441-20200601-00322

收稿日期 2020-06-05 本文编辑 宋培培

引用本文: 张娟, 周丽, 段瑶, 等. 脐带间充质干细胞对卵巢早衰模型家兔 TIMP1、FN 和 MMP9 表达的影响[J]. 中华生殖与避孕杂志, 2021, 41(12): 1071-1078. DOI: 10.3760/cmaj.cn101441-20200601-00322.

脐带间充质干细胞对卵巢早衰模型 家兔 TIMP1、FN 和 MMP9 表达 的影响

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【摘要】 目的 研究脐带间充质干细胞改善卵巢早衰家兔卵巢功能的潜在机制。方法 将 10 只家兔按随机数表法分为治疗组和模型组各 5 只, 均采用腹腔注射环磷酸酰胺 ($50 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, 连续 2 d) 构建卵巢早衰模型。造模 1 周后, 治疗组予以耳缘静脉注射人脐带间充质干细胞 (2 mL/d , 连续 3 d), 模型组予以注射等量无菌水。第 28 日后采集两组家兔卵巢组织标本, 通过苏木精-伊红染色法观察两组家兔卵巢组织形态结构, 并采用蛋白免疫印迹法、实时荧光定量 PCR 及免疫组织化学技术检测两组家兔卵巢组织内基质金属蛋白酶组织抑制物 1 (tissue inhibitor of metalloproteinases 1, TIMP1)、纤连蛋白 (fibronectin, FN)、纤维形成相关因子基质金属蛋白酶 9 (matrix metalloproteinases 9, MMP9) 在蛋白及 mRNA 水平上的表达。结果 ①模型组家兔卵巢组织内原始卵泡数量少, 闭锁卵泡多, 各级卵泡颗粒层排列紊乱, 卵细胞核出现固缩, 发生凋亡, 卵巢间质出现纤维化; 而治疗组家兔卵巢组织内原始、初级卵泡数量多, 闭锁卵泡少, 各级卵泡颗粒细胞排列规则。②与模型组相比较, 治疗组家兔卵巢组织内 TIMP1 蛋白 (0.546 ± 0.021 比 0.820 ± 0.085) 和 FN 蛋白表达量增多 (0.221 ± 0.065 比 0.516 ± 0.064) (P 均 < 0.001), 而 MMP9 蛋白表达量减少 (0.504 ± 0.049 比 0.204 ± 0.066 , $P < 0.001$)。③与模型组相比较, 治疗组家兔卵巢组织内 TIMP1 mRNA (0.217 ± 0.024 比 0.470 ± 0.039) 和 FN mRNA 的表达量增多 (0.039 ± 0.006 比 0.125 ± 0.012 , P 均 < 0.001), 而 MMP9 mRNA 的表达量减少 (0.009 ± 0.000 比 0.002 ± 0.000 , $P < 0.001$)。④TIMP1 和 FN 主要表达在颗粒细胞和卵细胞膜, TIMP1 还表达在卵巢间质组织, 治疗组 TIMP1 和 FN 的表达多于模型组, 差异均具有统计学意义 ($P < 0.001$, $P = 0.005$)。MMP9 主要表达在颗粒细胞和卵巢间质组织, 治疗组 MMP9 的表达少于模型组, 差异具有统计学意义 ($P < 0.001$)。结论 脐带间充质干细胞能够通过调节卵巢组织内 TIMP1、FN 和 MMP9 水平来改善卵巢功能。

【关键词】 间充质干细胞; 基质金属蛋白酶组织抑制物; 纤连蛋白; 基质金属蛋白酶; 卵巢早衰

基金项目: 湖北省自然科学基金项目 (2018CFC806)

Effect of umbilical cord-derived mesenchymal stem cells on the expression of TIMP1, FN and MMP9 in a rabbit model of premature ovarian failure

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【Abstract】 Objective To explore the potential molecular mechanism of umbilical cord-derived mesenchymal stem cells (UCMSCs) to improve ovarian function in premature ovarian failure (POF) rabbits. **Methods** Ten rabbits were randomly divided into 2 groups (five rabbits in each), treatment group and model group. A rabbit model of POF was established using an intraperitoneal injection of

cyclophosphamide for 2 d ($50 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$). After a week, the treatment group received UCMSCs intravenously via a marginal ear vein and model group received equal amounts of sterile water. Ovarian samples were collected on day 28 and ovaries morphology was observed by hematoxylin-eosin staining. Tissue inhibitor of metalloproteinases 1 (TIMP1), fibronectin (FN) and matrix metalloproteinases 9 (MMP9) protein and mRNA expression were detected by Western blotting, PCR, and immunohistochemistry. **Results** 1) In model group, ovaries of the ovarian tissue displayed as reduced number of primordial follicles, along with increased number of atretic follicles. The granular layer cells of every follicle grade were arranged in disorder. The oocyte nucleus appeared pyknotic and apoptotic changed. Fibrosis was performed in the ovarian stroma. While in treatment group, the number of primordial and primary follicles in the ovarian tissue was large, and there were few atretic follicles. The granule cells of every follicle grade were arranged regularly. 2) Compared with model group, the expressions of TIMP1 protein (0.546 ± 0.021 vs. 0.820 ± 0.085) and FN protein (0.221 ± 0.065 vs. 0.516 ± 0.064) in treatment group were significantly increased (all $P<0.001$), while the expression of MMP9 protein (0.504 ± 0.049 vs. 0.204 ± 0.066) in treatment group was significantly decreased ($P<0.001$). 3) Compared with model group, the expressions of TIMP1 mRNA (0.217 ± 0.024 vs. 0.470 ± 0.039) and FN mRNA (0.039 ± 0.006 vs. 0.125 ± 0.012) in treatment group were significantly increased (all $P<0.001$), while the expression of MMP9 mRNA (0.009 ± 0.000 vs. 0.002 ± 0.000) in treatment group was significantly decreased ($P<0.001$). 4) TIMP1 and FN were mainly expressed in the granule cells and egg cell membranes. TIMP1 was also expressed in ovarian interstitial tissue, and the expression levels were significantly increased in treatment group compared with model group ($P<0.001$, $P=0.005$). MMP9 was mainly expressed in granule cells and ovarian interstitial tissue, and the expression levels were significantly decreased in treatment group compared with model group ($P<0.001$). **Conclusion** UCMSCs were able to improve ovarian function by regulating the levels of TIMP1, FN and MMP9 in ovarian tissue.

【 Key words 】 Mesenchymal stem cells; Tissue inhibitor of metalloproteinases; Fibronectin; Matrix metalloproteinases; Premature ovarian failure

Fund program: Natural Science Foundation of Hubei Province (2018CFC806)

DOI: 10.3760/cma.j.cn101441-20210922-00420

收稿日期 2021-09-22 本文编辑 孙敏

引用本文: 谢珍珍, 阿拉努尔·穆合塔尔, 黄茹飞, 等. 自体骨髓有核细胞移植治疗卵巢功能减退的效果研究[J]. 中华生殖与避孕杂志, 2021, 41(12): 1079-1085. DOI: 10.3760/cma.j.cn101441-20210922-00420.

·干细胞专栏·

自体骨髓有核细胞移植治疗卵巢功能减退的效果研究

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谢珍珍和阿拉努尔·穆合塔尔对本文有同等贡献

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【摘要】 目的 探讨自体骨髓有核细胞移植对卵巢功能减退相关疾病的临床疗效。方法 基于 2020 年 9 月至 2021 年 8 月期间在上海计生所医院和上海新虹桥国际医学中心就诊的早发性卵巢功能不全、围绝经期综合征和反复辅助生殖失败的 28 例患者资料, 开展自身前后对照研究。对患者进行超声引导下自体骨髓有核细胞注入卵巢, 比较治疗前后患者自觉症状报告情况、子宫内膜厚度、双侧卵巢体积和、双侧卵巢卵泡个数及双侧卵巢卵泡最大径和的变化, 同时比较雌二醇、卵泡刺激素(follicle-stimulating hormone, FSH)、黄体生成素(luteinizing hormone, LH)、孕酮、泌乳素及睾酮水平的变化。结果 自体骨髓有核细胞移植治疗后, 患者双侧卵巢卵泡数、双侧卵巢卵泡最大径和分别增加(1.26±2.12)个和(5.40±8.92)mm, 差异均具有统计学意义($P=0.005$, $P=0.006$)。治疗后子宫内膜厚度、双侧卵巢体积和有增加趋势, 但差异均无统计学意义(P 均 >0.05)。但在治疗前后单侧变化幅度更大的卵巢体积、卵泡个数和卵泡最大径的分析显示, 治疗后卵巢体积、卵泡数量及卵泡最大径均增加, 差异均具有统计学意义($P=0.007$, $P<0.001$, $P=0.002$)。治疗后 FSH、LH、孕酮和泌乳素水平降低, 但差异均无统计学意义(P 均 >0.05)。疾病类型分层分析显示, 治疗后子宫内膜、双侧卵巢卵泡数和及卵泡最大径和呈增加趋势, 但仅在围绝经期综合征患者中双侧卵泡个数和以及卵泡最大径和的差异具有统计学意义($P=0.008$, $P=0.047$)。结论 本研究提示自体骨髓有核细胞治疗可能在一定程度上改善卵巢功能, 有望成为早发性卵巢功能不全、

围绝经期综合征、反复辅助生殖失败患者的新治疗方法，但尚需扩大样本量进行深入研究。

【关键词】 骨髓移植； 干细胞； 原发性卵巢功能不全； 治疗效果

A study on the effect of autologous bone marrow nucleated cell transplantation in the treatment of ovarian dysfunction

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【Abstract】 Objective To evaluate the clinical efficacy of autologous bone marrow nucleated cell transplantation on ovarian dysfunction-related diseases. **Methods** From September 2020 to August 2021, we conducted a before-after study in Shanghai Institute of Planned Parenthood Research Hospital and Shanghai New Hongqiao International Medical Center. A total of 28 patients with premature ovarian insufficiency, perimenopausal syndrome or repeated assisted reproduction failure were treated with ultrasound-guided autologous bone marrow nucleated cell transplantation into the ovaries. Clinical efficacy was evaluated by comparing the patients' self-reported symptoms, endometrial thickness, bilateral ovarian volume, the number of bilateral ovarian follicles, the maximum diameter of bilateral ovarian follicles, and the level of plasma estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, prolactin, and testosterone. **Results** After autologous bone marrow nucleated cell transplantation, the number of bilateral ovarian follicles and the maximum diameter of bilateral ovarian follicles statistically significantly increased by an average of 1.26 ± 2.12 ($P=0.005$) and (5.40 ± 8.92) mm ($P=0.006$), respectively. Endometrial thickness and bilateral ovarian volume increased after treatment although without statistical significance (all $P>0.05$). However, the ovarian volume, the number of follicles, and the maximum diameter of follicles with greater changes between the left and right sides of the treatment, were found to statistically significantly increase after treatment ($P=0.007$, $P<0.001$, $P=0.002$). Besides, the levels of FSH, LH, progesterone, and prolactin decreased with no statistical significance (all $P>0.05$). The stratified analysis of disease types found that endometrial thickness, the number of bilateral ovarian follicles, and the maximum diameter of bilateral ovarian follicles after treatment tended to increase, but only the number of bilateral follicles and the maximum diameter of bilateral ovarian follicles in patients with perimenopausal syndrome showed statistical significance ($P=0.008$, $P=0.047$). **Conclusion** The present study suggested that

autologous bone marrow nuclear cell therapy could improve ovarian function to some extent, and is expected to be a new treatment method for patients with premature ovarian insufficiency, perimenopausal syndrome, and repeated assisted reproduction failure. However, further studies with larger sample sizes are needed to corroborate the findings.

【Key words】 Bone marrow transplantation; Stem cells; Primary ovarian insufficiency; Treatment outcome

DOI: 10.3760/cmaj.cn101441-20210306-00103

收稿日期 2021-03-10 本文编辑 宋培培

引用本文: 陆茜林, 唐方祥, 汤亚兰, 等. 经血源性间充质干细胞治疗早发性卵巢功能不全的研究进展[J]. 中华生殖与避孕杂志, 2021, 41(12): 1086-1090. DOI: 10.3760/cmaj.cn101441-20210306-00103.

·干细胞专栏·

经血源性间充质干细胞治疗早发性卵巢功能不全的研究进展

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【摘要】 早发性卵巢功能不全 (premature ovarian insufficiency, POI) 严重影响着全球女性的生殖内分泌健康, 因此, 迫切需要一种疗效好、安全性高的治疗方式。间充质干细胞 (mesenchymal stem cells, MSCs) 是一种来源于中胚层的多能干细胞, 具有强大的增殖能力和自我更新能力, 经血源性间充质干细胞 (menstrual blood-derived mesenchymal stem cells, MenSCs) 作为 MSCs 的成员之一, 展现出作为种子细胞的易于多次获取的优越性, 可靶向归巢至受损卵巢部位并分化为卵巢细胞, 旁分泌多种生长因子、黏附因子和外泌体从而促进受损卵巢组织修复、血管再生和免疫调节。本文就 MenSCs 治疗 POI 的研究进展做一综述。

【关键词】 间质干细胞; 早发性卵巢功能不全; 经血

Progress of menstrual blood-derived mesenchymal stem cells in the treatment of primary ovarian insufficiency

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【Abstract】 Premature ovarian insufficiency (POI) has seriously affecting the reproductive and endocrine health of the female around the world. Therefore, there is an urgent need for a treatment with good curative effect and high safety. Mesenchymal stem cells (MSCs) are a type of pluripotent stem cells derived from mesoderm, which have strong ability of proliferation and self-renewal. As members of MSCs, menstrual blood-derived mesenchymal stem cells (MenSCs) have shown the advantage of being easy to obtain repeatedly as seed cells. They can target the damaged ovarian tissue and differentiate into ovarian cells. Otherwise, they're able to paracrine varieties of growth factors, adhesion factors and exosomes to promote damaged ovarian tissue repair, vascular regeneration and immune regulation. This article reviews the progress of MenSCs in the treatment of POI.

【Key words】 Mesenchymal stem cells; Premature ovarian insufficiency; Menstrual blood

DOI: 10.3760/cma.j.cn101441-20201119-00627

收稿日期 2020-11-26 责任编辑 李天琦

引用本文: 李璐, 孙博, 孙莹璞. 间充质干细胞来源外泌体治疗原发性卵巢功能不全机制研究进展[J]. 中华生殖与避孕杂志, 2021, 41(12): 1091-1095. DOI: 10.3760/cma.j.cn101441-20201119-00627.

·干细胞专栏·

间充质干细胞来源外泌体治疗原发性卵巢功能不全机制研究进展

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【摘要】 原发性卵巢功能不全(primary ovarian insufficiency, POI)是导致育龄期女性无法生育的临床最难以解决的病因之一,其发病率表现出逐年增加的趋势,且年轻患者的占比也越来越高,严重威胁患者的身心健康。引起POI的病因既复杂又多样,且到目前为止,其发病机制仍不明确。临床上治疗POI患者,多采用激素替代疗法(hormone replacement therapy, HRT)、供卵助孕、卵巢体外激活(*in vitro* activation, IVA)技术等,但都不能从根本上改善卵巢功能。间充质干细胞(mesenchymal stem cells, MSCs)来源广泛且具有多向分化的潜能,在临床前实验研究中证实,其对多种疾病的治疗具有一定的疗效,但相关机制尚不明确。作为细胞分泌的小囊泡,外泌体承载着细胞间信号转导的重要作用,近

年来在疾病的治疗及相关机制研究中表现出巨大潜能。本文内容主要论述 MSCs 来源的外泌体在治疗 POI 方面的进展及其可能的机制, 进一步展望其在该领域的发展前景。

【关键词】 原发性卵巢功能不全; 间充质干细胞; 外泌体

基金项目: 国家重点研发计划 (2019YFA0110900)

Research progress on the mechanism of exosomes derived from mesenchymal stem cell in the treatment of primary ovarian insufficiency

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【Abstract】 Primary ovarian insufficiency (POI) is one of the most intractable causes of infertility in women of childbearing age. In recent years, the incidence of POI is increasing and the proportion of patients become younger in average age, which seriously affects women's physical and mental health. The etiology of POI is diverse and complex, and its pathogenesis is not very clear. At present, hormone replacement therapy (HRT), oocyte donation and *in vitro* activation (IVA) technology are mainly used in clinical treatment, but they cannot fundamentally improve ovarian function. Mesenchymal stem cell (MSC) is a kind of cell with multi-directional differentiation potential. It has been proved that MSC has certain therapeutic effect on a variety of diseases in preclinical experimental research, but the related mechanism of its treatment is still unclear. Exosomes are small vesicles secreted by cells and carry a variety of bioactive substances. In recent years, exosomes have shown great potential in the treatment of disease and its related mechanisms research. In this paper, the progress of exosomes derived from MSC in the treatment of POI and its possible mechanism are discussed, and its development prospect in this field is prospected.

【Key words】 Primary ovarian insufficiency; Mesenchymal stem cell; Exosomes

Fund program: National Key R&D Program of China (2019YFA0110900)

DOI: 10.3760/cma.j.cn101441-20210510-00204

收稿日期 2021-05-12 本文编辑 王李艳

引用本文: 刘慧, 张朴尧, 于洋. 干细胞分化为生殖细胞及重构胚胎的研究进展[J]. 中华生殖与避孕杂志, 2021, 41(12): 1096-1102. DOI: 10.3760/cma.j.cn101441-20210510-00204.

·干细胞专栏·

干细胞分化为生殖细胞及重构胚胎的研究进展

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【摘要】 随着辅助生殖技术 (assisted reproduction technology, ART) 的发展, 其需求日益增长。但是 ART 目前对于缺少功能配子的患者尚无有效的解决方案。由于实验材料的稀缺和伦理限制, 科研人员只能对人类配子和胚胎进行有限的研究, 该领域迫切需求能够模拟生殖细胞及胚胎的体外模型。人工配子和体外重构胚胎的出现为生殖医学的基础研究和临床应用带来了新的希望。从成体干细胞和胚胎干细胞 (embryonic stem cells, ESCs) 分化来源的生殖细胞以及通过干细胞分化或不同类型干细胞组装构建类囊胚结构的技术已在一些非人类哺乳动物中实现, 部分也可在人的细胞中实现。本文综述了人工配子和体外重构胚胎在小鼠、猴子和人类等不同物种中的研究进展和可能的应用。

【关键词】 人工配子; 体外重构胚胎; 干细胞; 生殖医学

基金项目: 国家重点研究发展计划基金 (2017YCF1001003)

Research progress on artificial gametes and embryos specified from stem cells

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【Abstract】 With the development of assisted reproduction technology (ART), there is an increasing need but ART currently does not have an effective solution for patients who lack of functional gametes. Due to the scarcity of experimental materials and ethical restrictions, researchers can only conduct limited research on human gametes and embryos, and there is an urgent need for *in vitro* models that can simulate germ cells and embryo. The emergence of artificial gametes and *in vitro* reconstructed embryos has brought new hope for the basic research and clinical application of reproductive medicine. Techniques for the differentiation of germ cells from adult and embryonic stem cells (ESCs) and the construction of blastocyst-like structures by stem cell differentiation or assembly of different types of stem cells have been realized in some non-human mammals and in some human cells. This paper reviews the progress and possible applications of artificial gametes and *in vitro* reconstruction embryos in mice, monkeys and human.

【Key words】 Artificial gametes; *In vitro* reconstructed embryos; Stem cell; Reproductive medicine

Fund program: National Key R&D Program of China (2017YCF1001003)

DOI: 10.3760/cmaj.cn101441-20210520-00225

收稿日期 2021-05-20 本文编辑 王李艳

引用本文: 郝敏, 王亮, 汪翔, 等. 基于倾向性评分匹配法探讨胚胎移植液 EmbryoGlue 对冻胚移植临床结局的影响[J]. 中华生殖与避孕杂志, 2021, 41(12): 1103-1108. DOI: 10.3760/cma.j.cn101441-20210520-00225.

·临床研究·

基于倾向性评分匹配法探讨胚胎移植液 EmbryoGlue 对冻胚移植临床结局的影响

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【摘要】 目的 研究 EmbryoGlue 移植液对冻胚移植临床结局的影响。方法 回顾性队列研究分析 2016 年 1 月 1 日至 2020 年 12 月 31 日期间于海军军医大学第二附属医院生殖医学中心进行冻胚移植患者的共 2848 个周期, 根据移植培养液种类分为两组: G-2 组(1605 个周期)和 EmbryoGlue 组(1243 个周期), 比较两组患者基本情况及临床结局的差异。将两组患者的年龄、不孕因素、不孕年限、内膜准备方案、内膜厚度、移植胚胎数、移植优质胚胎数、移植胚胎阶段进行倾向性评分匹配(propensity score matching, PSM)后, 再次比较两组临床结局的差异。结果 PSM 前 EmbryoGlue 组与 G-2 组比较, 患者年龄 $[33.46 \pm 4.66]$ 岁比 $[31.92 \pm 4.62]$ 岁, $P < 0.001$ 、不孕年限 $[4.11 \pm 2.98]$ 年比 $[3.36 \pm 2.60]$ 年, $P < 0.001$ 、内膜厚度 $[9.51 \pm 1.77]$ mm 比 $[10.01 \pm 1.77]$ mm, $P < 0.001$ 、移植胚胎数 $[1.52 \pm 0.50]$ 比 $[1.59 \pm 0.49]$, $P = 0.001$ 、移植优质胚胎数 $[1.28 \pm 0.64]$ 比 $[1.47 \pm 0.57]$, $P < 0.001$ 差异具有统计学意义。PSM 后两组基本情况差异均无统计学意义(P 均 > 0.05)。EmbryoGlue 组和 G-2 组的生化妊娠率 $[61.1\% (609/996)]$ 比 $61.9\% (617/996)$, $P = 0.713$ 、临床妊娠率 $[56.5\% (563/996)]$ 比 $57.0\% (568/996)$, $P = 0.821$ 、植入率 $[44.3\% (674/1523)]$ 比 $44.4\% (691/1555)$, $P = 0.919$ 、异位妊娠率 $[1.8\% (10/563)]$ 比 $1.8\% (10/568)$, $P = 0.984$ 、流产率 $[16.9\% (95/563)]$ 比 $17.3\% (98/568)$, $P = 0.865$ 差异均无统计学意义。结论 使用 EmbryoGlue 作为胚胎移植液的临床结局与 G-2 相似, 尚不能认为 EmbryoGlue 移植液可以改善冻胚移植的临床结局。

【关键词】 EmbryoGlue; 胚胎移植; 临床妊娠率

基金项目: 国家自然科学基金青年项目(81901482); 上海市医学领先专业重点学科基金(201840315); 上海市科技发展基金(19411960700)

Effect of EmbryoGlue on the clinical outcomes in frozen-thawed embryo transfer based on propensity score matching

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【Abstract】 Objective To study the effect of embryo transfer medium EmbryoGlue on the clinical outcomes of frozen-thawed embryo transfer. **Methods** A retrospective cohort study was performed in 2848 cycles from patients undergoing frozen-thawed embryo transfer from January 1, 2016 to December 31, 2020 in the Reproductive Medicine Center, the Second Affiliated Hospital of Naval Medical University. According to the embryo transfer medium, those cycles were divided into two groups, the G-2 group including 1605 cycles and the EmbryoGlue group including 1243 cycles. Baseline characteristics and clinical outcomes were compared between the two groups. Propensity score matching (PSM) was performed on age, infertility factor, duration of infertility, endometrial preparation protocol, endometrial thickness, number of embryos transferred, number of good-quality embryos transferred and stage of embryo, then clinical outcomes were compared between the two groups again. **Results** There were significant differences of the age [(33.46±4.66) years vs. (31.92±4.62) years, $P<0.001$], duration of infertility [(4.11±2.98) years vs. (3.36±2.60) years, $P<0.001$], endometrial thickness [(9.51±1.77) mm vs. (10.01±1.77) mm, $P<0.001$], number of embryos transferred (1.52±0.50 vs. 1.59±0.49, $P=0.001$), number of good-quality embryos transferred (1.28±0.64 vs. 1.47±0.57, $P<0.001$) between EmbryoGlue group and G-2 group before PSM. There was no statistically significant difference in the baseline characteristics between the two groups after PSM (all $P>0.05$). There were no statistically significant differences in biochemical pregnancy rate [61.1% (609/996) vs. 61.9% (617/996), $P=0.713$], clinical pregnancy rate [56.5% (563/996) vs. 57.0% (568/996), $P=0.821$], implantation rate [44.3% (674/1523) vs. 44.4% (691/1555), $P=0.919$], ectopic pregnancy rate [1.8% (10/563) vs. 1.8% (10/568), $P=0.984$] and abortion rate [16.9% (95/563) vs. 17.3% (98/568), $P=0.865$] between the two groups. **Conclusion** Using EmbryoGlue as embryo transfer medium can obtain the same clinical outcomes as G-2, and EmbryoGlue cannot yet be considered to improve the clinical outcomes of frozen-thawed embryo transfer.

【Key words】 EmbryoGlue; Embryo transfer; Clinical pregnancy rate

Fund program: National Natural Science Foundation of China Youth Foundation Project(81901482); Shanghai Medical Leading Profession Major Subject Foundation (201840315); Shanghai Science & Technology Development Foundation (19411960700)

DOI: 10.3760/cma.j.cn101441-20210309-00115

收稿日期 2021-03-17 本文编辑 王李艳

引用本文: 许小凤, 顾灵, 涂春燕, 等. 滋肾育胎丸治疗早期先兆流产 HLA-G 介导的母-胎免疫耐受效应: 一项随机对照研究[J]. 中华生殖与避孕杂志, 2021, 41(12): 1109-1116. DOI: 10.3760/cma.j.cn101441-20210309-00115.

·临床研究·

滋肾育胎丸治疗早期先兆流产 HLA-G 介导的母-胎免疫耐受效 应: 一项随机对照研究

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【摘要】 目的 探讨滋肾育胎丸干预早期先兆流产人类白细胞抗原-G (human leukocyte antigen-G, HLA-G) 介导的母-胎免疫耐受效应。方法 采用单盲、随机、对照研究, 选取 2018 年 1 月至 2019 年 12 月期间于南京中医药大学附属苏州市中医医院妇二科门诊及住院治疗的 150 例早期先兆流产患者作为研究对象, 纳入患者通过计算机产生随机数进行随机化分组, 分为滋肾育胎丸组、补肾健脾方组和地屈孕酮片组, 每组 50 例, 分别给予滋肾育胎丸、补肾健脾方及地屈孕酮片治疗至孕 12 周, 主要结局指标为血清 HLA-G 和妊娠结局; 次要结局指标为①CD4、CD8、CD4/CD8、自然杀伤 (natural killer, NK) 细胞水平; ②血清雌二醇、孕酮、人绒毛膜促性腺激素 (human chorionic hormone, hCG) 水平; ③盆腔超声情况; ④中医证候评分。结果 ①HLA-G 水平: 治疗后三组均较治疗前升高 (P 均 <0.05), 治疗后滋肾育胎丸组 [(352.54 ± 102.40) IU/mL]、补肾健脾方组 [(353.76 ± 98.92) IU/mL] 较地屈孕酮片组 [(306.90 ± 60.74) IU/mL] 明显升高 ($P=0.024$, $P=0.016$), 滋肾育胎丸组与补肾健脾方组差异无统计学意义 ($P>0.05$)。②CD4 水平: 治疗后滋肾育胎丸组 ($34.82\% \pm 6.99\%$)、补肾健脾方组 ($36.10\% \pm 6.44\%$) 较治疗前下降 ($37.66\% \pm 7.43\%$, $P=0.004$; $39.72\% \pm 7.07\%$, $P<0.001$); CD8 水平: 治疗后三组均较治疗前明显下降 (P 均 <0.05), 治疗后滋肾育胎丸组 ($20.40\% \pm 4.12\%$)、补肾健脾方组 ($19.92 \pm 4.68\%$) 较地屈孕酮片组 ($24.06\% \pm 5.29\%$) 下降明显 ($P<0.001$, $P<0.001$); CD4/CD8: 治疗后三组较治疗前上升明显 ($P<0.001$, $P<0.001$, $P=0.001$), 治疗后补肾健脾方组 (1.94 ± 0.65) 较地屈孕酮片组 (1.64 ± 0.50) 显著上升 ($P=0.044$); NK 细胞水平: 治疗后滋肾育胎丸组 ($10.78\% \pm 2.79\%$)、补肾健脾方组 ($10.70\% \pm 3.22\%$) 均较治疗前 ($14.36\% \pm 3.73\%$, $15.12\% \pm 6.06\%$) 下降 (P 均

<0.001), 且分别明显低于地屈孕酮片组(14.03%±5.48%)($P=0.001$, $P=0.001$)。③雌二醇、孕酮、hCG 水平: 治疗后三组均较治疗前升高 (P 均<0.001), 其中治疗后孕酮水平滋肾育胎丸组 [(33.20±6.19) ng/L]、补肾健脾方组 [(33.92±7.83) ng/L] 较地屈孕酮片组 [(25.56±6.06) ng/L] 均显著升高 (P 均<0.001)。④中医证候评分: 治疗后三组均明显下降 (P 均<0.001), 其中滋肾育胎丸组 [2.00 (1.25) 分] 较补肾健脾方组 [3.00 (2.00) 分]、地屈孕酮片组 [9.00 (2.00) 分] 评分下降更为明显 ($P=0.002$, $P<0.001$)。⑤妊娠结局三组比较差异无统计学意义 ($P>0.05$)。结论 滋肾育胎丸通过上调 HLA-G 水平介导母-胎免疫耐受, 改善妊娠结局; 其临床效应与补肾健脾方相当, 并优于地屈孕酮片; 在安胎方面具有临床疗效确切, 携带、服用方便等优势, 值得在早期先兆流产治疗中推广使用。

【关键词】 早期先兆流产; 人类白细胞抗原-G; 免疫效应; 滋肾育胎丸

基金项目: 国家科技部/国家中医药管理局资助项目“国家重大科技专项——中医药行业科研专项”(201507001-02); 江苏省中医药科技发展计划重点项目(ZD201908); 罗元恺滋肾育胎丸中青年科研基金项目(2015—2018 年度)

Study on the maternal-fetal immune tolerance effect mediated by human leukocyte antigen-G with Zishen-Yutai pills in the treatment of early threatened abortion: a randomized controlled trial

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【Abstract】 **Objective** To investigate the maternal and fetal immune tolerance effect mediated by human leukocyte antigen-G (HLA-G) in the early threatened abortion patients given by Zishen-Yutai pills. **Methods** The current study was a single-blind randomized controlled trial. Totally 150 early threatened abortion patients were enrolled into this study, who had received outpatient and inpatient treatment in the Second Department of Gynecology, Suzhou Hospital of Traditional Chinese Medicine Affiliated to Nanjing University of Chinese Medicine from January 2018 to December 2019. Randomization was used according to a randomized number which was generated by computer. Patients were divided into the Zishen-Yutai Pills group ($n=50$), Bushen-Jianpi Recipe group ($n=50$) and Dydrogesterone Tablets group ($n=50$). They were treated until 12 weeks of gestation. Primary indicators were serum HLA-G and pregnancy outcome; minor indicators were: 1) level of CD4, CD8, CD4/CD8, natural killer (NK) cells; 2) level of serum oestradiol, progesterone, human chorionic hormone (hCG); 3) ultrasound situation of pelvic; 4) symptom scores of Traditional Chinese Medicine. **Results** 1) The HLA-G levels of the three groups were all increased after the treatment (all $P<0.05$), which were higher in Zishen-Yutai Pills group [(352.54±102.40) IU/mL] and Bushen-Jianpi Recipe group [(353.76±98.92) IU/mL] than in Dydrogesterone Tablets group [(306.90±60.74) IU/mL; $P=0.024$, $P=0.016$]. There was no statistical

significant difference between Zishen-Yutai Pills group and Bushen-Jianpi Recipe group ($P>0.05$). 2) The CD4 levels of the Zishen-Yutai Pills group ($34.82\pm 6.99\%$) and the Bushen-Jianpi Recipe group ($36.10\pm 6.44\%$) were decreased after the treatment ($37.66\pm 7.43\%$, $P=0.004$; $39.72\pm 7.07\%$, $P<0.001$). The CD8 levels of the three groups were all decreased after the treatment (all $P<0.05$), which decreased obviously in Zishen-Yutai Pills group ($20.40\pm 4.12\%$) and Bushen-Jianpi Recipe group ($19.92\pm 4.68\%$) compared with Dydrogesterone Tablets group ($24.06\pm 5.29\%$; $P<0.001$, $P<0.001$). The CD4/CD8 levels of the three groups were all increased ($P<0.001$, $P<0.001$, $P=0.001$), which were statistically higher in Bushen-Jianpi Recipe group (1.94 ± 0.65) than in Dydrogesterone Tablets group (1.64 ± 0.50) after the treatment ($P=0.044$). The NK cell levels of Zishen-Yutai Pills group ($10.78\pm 2.79\%$) and Bushen-Jianpi Recipe group ($10.70\pm 3.22\%$) were all decreased after the treatment ($14.36\pm 3.73\%$, $15.12\pm 6.06\%$; all $P<0.001$), which were significantly lower than that in Dydrogesterone Tablets group ($14.03\pm 5.48\%$; $P=0.001$, $P=0.001$). 3) The serum estradiol, progesterone, hCG levels of the three groups were all increased after the treatment (all $P<0.001$), the progesterone level of Zishen-Yutai Pills group [(33.20 ± 6.19) ng/L] and Bushen-Jianpi Recipe group [(33.92 ± 7.83) ng/L] was statistically significantly different from that of Dydrogesterone Tablets group [(25.56 ± 6.06) ng/L; $P<0.001$, $P<0.001$]. 4) The TCM symptoms' scores of the three groups were all decreased after the treatment (all $P<0.001$), while it was lower in Zishen-Yutai Pills group [2.00(1.25)] than that in Bushen-Jianpi Recipe group [3.00(2.00)] and Dydrogesterone Tablets group [9.00(2.00)] ($P=0.002$, $P<0.001$). 5) The clinical pregnancy outcome of the three groups had no significant difference ($P>0.05$). **Conclusion** The Zishen-Yutai pills can mediate maternal and fetal immune tolerance by upregulating HLA-G level, and improve the pregnancy outcome. Its clinical effect was similar to that of the Bushen-Jianpi Recipe, and better than that of the Dydrogesterone Tablets. It is worth popularizing in the treatment of early threatened abortion because of its definite clinical effect, convenient to carry and take.

【 Key words 】 Early threatened abortion; Human leukocyte antigen-G; Immune effect; Zishen Yutai Pills

Fund program: Project of Ministry of Science and Technology/State Administration of Traditional Chinese Medicine of China "National Science and Technology Major Project of China-Research Fund for Traditional Chinese Medicine of China" (201507001-02); Key Technologies R&D Program for Traditional Chinese Medicine of Jiangsu Province (ZD201908); Research Fund for Young and Middle-aged Scholarship of Luo Yuankai Zishenyutai Wan (2015—2018)

DOI: 10.3760/cma.j.cn101441-20200506-00261

收稿日期 2020-05-11 本文编辑 王李艳

引用本文: 郑嘉华, 赵双丹, 元文博, 等. 两种宫腔粘连大鼠模型稳定性的比较[J]. 中华生殖与避孕杂志, 2021, 41(12): 1117-1123. DOI: 10.3760/cma.j.cn101441-20200506-00261.

·实验研究·

两种宫腔粘连大鼠模型稳定性的比较

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【摘要】 目的 比较无水乙醇化学损伤法、刮宫与宫腔留置脂多糖双重损伤法建立 SD 大鼠宫腔粘连动物模型的造模效果, 探索模型稳定性。方法 110 只 SD 雌鼠采用随机数表随机分为正常组、双重损伤组和无水乙醇组。正常组每组 30 只, 余两组均为 40 只。无水乙醇组宫腔注射 95% 无水乙醇损伤子宫内膜, 双重损伤组刮宫后宫腔留置脂多糖棉线 2 d 损伤子宫内膜, 正常组行假手术。分别于术后 1 周、2 周、4 周、8 周、12 周采用随机数表每组各随机抽取 3 只动物收集子宫组织, 行 HE 染色和 Masson 染色, 对子宫内膜厚度、腺体数量和纤维化面积进行统计分析, 并行免疫组织化学染色观察 CD31 在子宫内膜间质上的表达情况。结果 ①两种模型子宫内膜厚度在造模 2 周后, 均小于正常组, 且趋于稳定。无水乙醇组子宫内膜厚度较双重损伤组减少更明显 (P 均 <0.05)。②两种模型子宫内膜腺体数量在造模 1 周后均明显小于正常组, 无水乙醇组子宫内膜腺体数量较双重损伤组减少更明显 (P 均 <0.05)。③两种模型子宫内膜间质纤维化面积在造模 1 周后均高于正常组 (P 均 <0.05), 但无水乙醇组纤维化面积在造模后 8 周开始减少。④两种模型子宫内膜间质 CD31 表达量在造模 1 周后均明显小于正常组 (P 均 <0.05), 无水乙醇组较双重损伤组减少更明显 (P 均 <0.05)。⑤2 周和 12 周模型鼠妊娠情况及胎鼠数目比较表明模型鼠生育能力均受到影响, 且无水乙醇组模型鼠生育能力所受影响比双重损伤模型组明显。结论 两种方法均能诱导宫腔粘连; 无水乙醇化学损伤法操作较简单、经济, 但纤维化稳定性欠佳, 其子宫内膜厚度、腺体数量及血管改变符合薄型子宫内膜病理变化, 更适用于薄型子宫内膜疾病的相关研究; 双重损伤模型贴近临床损伤方法, 且模型更稳定, 可以满足宫腔粘连相关研究需求。

【关键词】 宫腔粘连; 大鼠; 无水乙醇; 双重损伤; 稳定性

Exploration of the stability of two rat models of uterine adhesion

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【Abstract】 Objective To compare the modeling effects of anhydrous ethanol chemical injury method and uterine curettage combine uterine lipopolysaccharide indwelling double injury method, and to explore the stability of

the models. **Methods** Totally 110 SD female rats were randomly divided into normal group ($n=30$), dual injury group ($n=40$) and alcohol group ($n=40$) by using a random number table. In the alcohol group, 95% absolute ethanol was injected into the uterine cavity to damage the endometrium, and in the dual injury group, lipopolysaccharide cotton thread was retained in the uterine cavity for 2 d after uterine curettage, and sham operation was performed in the normal group. After retrieval of the uteri on the 1st, 2nd, 4th, 8th and 12th weeks post-procedure, they were embedded in paraffin, serially sectioned at 5 μm thickness and routinely stained with hematoxylin and eosin and masson stains. The sections obtained from the samples collected from the above were also used to detect the expression of CD31 (a vascular marker) on the uterine tissues by immunohistochemistry staining.

Results 1) Two weeks after operation, the endometrial thickness of the two models were smaller than that of the normal group, and tended to be stable. The thickness of endometrium in alcohol group decreased more significantly than that in dual injury group (all $P<0.05$). 2) One week post-procedure, the number of endometrial glands in the two models was significantly less than that in the normal group, and it was more obvious in the alcohol group than that in the dual injury group (all $P<0.05$). 3) The area of endometrial interstitial fibrosis in the model groups were both higher than that in the normal group from one week after operation (all $P<0.05$), but the fibrosis area in the alcohol group decreased from the 8th week. 4) One week post-procedure, the expression of CD31 in the endometrial stroma of the two models were significantly lower than that in the normal group ($P<0.05$), and the decrease in the alcohol group was more obvious than that in the dual injury group (all $P<0.05$). 5) The comparison of the pregnancy ability and the number of fetal mice between 2-week and 12-week model mice showed that the fertility of the model mice was affected, and the fertility of the alcohol group was more affected than that of the dual injury model group.

Conclusion The two methods can both induce uterine adhesion. Alcohol injury method is simple and economical, but the stability of fibrosis is poor, and the thickness of endometrium, the number of glands and the changes of blood vessels accord with the pathological changes of thin endometrium, which is more suitable for the study of thin endometrial diseases. The dual injury model is close to the clinical injury method, and the model is more stable, which can meet the needs of uterine adhesion related research.

【Key words】 Uterine adhesion; Rat; Alcohol; Dual injury; Stability

DOI: 10.3760/cmaj.cn101441-20210528-00244

收稿日期 2021-06-03 本文编辑 王李艳

引用本文: 宋东红, 张鹤立, 赵阳, 等. 进入 IVF-ET 治疗周期的 803 对不孕夫妻心理状况调查[J]. 中华生殖与避孕杂志, 2021, 41(12): 1124-1128. DOI: 10.3760/cmaj.cn101441-20210528-00244.

·现场调查·

进入 IVF-ET 治疗周期的 803 对不孕夫妻心理状况调查

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【摘要】 目的 研究不孕夫妻进入体外受精-胚胎移植 (*in vitro* fertilization-embryo transfer, IVF-ET) 治疗周期的心理状况。方法 采用横断面研究, 便利取样法选取 2019 年 10 月至 2020 年 8 月期间在北京大学第三医院生殖医学中心首次接受 IVF-ET 治疗的夫妻为研究对象。采用自设不孕不育基本情况调查表、生育困难相关压力量表、中文版生育生活质量问卷和状态-特质焦虑量表评估夫妻双方进入 IVF-ET 治疗周期的心理状况。结果 纳入夫妻 803 对, 生育压力得分为女性 (155.65 ± 22.07) 分, 男性 (153.70 ± 22.25) 分, 差异无统计学意义 ($P=0.101$); 生活质量得分女性 [90.60 ± 18.27] 高于男性 [84.24 ± 16.47] 分, 差异具有统计学意义 ($P<0.001$); 夫妻双方状态焦虑得分差异无统计学意义 ($P=0.074$); 特质焦虑得分男性 [43.38 ± 6.91] 高于女性 [41.93 ± 6.89] 分, $P<0.001$]。结论 在进入 IVF-ET 治疗周期时, 夫妻双方生育压力水平一致, 但男性特质焦虑水平高于女性, 且生活质量低于女性, 医务人员在给予夫妻治疗管理中应加强对男性的心理状态关注和干预。

【关键词】 受精, 体外; 胚胎移植; 生育; 焦虑; 夫妻生活质量
基金项目: 北京大学第三医院护理科研基金 (BYSYHL2019008)

Investigation on the psychological status of 803 infertile couples entering the IVF-ET treatment cycle

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【Abstract】 Objective To investigate the psychological status of infertile couples entering the *in vitro* fertilization-embryo transfer (IVF-ET) treatment cycle. **Methods** In this cross-sectional study, convenience sampling method was used to selected couples who received IVF-ET treatment for the first time in the Reproductive Medicine Center of Peking University Third Hospital from October 2019 to August 2020. We used the basic questionnaire of infertility designed by ourselves, fertility problem inventory, the Chinese version of the fertility quality of life to evaluate the Status-Trait anxiety scale. **Results** Totally 803 couples were included. The fertility stress score was 155.65 ± 22.07 in female and 153.70 ± 22.25 in male with no statistical difference ($P=0.101$). The quality of life score was 90.60 ± 18.27 in female and 84.24 ± 16.47 in male. Female had better quality of life than male ($P<0.001$). No statistical difference was observed in state anxiety scores ($P=0.074$). The male trait anxiety score (43.38 ± 6.91) was higher than that in female (41.93 ± 6.89) ($P<0.001$). **Conclusion** When entering the IVF-ET treatment cycle, the fertility pressure level of the couple is the same, but the level of male anxiety characteristics is higher than that in women, and the quality of life is lower than that in women. Medical staff should strengthen the attention and intervention to the psychological state of men in the management of marital treatment.

【Key words】 Fertilization *in vitro*; Embryo transfer; Fertility; Anxiety; Couples quality of life

Fund program: Peking University Third Hospital Nursing Research Fund (BYSYHL2019008)

DOI: 10.3760/cma.j.cn101441-20200702-00371

收稿日期 2020-07-10 本文编辑 宋培培

引用本文: 林顺和, 黄鹏辉, 郭玉燕, 等. 深部型宫颈子宫内位囊肿合并子宫腺肌病 1 例报告并文献复习[J]. 中华生殖与避孕杂志, 2021, 41(12): 1129-1133. DOI: 10.3760/cma.j.cn101441-20200702-00371.

·个案报道·

深部型宫颈子宫内位囊肿合并子宫腺肌病 1 例报告并文献复习

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【摘要】 目的 探讨深部型宫颈子宫内膜异位症合并子宫腺肌病的临床表现、诊断方法和治疗要点。方法 报道 2020 年 5 月就诊于福建医科大学附属福建省妇幼保健院的 1 例深部型宫颈子宫内膜异位囊肿合并子宫腺肌病患者的临床资料及诊治经过, 并对相关文献进行系统性回顾。结果 本例患者并无明显临床症状, 宫颈子宫内膜异位囊肿为深部型, 同时合并子宫腺肌病, 行腹腔镜子宫切除术治疗, 预后良好。结论 宫颈子宫内膜异位症的发病机制尚不明确, 缺乏特异性临床表现, 治疗方法亦未形成统一共识。对于深部型患者如无生育要求或合并其他子宫病变时, 可考虑行全子宫切除术治疗。

【关键词】 子宫内膜异位症; 子宫腺肌病; 宫颈; 深部型; 手术
基金项目: 福建省自然科学基金 (2017J01236)

Cervical endometriosis with adenomyosis: a case report and literature review

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【 Abstract 】 Objective To discuss the pathogenesis, clinical manifestations, diagnosis and treatment of cervical endometriosis with adenomyosis. **Methods** The clinical data, diagnosis and treatment of the deep cervical endometriosis patient with adenomyosis who was collected in Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University in May 2020 were analyzed, and the related literatures were reviewed systematically. **Results** The patient had no obvious clinical symptoms. Cervical endometriosis cyst was of deep type. Laparoscopic hysterectomy was performed and the prognosis was good. **Conclusion** The pathogenesis of cervical endometriosis is not clear, the lack of specific clinical manifestations, treatment methods have not formed a consensus. Hysterectomy may be considered for patients with deep type if no fertility requirement or other uterine lesions are present.

【 Key words 】 Endometriosis; Adenomyosis; Cervical; Deep type; Surgery

Fund program: Natural Science Foundation of Fujian Province (2017J01236)

DOI: 10.3760/cma.j.cn101441-20200602-00326

收稿日期 2020-06-09 本文编辑 王李艳

引用本文: 周焕宇, 王莹, 石玉华. 黄体期促排卵方案的临床应用进展[J]. 中华生殖与避孕杂志, 2021, 41(12): 1134-1138. DOI: 10.3760/cma.j.cn101441-20200602-00326.

·综述·

黄体期促排卵方案的临床应用进展

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【摘要】 卵泡波理论的提出和胚胎冷冻技术的进步,使得黄体期促排卵方案得以应用。这一方案应用于不同卵巢功能的人群所获得的助孕结局不尽相同,对于卵巢储备功能低下、卵巢低反应和紧急生育力保存人群,该方案可打破月经周期的限制,有效控制早发黄体生成素峰,相较于卵泡期促排卵可能会获得更多具有正常发育潜能的卵子和胚胎。双刺激方案可在短时间内获得更多可用的卵子及胚胎,从而改善时间敏感性患者的助孕结局。作为超促排卵方案的一种,黄体期促排卵的结局受卵泡期处理、促排卵启动时机和用药方案影响,本文将从以上方面对黄体期促排卵的影响进行综述。

【关键词】 卵泡波; 卵巢刺激; 黄体期; 双刺激方案; 卵巢反应低下

基金项目:国家重点研发计划项目(2021YFC2700404、2018YFC1003202);泰山学者工程专项经费(No.ts201712103)

Progress in clinical application of luteal-phase ovulation stimulation

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【Abstract】 The luteal-phase ovarian stimulation protocol has benefited from the proposal of follicular waves theory and the improvement of embryo cryopreservation technology. The effect of luteal-phase protocol on pregnancy outcome varies among women with different ovarian functions. For women with diminished ovarian reserve (DOR), poor ovarian response (POR) or fertility preservation requirements, this protocol could break the limitation of menstrual

cycle, and effectively control the premature luteinizing hormone (LH) peak which provides a chance to obtain more eligible eggs and embryos compared with the follicular-phase protocol. Double stimulation may obtain more eligible eggs and embryos within a short period, which could improve the pregnancy outcomes of the time-sensitivity patients. As one of controlled ovarian hyperstimulation regimens, the outcome of luteal-phase ovulation stimulation is influenced by follicular-phase management, the timing of ovarian stimulation and medication regimen. Therefore, this article will finish the overview about the influences of aforesaid factors to the luteal-phase ovulation stimulation.

【Key words】 Follicular waves; Ovarian stimulation; Luteal phase; Double stimulation; Poor ovarian response

Fund program: National Key Research and Development Program of China (2021YFC2700404, 2018YFC1003202); Taishan Scholar Project Special Funds (No.ts201712103)

DOI: 10.3760/cma.j.cn101441-20210210-00065

收稿日期 2021-02-23 本文编辑 王李艳

引用本文: 李明月, 田焯, 张慧英, 等. 多不饱和脂肪酸对多囊卵巢综合征的影响及其机制[J]. 中华生殖与避孕杂志, 2021, 41(12): 1139-1142. DOI: 10.3760/cma.j.cn101441-20210210-00065.

·综述·

多不饱和脂肪酸对多囊卵巢综合征的影响及其机制

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【摘要】 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 是育龄期女性常见的生殖内分泌疾病, 表现为生殖功能障碍、糖脂代谢异常与慢性炎症。近年来动物、临床研究提示, 多不饱和脂肪酸可以改善 PCOS 患者的生殖内分泌紊乱、代谢异常, 然而其具体机制说法不一。本文就多不饱和脂肪酸对 PCOS 的影响及其机制做一综述, 为 PCOS 的治疗提供理论依据。

【关键词】 多囊卵巢综合征; 多不饱和脂肪酸; 高雄激素血症; 胰岛素抵抗

基金项目：京津冀基础研究合作专项（19JCZDJC65000（Z））；国家自然科学基金青年项目（81701410）；天津市自然科学基金项目（20JCQNJC00470）；天津市卫生健康科技项目（ZC20005）

Effect of polyunsaturated fatty acids on polycystic ovary syndrome and its mechanism

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【Abstract】 Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. It is characterized by reproductive abnormalities, abnormal glucose metabolism, dyslipidemia and chronic inflammation. In recent years, polyunsaturated fatty acids can improve reproductive abnormalities and metabolic abnormalities in PCOS patients during dietary intervention, but the specific mechanism has been disputed. This paper summarizes the possible mechanism of polyunsaturated fatty acids on PCOS, so as to provide theoretical basis for the treatment of PCOS.

【Key words】 Polycystic ovary syndrome; Polyunsaturated fatty acids; Hyperandrogenism; Insulin resistance

Fund program: Beijing-Tianjin-Hebei Basic Research Cooperation Program (19JCZDJC65000(Z)); National Natural Science Youth Program of China (81701410); Natural Science Foundation of Tianjin (20JCQNJC00470); Health Science and Technology Project of Tianjin (ZC20005)

·综述·

DOI: 10.3760/cma.j.cn101441-20200525-00308

收稿日期 2020-05-29 本文编辑 李天琦

引用本文: 李庆芳, 朱依敏. 肌醇应用于多囊卵巢综合征不孕患者的相关研究进展[J]. 中华生殖与避孕杂志, 2021, 41(12): 1143-1148. DOI: 10.3760/cma.j.cn101441-20200525-00308.

肌醇应用于多囊卵巢综合征不孕患者的相关研究进展

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【摘要】 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 是一种多因素导致的内分泌及代谢疾病, 常伴有胰岛素抵抗、月经周期紊乱和生育障碍等状况, 占无排卵性不孕症的 75%。目前多项临床研究证实, 肌醇可以改善 PCOS 患者内分泌及代谢情况, 改善高雄激素血症、氧化应激异常及妊娠结局, 且以肌肉肌醇: D-手性肌醇为 40:1 的比例治疗效果最佳。另外, 以肌醇为基础的联合用药对 PCOS 患者也有一定的治疗效果, 如二甲双胍、枸橼酸氯米芬及口服避孕药等与肌醇的联合用药。此外, 针对 PCOS 患者肌醇耐受的问题, 也有研究进行了探索, 本文就此展开综述。

【关键词】 多囊卵巢综合征; 不孕症; 肌醇; 联合用药; 妊娠结局
基金项目: “十三五” 国家科技支柱计划 (2016YFC1000302)

Advances in the application of inositol in infertile patients with polycystic ovary syndrome

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【Abstract】 Polycystic ovary syndrome (PCOS) is a kind of endocrine and metabolic disease caused by multiple factors, often accompanied by insulin resistance, menstrual cycle disorders and reproductive disorders, accounting for 75% of the anovulatory infertility. Lots of clinical studies suggested that inositol could improve the endocrine and metabolism status of patients with PCOS, ameliorating hyperandrogenism, abnormal oxidative stress and pregnancy outcomes. The 40:1 ratio of myo-inositol:D-chiro-inositol represented the best treatment effect. In addition, combination therapy based on inositol exerts certain therapeutic effects in PCOS patients, such as metformin, citrate clomiphene and oral contraceptives. Additionally, there are also studies which explored the therapy resistance of inositol on patients with PCOS. Hence, we conduct a review on this research area.

【Key words】 Polycystic ovary syndrome; Infertility; Inositol; Drug combination; Pregnancy outcomes

Fund program: The National Science & Technology Pillar Program during the 13th Five-year Plan Period (2016YFC1000302)

DOI:10.3760/cma.j.cn101441-20200526-00312

收稿日期 2020-06-11 本文编辑 宋培培

引用本文: 贾晓彤, 徐杰, 黄羽佳, 等. 维生素 D 与女性生殖系统健康关系的研究进展[J]. 中华生殖与避孕杂志, 2021, 41(12): 1149-1153. DOI: 10.3760/cma.j.cn101441-20200526-00312.

·综述·

维生素 D 与女性生殖系统健康关系的研究进展

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【摘要】 维生素 D 是固醇类衍生物, 除了调节钙磷代谢维持骨质平衡的经典作用外, 还具有调节免疫反应、调节细胞增殖和分化等非经典作用。近年来大量研究显示维生素 D 缺乏与女性生殖系统疾病的发生发展有密切关系, 补充维生素 D 对女性生殖健康有重要意义。本文就维生素 D 与女性卵巢、子宫以及妊娠期相关疾病的关系及机制做简要综述。

【关键词】 维生素 D; 妊娠; 子宫; 卵巢

基金项目: 国家自然科学基金 (82001577); 黑龙江省自然科学基金 (QC2017089); 黑龙江省普通本科高等学校青年创新人才培养计划 (UNPYSCT-2018054); 中国博士后基金 (2018M640304); 黑龙江省博士后基金 (LBH-Z18108)

Recent advances in the research of vitamin D in female reproductive system

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【Abstract】 Vitamin D is a sterol derivative, which can not only regulate the balance of calcium and phosphorus metabolism and affect bone growth, but also involve in a variety of non-classical effects, such as regulating immune response, cell proliferation and differentiation. In recent years, many studies have shown that vitamin D deficiency is associated with the occurrence and development of female reproductive diseases. Vitamin D supplementation has certain significance for female reproductive health. The article provides a brief review on the current progress in the research of vitamin D in ovarian, uterine and pregnancy-related diseases.

【Key words】 Vitamin D; Pregnancy; Uterine; Ovarian

Fund program: National Natural Science Foundation of China (82001577); Heilongjiang Natural Science Foundation (QC2017089); University Nursing Program for Young Scholars with Creative Talents in Heilongjiang Province (UNPYSCT-2018054); China Postdoctoral Foundation (2018M640304); Heilongjiang Postdoctoral Foundation (LBH-Z18108)

DOI: 10.3760/cmaj.cn101441-20200604-00330

收稿日期 2020-06-08 本文编辑 孙敏

引用本文: 马玉聪, 杨爱敏, 张拴成, 等. 核因子 E2 相关因子 2/抗氧化反应元件信号通路在生殖系统中的研究进展 [J]. 中华生殖与避孕杂志, 2021, 41(12): 1154-1159. DOI: 10.3760/cmaj.cn101441-20200604-00330.

核因子 E2 相关因子 2/抗氧化反应元件信号通路在生殖系统中的研究进展

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【摘要】 氧化应激是氧化与抗氧化的失衡状态, 活性氧参与了生殖系统生理病理过程。核因子 E2 相关因子 2/抗氧化反应元件 (nuclear factor erythroid 2 related factor 2/antioxidant response element, Nrf2/ARE) 是重要的抗氧化应激通路, Nrf2 可被诸多因素如活性氧、抗氧化剂等激活进入细胞核, 与小 Maf 蛋白和 ARE 结合, 调控多种抗氧化酶的表达, 从而发挥抗氧化作用。研究表明, Nrf2/ARE 抗氧化通路在生殖系统疾病中发挥了重要的调控作用。本文就近年来国内外关于 Nrf2/ARE 信号通路在生殖系统中的研究进展进行综述, 并对存在的问题及今后研究方向进行探讨及展望。

【关键词】 核因子 E2 相关因子 2/抗氧化反应元件信号通路; 生殖系统; 氧化应激

基金项目: 国家自然科学基金项目 (81774359); 河北省研究生创新资助项目 (CXZZBS2018150)

Research advances of nuclear factor erythroid 2 related factor 2/antioxidant response element signaling pathway in reproductive system

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【Abstract】 Oxidative stress is the imbalance between oxidation and anti-oxidation, and reactive oxygen species participate in the physiological and pathological process of reproductive system. Nuclear factor erythroid 2 related factor 2/antioxidant response element (Nrf2/ARE) is an important antioxidant stress pathway. Nrf2 can be activated into the nucleus by various factors such as reactive oxygen species and antioxidants, and combine with small Maf protein and ARE to regulate the expression of various antioxidant enzymes, thus playing an antioxidant role. Studies have shown that the Nrf2/ARE antioxidant pathway plays an important regulatory role in reproductive system diseases. In this paper, the research progress of Nrf2/ARE signaling pathway in reproductive system at home and abroad in recent years is reviewed, and the existing problems and future research directions are discussed and prospected.

【Key words】 Nuclear factor erythroid 2 related factor 2/antioxidant response element signaling pathways; Reproductive system; Oxidative stress

Fund program: National Natural Science Foundation of China (81774359); Hebei Graduate Innovation Funded Project (CXZZBS2018150)