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目 次

MDT专家视角专栏

复杂子宫腺肌病合并不孕患者的诊疗策略·····549

王国云 王凯

再谈子宫腺肌病相关生育问题的多学科诊疗·····554

陈子江 颜磊

临床研究

植入前遗传学非整倍体筛查对反复种植失败患者疗效的观察·····557

陈虹 郑锦霞 孙子莉 伍园园 陈智勤

辅助生殖技术受孕双绒毛膜双胎之一胎死宫内的存活儿

围产期预后分析·····566

梅洁 孙彦欣 山惠枝 王俊霞

AMH水平对IVF/ICSI早期妊娠丢失及累积妊娠结局的影响·····574

田萌萌 张琰钧 高亚谊 刘慧 杜明泽 任炳楠 王兴玲

多囊卵巢综合征合并焦虑状态的相关因素研究·····582

夏和霞 王荣敏 管海云 唐芷菁 黄钰怒 张炜

围绝经期和绝经后女性绝经症状与日常认知功能的相关性研究·····589

黄文俊 耿露露 蒋素素 李长滨 陶敏芳

实验研究

红景天苷通过抑制NF-κB通路降低多囊卵巢综合征模型小鼠的

炎症反应·····595

姬锐 高玥 邹文 杨菁

多囊卵巢综合征小鼠卵母细胞miR-320-3p低表达对胚胎发育

潜能的影响·····604

张珊 张磊 陈欢欢 崔趁趁 梁守婧 陈圆辉 梁琳琳 张翠莲

临床报道

辅助生殖技术助孕出生单胎新生儿第二性别比分析·····615

吴丽敏 高敏 王晓涵 桑美英 许波 周桂香 付应云 栾红兵

骆丽华 刘雨生 金仁桃 童先宏

个案报道

体外受精-胚胎移植中单角子宫并卵巢异位2例报道

并文献复习·····621

王雅琴 漆倩荣 徐望明 周小燕 杨菁

综 述

miRNA-17~92基因簇在多囊卵巢综合征发生发展中的作用研究进展	626
孙春青 冯丹 毕星宇 王耀琴 许素铭 武学清	
肠道微生物与子宫内膜异位症发病机制的研究进展	633
吴小梅 孙兰 武泽	
慢性子宫内膜炎的诊断及生育相关的发病机制研究进展	637
吴小华 冯政利	
褪黑素在女性不孕相关疾病中的生殖调节研究	642
谢芬芬 刘雅静 曹云霞	
胚胎植入前遗传学检测女性婚姻质量综述	646
蔡丽君 戴甜甜 黄荷凤	
我国绝经后妇女宫内节育器取出问题综述	652
李昭润 秦鸣妍 钱序 程利南	
《中华生殖与避孕杂志》第二届编辑委员会成员名单	594
《中华生殖与避孕杂志》第二届通讯编辑委员会成员名单	632
本刊稿约见本卷第1期封三	
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CONTENTS IN BRIEF

MDT Expert Perspective Column

- Diagnosis and treatment strategies for infertility patients with complex adenomyosis**549
Wang Guoyun, Wang Kai
- Talk about the multi-disciplinary team of adenomyosis related fertility problems again**554
Chen Zijiang, Yan Lei

Clinical Studies

- Clinical research of preimplantation genetic testing for aneuploidies in patients with recurrent implantation failure**557
Chen Hong, Zheng Jinxia, Sun Zili, Wu Yuanyuan, Chen Zhiqin
- Analysis of perinatal risks for the surviving infant of dichorionic twins vanishing twin syndrome following assisted reproductive technology**566
Mei Jie, Sun Yanxin, Shan Huizhi, Wang Junxia
- Effects of anti-Müllerian hormone levels on early pregnancy loss and cumulative pregnancy outcome in *in vitro* fertilization/intracytoplasmic sperm injection**574
Tian Mengmeng, Zhang Lijun, Gao Yayi, Liu Hui, Du Mingze, Ren Bingnan, Wang Xingling
- A study of quality of life and associated factors for complicated anxiety in patients with polycystic ovary syndrome**582
Xia Hexia, Wang Rongmin, Guan Haiyun, Tang Zhijing, Huang Zengshu, Zhang Wei
- Study on the relationship between menopausal symptoms and everyday cognition in perimenopausal and postmenopausal women**589
Huang Wenjun, Geng Lulu, Jiang Susu, Li Changbin, Tao Minfang

Laboratory Studies

- Salidroside attenuates inflammatory response in mice with polycystic ovary syndrome by inhibiting NF- κ B signaling pathway**595
Ji Rui, Gao Yue, Zou Wen, Yang Jing
- Effects of low expression of miR-320-3p on embryonic developmental potential in polycystic ovary syndrome mouse oocytes**604
Zhang Shan, Zhang Lei, Chen Huanhuan, Cui Chenchan, Liang Shoujing, Chen Yuanhui, Liang Linlin, Zhang Cuilian

Clinical Reports

- Secondary sex ratio analysis of singleton babies born following assisted reproductive technology**615
Wu Limin, Gao Min, Wang Xiaohan, Sang Meiyang, Xu Bo, Zhou Guixiang, Fu Yingyun, Luan Hongbing, Luo Lihua, Liu Yusheng, Jin Rentao, Tong Xianhong

Case Reports

- Two cases of unicornuate uterus with ectopic ovary in IVF-ET and literature review**621
Wang Yaqin, Qi Qianrong, Xu Wangming, Zhou Xiaoyan, Yang Jing

Reviews

- Roles of miRNA-17-92 gene cluster in the pathogenesis of polycystic ovary syndrome**626
Sun Chunqing, Feng Dan, Bi Xingyu, Wang Yaoqin, Xu Suming, Wu Xueqing
- Advances in intestinal microorganisms and the pathogenesis of endometriosis**633
Wu Xiaomei, Sun Lan, Wu Ze
- Research progress in diagnosis and pathogenesis of chronic endometritis**637
Wu Xiaohua, Feng Zhengli
- Study on reproductive regulation of melatonin in female infertility related diseases**642
Xie Fenfen, Liu Yajing, Cao Yunxia
- Marital quality of preimplantation genetic testing women: a literature review**646
Cai Lijun, Dai Tiantian, Huang Hefeng
- A review on removal of intrauterine device in postmenopausal women in China**652
Li Zhaorun, Qin Mingyan, Qian Xu, Cheng Linan

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· MDT 专家视角专栏 ·

复杂子宫腺肌病合并不孕患者的诊疗策略

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【摘要】 子宫腺肌病是育龄期妇女的常见病, 主要表现为痛经、月经量多、不孕不育和子宫增大。近年来随着生育政策的调整以及生育年龄的延迟, 子宫腺肌病和不孕不育的相关性日益受到重视。子宫腺肌病往往不单独存在, 经常合并子宫肌瘤、卵巢子宫内膜异位囊肿、深部子宫内膜异位症以及输卵管积水等复杂妇科疾病情况。合并疾病的存在增加了子宫腺肌病相关不孕的诊治难度。对于复杂子宫腺肌病合并不孕患者, 如何进行有效的诊断和针对性的治疗, 以提高妊娠率和改善妊娠结局? 本文对复杂子宫腺肌病相关不孕患者的诊疗进行专题述评, 旨在为复杂子宫腺肌病合并不孕患者探索有效的诊疗模式, 提高其妊娠和活产率, 改善新生儿预后。

【关键词】 子宫腺肌病; 不孕症; 子宫肌瘤; 子宫内膜异位症; 输卵管积水

Diagnosis and treatment strategies for infertility patients with complex adenomyosis

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【Abstract】 Adenomyosis is a common disease in women of childbearing age, mainly manifested as dysmenorrhea, heavy menstrual flow, infertility and enlarged uterus. In recent years, with the adjustment of fertility policy and the delay of reproductive age, the correlation between adenomyosis and infertility has been paid more and more attention. Adenomyosis often does not exist alone, and is often

associated with complex gynecological diseases such as uterine fibroids, ovarian endometriotic cysts, deep endometriosis, and hydrosalpinx. The existence of comorbid diseases increases the difficulty of diagnosis and treatment of adenomyosis-related infertility. How to make effective diagnosis and targeted treatment for patients with complex adenomyosis and infertility to increase pregnancy rate and improve pregnancy outcome? This article provided a special review of infertility patients with complex adenomyosis, and aimed to explore an effective diagnosis and treatment model for patients with complex adenomyosis and infertility, increase their pregnancy and live birth rates, and improve the prognosis of newborns.

【 Key words 】 Adenomyosis; Infertility; Hysteromyoma; Endometriosis; Hydrosalpinx

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·MDT 专家视角专栏·

再谈子宫腺肌病相关生育问题的多学科诊疗

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【摘要】 本刊针对子宫腺肌病患者的生育问题, 尤其是合并不孕症的处理, 邀请 9 位专家从不同角度进行了述评, 旁征博引, 阐述观点, 为遇到该问题时如何进行多学科诊疗提供指引。本文将归纳总结诸位专家观点, 提出有争议可研究的热点问题, 并对如何更好地解决子宫腺肌病相关生育问题进行多学科诊疗再提几点建议。

【关键词】 子宫腺肌病; 不孕症; 多学科综合诊疗

Talk about the multi-disciplinary team of adenomyosis related fertility problems again

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【Abstract】 In view of the fertility problems of patients with adenomyosis, especially when combined with infertility, nine experts were invited to comment on this issue from different angles, and to elaborate their views and point out the direction of how to conduct multi-disciplinary team when meeting this problem. We will summarize the opinions of the invited experts, put forward the hot issues that are controversial and can be further studied, and give some suggestions on how to better conduct multi-disciplinary team.

【Key words】 Adenomyosis; Infertility; Multi-disciplinary team

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·临床研究·

植入前遗传学非整倍体筛查对反复种植失败患者疗效的观察

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陈虹和郑锦霞对本文有同等贡献

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【摘要】 目的 探讨基于二代测序(next-generation sequencing, NGS)技术的胚胎植入前遗传学非整倍体筛查(preimplantation genetic testing for aneuploidies, PGT-A)对反复种植失败(recurrent implantation failure, RIF)患者的临床疗效。方法 回顾性队列研究分析2018年12月至2020年1月期间在同济大学附属第一妇婴保健院生殖医学科接受PGT-A治疗的63例RIF患者为研究组;选取同期采用常规体外受精(*in vitro* fertilization, IVF)治疗的179例RIF患者为对照组,采用倾向性得分匹配的方法(propensity score matching, PSM)对女方年龄进行匹配,分析比较两组患者一般资料、促排卵结果和妊娠结局等,并采用logistic回归分析影响每移植周期累计活产率的因素。结果 最终203例患者纳入

分析, 其中研究组 61 例, 对照组 142 例, 匹配了年龄差异后两组间患者的年龄、体质量指数、不孕因素、不孕年限、既往移植失败次数、基础卵泡刺激素 (follicle-stimulating hormone, FSH)、窦卵泡计数和卵巢刺激方案差异均无统计学意义 (均 $P>0.05$)。研究组的无可移植胚胎数比例 [45.90% (28/61)] 高于对照组 [13.38% (19/142)], 而可移植胚胎数 [1 (0, 2) 个] 低于对照组 [2 (1, 4) 个], 差异均有统计学意义 (均 $P<0.001$)。研究组的胚胎种植率 [61.54% (24/39)]、每移植周期临床妊娠率 [61.54% (24/39)]、每移植周期持续妊娠率 [61.54% (24/39)] 和每移植周期活产率 [61.54% (24/39)] 均高于对照组 [27.47% (75/273)], $P<0.001$; 41.51% (66/159), $P=0.024$; 37.11% (59/159), $P=0.006$ 和 37.11% (59/159), $P=0.006$]; 但其累计活产率 [39.34% (24/61)] 与对照组 [41.55% (59/142)] 相比差异无统计学意义 ($P=0.770$)。多因素 logistics 回归分析显示是否采用 PGT-A 治疗为影响每移植周期活产率的独立危险因素 [OR (95% CI) = 2.71 (1.32~5.58)], $P=0.007$], 而对累计活产率没有显著影响 [OR (95% CI) = 2.49 (0.87~7.13)], $P=0.089$]。结论 相较常规 IVF 治疗, NGS-PGT 策略虽然能提高 RIF 患者的每移植周期活产率, 但不会提高其累计活产率。因此, NGS-PGT 策略在 RIF 患者中的临床应用价值仍值得商榷。

【关键词】 生殖技术, 辅助; 胚胎植入前遗传学非整倍体筛查; 受精, 体外; 反复种植失败; 胚胎移植; 累计活产率

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Clinical research of preimplantation genetic testing for aneuploidies in patients with recurrent implantation failure

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【Abstract】 **Objective** To investigate the effect of preimplantation genetic testing for aneuploidies (PGT-A) based on next-generation sequencing technology (NGS) on the clinical outcomes of patients with recurrent implantation failure (RIF). **Methods** A retrospective cohort study was conducted and the outcomes of patients with a history of RIF were analyzed, of which 63 women underwent PGT-A strategy (study group) and 179 women who underwent conventional *in vitro* fertilization (IVF) treatment (control group) at the Centre of Assisted Reproduction in Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine from December 2018 to January 2020. Propensity score matching (PSM) was conducted by female age. Baseline characteristics,

stimulation characteristics and pregnancy outcomes were analyzed between the two groups. Logistic regression model was used to evaluate the relative prognostic significance of independent variables in relation to the live birth rate (LBR) and cumulative live birth rate (CLBR). **Results** Totally 203 patients including 61 patients in study group and 142 patients in control group remained in each group after PSM, there were no significant differences in female age, body mass index, cause of infertility, duration of infertility, number of previous embryo transfer failures, basal follicle-stimulating hormone (bFSH), antral follicle count and ovarian stimulation protocols after matching (all $P>0.05$). More patients had unavailable embryos in study group than in control group [45.90% (28/61) vs. 13.38% (19/142), $P<0.001$], while the number of transferable embryos was significantly lower than that in control group [1(0, 2) vs. 2(1, 4), $P<0.001$]. The implantation rate [61.54% (24/39)], the clinical pregnancy rate [61.54% (24/39)], the ongoing pregnancy rate [61.54% (24/39)] and the live birth rate [61.54% (24/39)] per embryo transfer cycle in study group were significantly higher than those in control group [27.47% (75/273), $P<0.001$; 41.51% (66/159), $P=0.024$; 37.11% (59/159), $P=0.006$ and 37.11% (59/159), $P=0.006$, respectively]. However, there was no significant difference in CLBR between the two groups [39.34% (24/61) vs. 41.55% (59/142), $P=0.770$]. Logistic regression revealed that women used PGT was 2.71 times more likely to achieve live birth per transfer cycle compared with those women used non-PGT [OR (95% CI)=2.71(1.32–5.58), $P=0.007$], however, the use of PGT was not associated with CLBR [OR (95% CI)=2.49(0.87–7.13), $P=0.089$]. **Conclusion** Compared with conventional IVF treatment, NGS-PGT strategy can improve the live birth rate per embryo transfer cycle, but cannot improve the cumulative live birth rate in RIF patients. Therefore, the clinical value of NGS-PGT strategy in RIF patients is still debatable.

【Key words】 Reproductive technology, assisted; Preimplantation genetic testing for aneuploidies; Fertilization, *in vitro*; Recurrent implantation failure; Embryo transfer; Cumulative live birth rate

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·临床研究·

辅助生殖技术受孕双绒毛膜双胎之一胎死宫内的存活儿围产期预后分析

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梅洁和孙彦欣对本文有同等贡献

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【摘要】 目的 探讨辅助生殖技术受孕的双绒毛膜双胎之一胎死宫内(single intrauterine fetal demise, sIUFD)存活儿的围产期结局。方法 回顾性队列研究分析 2013 年 1 月至 2018 年 12 月期间在南京大学医学院附属鼓楼医院生殖医学科行冻融胚胎移植(frozen-thawed embryo transfer, FET)/新鲜胚胎移植的 4922 个周期(包括 3116 个 FET 周期的单胎活产周期和 1806 个新鲜胚胎移植周期的单胎活产周期)。其中新鲜周期的对照组纳入 1000 个单分裂胚移植后的单胎活产周期, 消失双胎综合征(vanishing twin syndrome, VTS)组纳入 806 个双分裂胚移植后双绒毛膜 sIUFD 幸存者单胎活产的 VTS 周期。冻融周期的对照组纳入 2445 个单胚胎移植(613 例分裂胚和 1832 例囊胚)后单胎活产周期, VTS 组纳入 385 个双分裂胚移植和 286 个双囊胚移植后双绒毛膜 sIUFD 幸存者单胎活产的 VTS 周期。分别比较两组的基线资料, 以及孕龄、出生体质量、早产率、低出生体质量率、小于胎龄儿率和先天畸形率等围产期结局的差异。结果 在囊胚移植的冻融周期中, VTS 组出生体质量低 [$(3\ 316.82\pm 617.69)$ g 比 $(3\ 405.16\pm 550.68)$ g, $P=0.013$], 低出生体质量的发生风险高 [$aOR(95\% CI)=2.70(1.46\sim 5.00)$, $P=0.002$], 但在分裂胚移植周期中, VTS 组和对照组围产期预后差异均无统计学意义(均 $P>0.05$)。结论 冻融周期囊胚移植后受孕的 VTS 幸存者围产期风险升高, 选择性单胚移植是改善辅助生殖技术受孕患者妊娠预后的关键。

【关键词】 生殖技术, 辅助; 消失双胎综合征; 围产期结局

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Analysis of perinatal risks for the surviving infant of dichorionic twins vanishing twin syndrome following assisted reproductive technology

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【Abstract】 Objective To analyze the perinatal risks for the surviving infant of dichorionic twins vanishing twin syndrome (VTS) conceived by assisted reproductive technology (ART). **Methods** We used a retrospective cohort study to analyze the clinical data of 4922 frozen-thawed embryo transfer (FET)/fresh embryo transfer cycles in the Department of Reproductive Medicine of the Affiliated Drum Tower Hospital of Nanjing University Medical School from January 2013 to December 2018. This study assessed 4922 cycles (3116 singleton live births from FET cycles and 1806 singleton live births from fresh embryo transfer cycles). The fresh embryo transfer cycles included 1000 singletons following cleavage-stage SET and 806 survivors of VTS following cleavage-stage double embryo transfer (DET). The FET cycles included 2445 singletons (613 cleavage-stage embryo transfer cycles and 1832 blastocyst transfer cycles) following single embryo transfer (SET) and 671 survivors of VTS (385 cleavage-stage embryo transfer cycles and 286 blastocyst transfer cycles) following DET. Baseline characteristics and obstetric outcomes, including gestational age, preterm birth, birth weight, low birth weight, and small-for-gestational-age were analyzed between the two groups. **Results** In frozen-thawed blastocyst transfer cycles, VTS group had lower birth weight [(3 316.82±617.69) g vs. (3 405.16±550.68) g, $P=0.013$] and higher risk of low birth weight [aOR(95% CI)=2.70(1.46–5.00), $P=0.002$] compared with control group, but no differences of perinatal outcomes were found between VTS and control groups in cleavage-stage transfer cycles. **Conclusion** Surviving infant of dichorionic twins VTS may have higher perinatal risks in blastocyst-stage FET. Selective SET is recommended to obtain singleton pregnancies with a more favorable pregnancy outcome from ART.

【Key words】 Reproductive technology, assisted; Vanishing twin syndrome; Perinatal risk

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·临床研究·

AMH 水平对 IVF/ICSI 早期妊娠丢失及累积妊娠结局的影响

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【摘要】 目的 探讨抗苗勒管激素 (anti-Müllerian hormone, AMH) 水平对体外受精/卵胞质内单精子注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 早期妊娠丢失及累积妊娠结局的影响, AMH 是否可以作为评价卵母细胞质量的指标。方法 选取 2015 年 12 月至 2019 年 12 月期间于郑州大学第三附属医院生殖医学中心行 IVF/ICSI 助孕首次取卵周期的 3701 例女性进行回顾性队列分析, 按年龄分为高龄组 (≥ 35 岁) 和低龄组 (< 35 岁), 参考博洛尼亚和波塞冬标准, 按 AMH 水平分为 3 组, 低 AMH 组 ($AMH \leq 1 \mu g/L$)、中低 AMH 组 ($1 \mu g/L < AMH < 2 \mu g/L$) 和正常 AMH 组 ($2 \mu g/L \leq AMH < 6 \mu g/L$)。比较各组女性的一般资料及临床数据, 探讨各组间早期妊娠丢失、累积妊娠率、累积活产率的差异。应用二元 logistic 回归, 以正常 AMH 组为参照组, 控制混杂因素 (年龄、不孕原因、刺激方案、人绒毛膜促性腺激素注射日内膜厚度、基础卵泡刺激素水平), 分析 AMH 水平对妊娠结局的影响。结果 无论低龄或是高龄患者, 不同 AMH 水平间每移植周期临床妊娠率、活产率、早期妊娠丢失率差异均无统计学意义 (均 $P > 0.05$)。低龄患者中, 低 AMH 组、中低 AMH 组和正常 AMH 组累积妊娠率分别为 61.9% (211/341)、66.0% (319/483)、69.3% (1219/1760), 差异具有统计学意义 ($P = 0.020$); 累积活产率分别为 50.1% (171/341)、57.8% (279/483)、57.1% (1005/1760), 差异具有统计学意义 ($P = 0.047$)。二元逻辑回归校正混杂因素后, 低龄患者中低 AMH 组累积妊娠率、累积活产率均低于正常 AMH 组 ($OR = 0.617$, 95% $CI = 0.460 \sim 0.829$, $P = 0.001$; $OR = 0.660$, 95% $CI = 0.496 \sim 0.878$, $P = 0.004$); 中低 AMH 组累积妊娠率、累积活产率低于正常 AMH 组, 但差异均无统计学意义 (均 $P > 0.05$)。高龄组中 AMH 水平不同的 3 组间累积妊娠率、累积活产率差异均无统计学意义 (均 $P > 0.05$)。结论 在行 IVF/ICSI 助孕女性首次取卵周期中, AMH 水平与早期妊娠丢失的发生率无关。在低龄女性中, AMH 水平是影响累积妊娠结局的独立影响因素, $AMH \leq 1 \mu g/L$ 的女性助孕结局明显降低。在高龄女性中, AMH 水平与累积妊娠结局没有显著的相关性。因此 AMH 水平可能不是卵母细胞质量的评价指标。

【关键词】 抗苗勒管激素; 受精, 体外; 精子注射, 细胞质内; 妊娠结局; 胚胎丢失; 卵母细胞; 活胎产

Effects of anti-Müllerian hormone levels on early pregnancy loss and cumulative pregnancy outcome in *in vitro* fertilization/intracytoplasmic sperm injection

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【Abstract】 Objective To investigate the effect of anti-Müllerian hormone (AMH) level on early pregnancy loss and cumulative pregnancy outcome of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI), and whether AMH level can be used as an indicator to evaluate the quality of oocytes. **Methods** A retrospective cohort analysis was performed on 3701 women undergoing their first oocyte retrieval for IVF/ICSI at the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University from December 2015 to December 2019. According to the age, patients were divided into elderly group (≥ 35 years old) and younger group (< 35 years old). References to the Bologna criteria and POSEIDON criteria, patients were divided into three groups: low AMH group ($AMH \leq 1 \mu g/L$), moderately low AMH group ($1 \mu g/L < AMH < 2 \mu g/L$), normal AMH group ($2 \mu g/L \leq AMH < 6 \mu g/L$). The basic data and clinical data, the differences of early pregnancy loss, cumulative pregnancy rate and cumulative live birth rate among each group were compared. Binary logistic regression was used to analyze the effect of AMH on pregnancy outcome by control confounders (such as age, infertility reason, stimulation protocol, endometrial thickness on the day of human chorionic gonadotropin injection, basic follicle-stimulating hormone level). **Results** There were no significant differences in clinical pregnancy rate, live birth rate and early pregnancy loss rate among the three groups (all $P > 0.05$) whether in the elderly group or the younger group. The cumulative pregnancy rates were 61.9% (211/341), 66.0% (319/483), 69.3% (1219/1760), and the cumulative live birth rates were 50.1% (171/341), 57.8% (279/483), 57.1% (1005/1760) in low AMH group, moderately low AMH group and normal AMH group of the younger group, respectively, and there were statistical differences ($P = 0.020$, $P = 0.047$). After adjusting for confounding factors, in the younger group, cumulative pregnancy rate and cumulative live birth rate in the low AMH group were lower than those in the normal AMH group ($OR = 0.617$, 95% $CI = 0.460 - 0.829$, $P = 0.001$; $OR = 0.660$, 95% $CI = 0.496 - 0.878$, $P = 0.004$), the cumulative pregnancy rate and the cumulative live birth rate in the moderately low AMH group were lower than those in the normal AMH group, but there was no statistical difference (all $P > 0.05$). There were no significant differences in cumulative pregnancy rate and cumulative live birth rate among the three groups with different AMH levels in the elderly group (all $P > 0.05$). **Conclusion** AMH is not associated with the incidence of early pregnancy loss during the their first oocyte retrieval in IVF/ICSI. AMH level is an independent factor affecting the cumulative pregnancy outcome in the younger group, the pregnancy outcome of women with $AMH \leq 1 \mu g/L$ decreased significantly. In the elderly women, AMH was not significantly associated with cumulative pregnancy outcome. AMH level may not be an indicator of oocyte quality.

【 Key words 】 Anti-Müllerian hormone; Fertilization, *in vitro*; Sperm injections, intracytoplasmic; Embryo loss; Pregnancy outcome; Oocytes; Live birth

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临床研究

多囊卵巢综合征合并焦虑状态的相关因素研究

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【摘要】 目的 探讨多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 合并焦虑对生活质量的影响及其相关因素。方法 横断面研究分析 2019 年 5 月至 2022 年 1 月期间于复旦大学附属妇产科医院生殖内分泌门诊就诊的 PCOS 患者行焦虑及生活质量评分, 将 PCOS 患者分为合并焦虑组和非合并焦虑组, 比较两组的临床特征、内分泌、卵巢功能及代谢状态中, 并采用 logistic 回归分析及受试者工作特征 (receiver operator characteristic, ROC) 曲线分析筛选出 PCOS 合并焦虑的相关因素。结果 共纳入 125 例 PCOS 患者, 合并焦虑组与 PCOS 非合并焦虑组患者分别为 44 例与 81 例。合并焦虑的患者涉及肥胖、月经异常及 PCOS 病情本身的生活质量得分 (12.7 ± 1.4 , 17.9 ± 0.9 及 28.3 ± 1.6) 均低于非合并焦虑者 (18.8 ± 0.9 , $P<0.001$; 23.2 ± 0.6 , $P<0.001$ 及 35.0 ± 0.9 , $P<0.001$), PCOS 合并焦虑患者体质量指数 (body mass index, BMI) [25.74 ± 0.97 kg/m² 比 23.46 ± 0.45 kg/m², $P=0.038$] 及胰岛素曲线下面积 (area of insulin under the curve, IAUC) [2844.28 ± 303.61 pmol/L 比 1834.28 ± 147.89 pmol/L, $P=0.001$] 均较 PCOS 非合并焦虑患者高, 性激素结合球蛋白 (sex hormone binding globulin, SHBG) [33.29 ± 6.21 nmol/L 比 41.94 ± 4.11 nmol/L, $P=0.045$] 水平较 PCOS 非合并焦虑患者低, 差异均有统计学意义。logistic 回归分析筛选出与 PCOS 并发焦虑的相关因素为 BMI ($OR=1.113$, 95% $CI=1.016\sim 1.219$, $P=0.021$) 与 IAUC ($OR=1.001$, 95% $CI=1.000\sim 1.001$, $P=0.003$); ROC 分析显示, IAUC 是 PCOS 合并焦虑的相关因素, 其曲线下面积为 0.701 ($P=0.020$)。结论 PCOS 合并焦虑的患者生活质量低于非合并焦虑 PCOS 患者, 焦虑可能与体质量的增加及高胰岛素血症/胰岛素抵抗的状态相关, IAUC 可能与 PCOS 合并焦虑具有一定的相关性。

【关键词】 多囊卵巢综合征； 焦虑； 生活质量； 体质量指数； 胰岛素抵抗

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A study of quality of life and associated factors for complicated anxiety in patients with polycystic ovary syndrome

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【Abstract】 Objective To explore the influence of anxiety on the quality of life and its associated factors in patients with polycystic ovary syndrome (PCOS). **Methods** PCOS patients were enrolled in this cross sectional study in Reproductive Endocrinology, Obstetrics and Gynecology Hospital of Fudan University from May 2019 to January 2022. Anxiety and quality of life were scored for patients diagnosed with PCOS. All patients were divided into PCOS with or without anxiety group. The associated factors of PCOS complicated with anxiety were screened from clinical features, endocrine, ovarian reserve function and metabolic status by logistic analysis and receiver operating characteristic (ROC). **Results** Totally 125 PCOS patients were enrolled, of whom 44 were complicated with anxiety. The scores for the quality of life in patients with PCOS and anxiety related to obesity (12.7 ± 1.4 vs. 18.8 ± 0.9 , $P < 0.001$), abnormal menstruation (17.9 ± 0.9 vs. 23.2 ± 0.6 , $P < 0.001$) and PCOS itself (28.3 ± 1.6 vs. 35.0 ± 0.9 , $P < 0.001$) were all lower than those in PCOS patients without anxiety. The body mass index (BMI) [25.74 ± 0.97 kg/m² vs. 23.46 ± 0.45 kg/m², $P = 0.038$] and area of insulin under the curve (IAUC) [2844.28 ± 303.61 pmol/L vs. 1834.28 ± 147.89 pmol/L, $P = 0.001$] of PCOS patients with anxiety were all higher, while sex hormone binding globulin (SHBG) levels [33.29 ± 6.21 nmol/L vs. 41.94 ± 4.11 nmol/L, $P = 0.045$] were lower than those without anxiety, and the differences were all statistically significant. Logistic regression analysis screened out the most relevant factor with anxiety in PCOS as IAUC ($OR = 1.001$, 95% $CI = 1.000 - 1.001$, $P = 0.021$) and BMI ($OR = 1.113$, 95% $CI = 1.016 - 1.219$, $P = 0.003$). ROC analysis showed that IAUC was an associated factor for PCOS complicated with anxiety, and the area under the ROC curve were 0.701 ($P = 0.020$). **Conclusion** The prevalence of anxiety in PCOS patients is higher than that in the general population. The quality of life is lower in PCOS patients with anxiety than those without. Anxiety may be closely related to weight gain and hyperinsulinemia/insulin resistance in PCOS patients.

【Key words】 Polycystic ovary syndrome; Anxiety; Quality of life; Body mass index; Insulin resistance

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·临床研究·

围绝经期和绝经后女性绝经症状与日常认知功能的相关性研究

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【摘要】 目的 探讨围绝经期和绝经后女性绝经症状与日常认知功能的相关性。方法 采用横断面研究, 分析 2018 年 10 月至 2020 年 10 月期间初次就诊于上海交通大学附属第六人民医院妇产科绝经门诊的 314 例患者的临床资料。采用改良 Kupperman 绝经指数 (Kupperman menopausal index, KMI) 量表评估绝经症状及其严重程度; 简短版日常认知功能 (everyday cognition, ECog) 量表评估日常认知功能。多元线性回归分析围绝经期和绝经后女性绝经症状与日常认知功能的相关性。结果 314 例患者 ECog 分数为 1.50 ± 0.49 。KMI 分数为 12.67 ± 7.88 , 74.8% (235/314) 患者有绝经症状, 其中 34.7% (109/314) 有中重度绝经症状。相比无绝经症状患者 (ECog 得分: 1.27 ± 0.29), 有绝经症状的患者 ECog 得分更高 (轻度症状组 ECog 得分: 1.48 ± 0.47 , $P=0.005$; 中重度症状组 ECog 得分: 1.69 ± 0.55 , $P<0.001$)。相关性分析表明, KMI 的 5 个症状 (潮热出汗、失眠、情绪波动、抑郁和疲乏) 均与日常认知功能下降相关 ($P<0.001$)。多元线性回归分析显示潮热出汗 [$\beta=0.060$, 95% 置信区间 (confidence interval, CI)= $0.002 \sim 0.117$, $P=0.043$]、抑郁 ($\beta=0.163$, 95% CI= $0.073 \sim 0.253$, $P<0.001$) 和疲乏 ($\beta=0.138$, 95% CI= $0.071 \sim 0.205$, $P<0.001$) 症状仍与日常认知功能下降相关。结论 潮热出汗、抑郁和疲乏症状是围绝经期和绝经后女性日常认知功能下降的独立危险因素。

【关键词】 围绝经期; 绝经症状; 日常认知功能; 相关性

Study on the relationship between menopausal symptoms and everyday cognition in perimenopausal and postmenopausal women

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【Abstract】 Objective To evaluate the relationship between menopausal symptoms and everyday cognition in perimenopausal and postmenopausal women. **Methods** A cross-sectional study was used to analyze the clinical data of 314 women who first visited the menopausal clinic of Department of Gynecology and Obstetrics of Shanghai Jiao Tong University Affiliated Sixth People's Hospital from October 2018 to October 2020. The modified Kupperman menopausal index (KMI) scale was used to assess the prevalence and severity of menopausal symptoms, and a short version of everyday cognition (ECog) scale was used to evaluate everyday cognition. Multiple linear regression was used to analyze the relationship between menopausal symptoms and everyday cognition in perimenopausal and postmenopausal women. **Results** The ECog score of 314 patients was 1.50 ± 0.49 . The score of KMI was 12.67 ± 7.88 , 74.8% (235/314) of the patients had menopausal symptoms, and 34.7% (109/314) had moderate to severe menopausal symptoms. Compared with asymptomatic patients (ECog scores: 1.27 ± 0.29), symptomatic patients had higher ECog scores (mild symptoms group: 1.48 ± 0.47 , $P=0.005$; moderate to severe symptoms group: 1.69 ± 0.55 , $P<0.001$). Correlation analysis showed that the five symptoms of KMI (hot flashes/sweating, insomnia, irritability, melancholia and fatigue) were associated with the decline of everyday cognition ($P<0.001$). Multiple linear regression analysis showed that the symptoms of hot flashes/sweating [$\beta=0.060$, 95% confidence interval (CI) =0.002–0.117, $P=0.043$], melancholia ($\beta=0.163$, 95% CI=0.073–0.253, $P<0.001$) and fatigue ($\beta=0.138$, 95% CI=0.071–0.205, $P<0.001$) were still associated with the decline of everyday cognition. **Conclusion** The symptoms of hot flashes/sweating, melancholia and fatigue are independent risk factors for the decline of everyday cognition in perimenopausal and postmenopausal women.

【Key words】 Perimenopause; Menopausal symptoms; Everyday cognition; Relationship

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·实验研究·

红景天苷通过抑制 NF- κ B 通路降低 多囊卵巢综合征模型小鼠的炎症反 应

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【摘要】 目的 研究红景天苷 (Salidroside, Sal) 对多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 模型小鼠炎症水平的调节作用及其与核转录因子- κ B (nuclear factor- κ B, NF- κ B) 的关系。方法 将 28 只 3 周龄 C57B/6J 雌性小鼠按照计算机随机生成数字的方式分为对照组、Sal 组、PCOS 组和 PCOS+Sal 组, 每组 7 只, 进行 21 d 造模及治疗。造模结束行糖耐量测试, 取卵巢组织行免疫组织化学染色检测肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、p-NF- κ B p65 的表达水平, 酶联免疫吸附试验 (enzyme-linked immunosorbent assay, ELISA) 检测小鼠血清性激素和炎症因子表达水平。培养的人卵巢颗粒细胞系 (human ovary granulosa cell line, KGN) 分为对照组、脂多糖 (lipopolysaccharide, LPS) (0.5 mg/L) 组、Sal (30 μ mol/L) 组和 LPS (0.5 mg/L) +Sal (15 μ mol/L、30 μ mol/L、60 μ mol/L) 组, 处理 24 h 后检测各组炎症因子 mRNA 的表达水平以及 NF- κ B 相关蛋白的表达水平。结果 与对照组相比, PCOS 组小鼠血清睾酮 [(2.11 \pm 0.60) μ g/L]、黄体生成素 (luteinizing hormone, LH) [(2.54 \pm 0.27) U/L]、LH/卵泡刺激素 (follicle-stimulating hormone, FSH) (0.12 \pm 0.01) 及炎症因子白细胞介素 (interleukin, IL)-1 β [(107.83 \pm 12.05) ng/L]、IL-6 [(56.70 \pm 7.33) ng/L] 和 TNF- α [(74.72 \pm 14.64) ng/L] 水平均显著高于对照组 [(0.77 \pm 0.06) μ g/L、(1.07 \pm 0.21) U/L、0.05 \pm 0.01、(33.83 \pm 4.96) ng/L、(28.91 \pm 8.53) ng/L、(37.07 \pm 5.48) ng/L, 均 P <0.001], Sal 治疗后睾酮 [(1.47 \pm 0.25) μ g/L, P =0.012]、LH [(1.73 \pm 0.17) U/L, P <0.001]、LH/FSH (0.08 \pm 0.01, P <0.001)、IL-1 β [(74.21 \pm 10.64) ng/L, P <0.001]、IL-6 [(40.90 \pm 5.01) ng/L, P =0.002] 与 TNF- α [(55.42 \pm 8.78) ng/L, P =0.017] 水平较 PCOS 组均降低; 免疫组织化学结果显示 PCOS 组小鼠卵巢颗粒细胞中 TNF- α 和 p-NF- κ B p65 的表达上调, Sal 处理后减少。LPS 组 KGN IL-1 β (1.76 \pm 0.09)、IL-6 (1.79 \pm 0.20) 和 TNF- α mRNA (1.56 \pm 0.19) 水平显著高于对照组 [0.50 \pm 0.20、0.80 \pm 0.10、0.70 \pm 0.30, 均 P <0.001], Sal 处理 (15 μ mol/L、30 μ mol/L、60 μ mol/L) 后, IL-1 β (1.09 \pm 0.07、1.00 \pm 0.02、0.96 \pm 0.03, 均 P <0.001)、IL-6 (1.47 \pm 0.12、0.93 \pm 0.18、0.91 \pm 0.27, 均 P <0.001) 和 TNF- α (1.21 \pm 0.25、0.94 \pm 0.35、0.76 \pm 0.07, 均 P <0.001) 的 mRNA 水平明显下降; 与对照组相比, LPS 组 p-NF- κ B p65 (0.49 \pm 0.07 比 0.31 \pm 0.03, P =0.013) 和 p-I κ B α (0.48 \pm 0.06 比 0.26 \pm 0.04, P =0.012) 的蛋白表达水平明显升高, Sal 处理后, p-NF- κ B p65 (0.33 \pm 0.05, P =0.024) 和 p-I κ B α (0.31 \pm 0.06, P =0.046) 的蛋白水平显著下降。结论 Sal 可通过抑制 NF- κ B 通路降低 PCOS 模型小鼠的炎症水平。

【关键词】 多囊卵巢综合征; 人卵巢颗粒细胞; 核转录因子- κ B; 炎症; 红景天苷

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Salidroside attenuates inflammatory response in mice with polycystic ovary syndrome by inhibiting NF- κ B signaling pathway

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【Abstract】 Objective To investigate the regulatory effects of salidroside (Sal) on mice in an inflammatory state with polycystic ovary syndrome (PCOS) and the link with nuclear factor- κ B (NF- κ B) signaling pathway. **Methods** Totally twenty-eight female C57B/6J mice aged 21 d were divided into control group, Sal group, PCOS group and PCOS+Sal group with 7 mice per group based on numbers randomly generated by computer and 21 d treatment was taken. Glucose tolerance test (GTT) was performed when the treatment was finished, ovarian tissues were taken for HE staining and morphological analysis, immunohistochemistry was used to detect tumor necrosis factor (TNF)- α and p-NF- κ B p65 protein levels in the ovaries, and enzyme-linked immunosorbent assay (ELISA) was taken to detect the levels of serum sex hormones and inflammatory cytokines. Human ovarian granulosa cell line (KGN cells) were divided into four groups: control group, Sal (30 μ mol/L) group, lipopolysaccharide (LPS) (0.5 mg/L) group and LPS (0.5 mg/L) +Sal (15 μ mol/L, 30 μ mol/L, 60 μ mol/L) group. Inflammatory cytokines mRNA levels and nuclear factor (NF)- κ B associated protein levels were detected after culture for 24 h. **Results** The levels of testosterone [(2.11 \pm 0.60) μ g/L vs. (0.77 \pm 0.06) μ g/L, P <0.001], luteinizing hormone (LH) [(2.54 \pm 0.27) U/L vs. (1.07 \pm 0.21) U/L, P <0.001], LH/follicle-stimulating hormone (FSH) (0.12 \pm 0.01 vs. 0.05 \pm 0.01, P <0.001) and inflammatory cytokines interleukin (IL)-1 β [(107.83 \pm 12.05) ng/L vs. (33.83 \pm 4.96) ng/L, P <0.001], IL-6 [(56.70 \pm 7.33) ng/L vs. (28.91 \pm 8.53) ng/L, P <0.001], TNF- α [(74.72 \pm 14.64) ng/L vs. (37.07 \pm 5.48) ng/L, P <0.001] increased in PCOS mice compared with control group, but the levels of testosterone [(1.47 \pm 0.25) μ g/L, P =0.012], LH [(1.73 \pm 0.17) U/L, P <0.001], LH/FSH (0.08 \pm 0.01, P <0.001), IL-1 β [(74.21 \pm 10.64) ng/L, P <0.001], IL-6 [(40.90 \pm 5.01) ng/L, P =0.002] and TNF- α [(55.42 \pm 8.78) ng/L, P =0.017] decreased significantly following Sal treatment. Immunohistochemical staining showed that TNF- α and p-NF- κ B p65 protein levels in granulosa cells increased in PCOS mice but decreased after Sal treatment. Besides, IL-1 β (1.76 \pm 0.09 vs. 0.50 \pm 0.20, P <0.001), IL-6 (1.79 \pm 0.20 vs. 0.80 \pm 0.10, P <0.001), TNF- α (1.56 \pm 0.19 vs. 0.70 \pm 0.30, P <0.001) mRNA levels increased significantly in LPS induced KGN cells, after Sal treatment (15 μ mol/L, 30 μ mol/L and 60 μ mol/L), the mRNA levels of IL-1 β (1.09 \pm 0.07, 1.00 \pm 0.02, 0.96 \pm 0.03, all P <0.001), IL-6 (1.47 \pm 0.12, 0.93 \pm 0.18, 0.91 \pm 0.27, P <0.001) and TNF- α (1.21 \pm 0.25, 0.94 \pm 0.35, 0.76 \pm 0.07, all P <0.001) apparently decreased. In addition, p-NF- κ B p65 (0.49 \pm 0.07 vs. 0.31 \pm 0.03, P =0.013) and p-I κ B α (0.48 \pm 0.06 vs. 0.26 \pm 0.04, P =0.012) protein levels increased apparently in LPS induced KGN cells, but the protein levels of p-NF- κ B p65 (0.33 \pm 0.05, P =0.024) and p-I κ B α (0.31 \pm 0.06, P =0.046) decreased following Sal

treatment. **Conclusion** Sal can attenuate inflammation levels in mice with PCOS by inhibiting NF- κ B signaling pathway.

【Key words】 Polycystic ovary syndrome; Granulosa cells; Nuclear factor- κ B; Inflammation; Salidroside

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·实验研究·

多囊卵巢综合征小鼠卵母细胞 miR-320-3p 低表达对胚胎发育潜 能的影响

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【摘要】 目的 探究多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 小鼠卵母细胞中 miR-320-3p 低表达对胚胎发育潜能的影响, 并初步探讨相关分子机制。方法 脱氢表雄酮皮下注射法构建 40 只 PCOS 小鼠模型, 40 只对照组小鼠注射等量油剂。通过发情周期变化和卵巢组织苏木素-伊红染色, 评估模型构建效果, 超数排卵获取模型鼠的 M_{II} 期卵母细胞, 胞质内注射 miR-320-3p 模拟物 (miR-320-3p mimics) 或阴性对照物 (negative control, NC), 分为对照+NC 组、PCOS+NC 组、PCOS+miR-320-3p mimics 组。①通过 qRT-PCR 方法检测三组小鼠 M_{II} 期卵母细胞中 miR-320-3p 的表达; ②三组 M_{II} 期卵母细胞行卵胞质内单精子注射, 收集双原核 (two pronuclei, 2PN) 受精卵进行体外培养, 于受精后 48 h、84 h 记录 4-细胞期胚胎和囊胚的数量。③三组囊胚分别进行滋养外胚层分子标志物 CDX2 染色和脱氧核糖核苷酸末端转移酶介导缺口末端标记法细胞凋亡检测, 统计各组总细胞

数、滋养外胚层 (trophectoderm, TE) 细胞数、内细胞团 (inner cell mass, ICM) 细胞数和凋亡细胞数; ④通过 qRT-PCR 方法检测三组 4-细胞胚胎中 miR-320-3p 的靶基因 (*Ulk1*、*Pbx3*、*Kdm5b*、*Satb2*) 及发育相关基因 (*Pou5f1*、*Myc*、*Klf4*、*Ago2*、*Dppa3*、*Wdr5*) 的表达变化。结果 ①qRT-PCR 显示, 与对照+NC 组相比, PCOS+NC 组小鼠卵母细胞中 miR-320-3p 表达相对下调, 差异具有统计学意义 ($P=0.009$); PCOS+miR-320-3p mimics 组中 miR-320-3p 表达量显著多于 PCOS+NC 组 ($P=0.002$); 对照+NC 组与 PCOS+miR-320-3p mimics 组组间差异无统计学意义 ($P=0.146$)。②对照+NC 组、PCOS+NC 组、PCOS+miR-320-3p mimics 组的 4-细胞率组间差异均无统计意义 (均 $P>0.05$); 三组囊胚形成率分别是 75.89% (85/112)、59.22% (61/103)、72.64% (77/106), 与对照+NC 组相比, PCOS+NC 组囊胚率显著降低 ($P=0.009$); 与 PCOS+NC 组相比, PCOS+miR-320-3p mimics 组囊胚率显著升高 ($P=0.041$)。③对照+NC 组、PCOS+NC 组、PCOS+miR-320-3p mimics 组囊胚的总细胞数分别是 85.81 ± 9.26 、 67.29 ± 7.07 、 82.71 ± 8.40 , TE 细胞数分别是 69.19 ± 7.01 、 52.38 ± 6.34 、 65.38 ± 8.30 , ICM 细胞数分别是 17.62 ± 3.60 、 14.90 ± 2.39 、 17.29 ± 3.90 , 凋亡细胞数分别是 8.64 ± 2.80 、 11.73 ± 2.07 、 9.55 ± 2.81 , 凋亡率分别是 $9.64\%\pm 2.78\%$ 、 $16.68\%\pm 2.81\%$ 、 $11.18\%\pm 2.61\%$ 。对照+NC 组囊胚的总细胞数、TE 及 ICM 细胞数均显著多于 PCOS+NC 组 ($P<0.001$ 、 $P<0.001$ 、 $P=0.011$), 凋亡细胞数、凋亡率均显著低于 PCOS+NC 组 (均 $P<0.001$); PCOS+miR-320-3p mimics 组总细胞数、TE 及 ICM 细胞数也均显著多于 PCOS+NC 组 ($P<0.001$ 、 $P<0.001$ 、 $P=0.025$), 凋亡细胞数、凋亡率均显著低于 PCOS+NC 组 ($P=0.007$ 、 $P<0.001$)。对照+NC 组与 PCOS+miR-320-3p mimics 组组间囊胚的总细胞数、TE 及 ICM 细胞、凋亡细胞数、凋亡率差异均无统计学意义 (均 $P>0.05$), 三组 TE/ICM 的比值组间差异无统计学意义 ($P>0.05$)。④与对照+NC 组相比, *Ulk1*、*Pbx3*、*Myc*、*Dppa3* 在 PCOS+NC 组 4-细胞胚胎中相对表达下调 ($P=0.012$ 、 $P=0.002$ 、 $P<0.001$ 、 $P=0.001$), *Kdm5b*、*Satb2* 相对表达上调 ($P<0.001$ 、 $P<0.001$); 与 PCOS+miR-320-3p mimics 组相比, *Ulk1*、*Pbx3*、*Myc*、*Dppa3* 在 PCOS+NC 组 4-细胞胚胎中相对表达下调 ($P=0.005$ 、 $P=0.001$ 、 $P=0.001$ 、 $P=0.004$), *Kdm5b*、*Satb2* 相对表达上调 ($P<0.001$ 、 $P=0.001$), 对照+NC 组与 PCOS+miR-320-3p mimics 组组间差异均无统计学意义 (均 $P>0.05$); 与对照+NC 组相比, *Wdr5* 在 PCOS+NC 组和 PCOS+miR-320-3p mimics 组中相对表达均上调 ($P=0.001$ 、 $P=0.003$), PCOS+NC 组与 PCOS+miR-320-3p mimics 组中差异无统计学意义 ($P>0.05$)。 *Pou5f1*、*Klf4*、*Ago2* 在三组间差异均无统计学意义 (均 $P>0.05$)。结论 PCOS 小鼠卵母细胞中 miR-320-3p 低表达影响胚胎植入前的囊胚形成率和囊胚质量, PCOS 卵母细胞中补偿 miR-320-3p 能够改善胚胎发育潜能, 提高胚胎质量。

【关键词】 多囊卵巢综合征; 卵母细胞; 胚胎发育; 小鼠; miR-320-3p

Effects of low expression of miR-320-3p on embryonic developmental potential in polycystic ovary syndrome mouse oocytes

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【Abstract】 Objective To explore the effect of low expression of miR-320-3p in oocytes of polycystic ovary syndrome (PCOS) mouse on embryonic developmental potential, and to preliminarily explore the relevant molecular mechanisms. **Methods** Subcutaneous injection of dehydroepiandrosterone was used to construct 40 PCOS mouse model, 40 control mice were injected with the same amount of oil. The estrous cycle changes and hematoxylin-eosin staining of ovarian tissue were used to evaluate the effect of model construction. After superovulation, the M_{II} stage oocytes of the model mouse were obtained, and miR-320-3p mimics or negative control (NC) were injected into the cytoplasm. Oocytes were divided into three groups: control+NC group, PCOS+NC group, PCOS+miR-320-3p mimics group. 1) The expression of miR-320-3p in M_{II} stage oocytes of control+NC group, PCOS+NC group and PCOS+miR-320-3p mimics group was detected by qRT-PCR method. 2) *In vitro* fertilization was performed after microinjection of three groups of M_{II} oocytes. Two pronuclei (2PN) fertilized oocytes were collected for *in vitro* culture. The number of 4-cell stage embryos and blastocysts was recorded 48 h and 84 h after fertilization. 3) The blastocysts of three groups were stained with trophectoderm molecular marker CDX2 and detected by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling method. The number of total cells, trophectoderm (TE) cells, inner cell mass (ICM) cells, and apoptotic cells was calculated. 4) Expression changes of miR-320-3p target genes (*Ulk1*, *Pbx3*, *Kdm5b*, *Satb2*) and development-related genes (*Pou5f1*, *Myc*, *Klf4*, *Ago2*, *Dppa3*, *Wdr5*) in three groups of 4-cell embryos were detected by qRT-PCR. **Results** 1) qRT-PCR detection showed that compared with the control+NC group, the expression of miR-320-3p was relatively down-regulated in the oocytes of PCOS mouse, and the difference was statistically significant ($P=0.009$). The expression of miR-320-3p in the PCOS+miR-320-3p mimics group was significantly higher than that in the PCOS+NC group ($P=0.002$). There was no statistical difference between the control+NC group and the PCOS+miR-320-3p mimics group ($P=0.146$). 2) There were no significant differences in the 4-cell rate between each two groups of the control+NC group, PCOS+NC group and PCOS+miR-320-3p mimics group (all $P>0.05$). The blastocyst formation rates of the control+NC group, PCOS+NC group and PCOS+miR-320-3p mimics group were 75.89% (85/112), 59.22% (61/103), 72.64% (77/106), compared with the control+NC group, the blastocyst rate in the PCOS+NC group was significantly lower ($P=0.009$). Compared with the PCOS+NC group, the blastocyst rate in PCOS+miR-320-3p mimics group was significantly increased ($P=0.041$). 3) The total number of blastocysts in the control+NC group, PCOS+NC group and PCOS+miR-320-3p mimics group was 85.81 ± 9.26 , 67.29 ± 7.07 , 82.71 ± 8.40 , respectively. The number of TE cells was 69.19 ± 7.01 , 52.38 ± 6.34 , 65.38 ± 8.30 , and the number of ICM cells was 17.62 ± 3.60 , 14.90 ± 2.39 , 17.29 ± 3.90 , respectively. The number of apoptotic cells was 8.64 ± 2.80 , 11.73 ± 2.07 , 9.55 ± 2.81 , and apoptosis rates were $9.64\%\pm 2.78\%$, $16.68\%\pm 2.81\%$, $11.18\%\pm 2.61\%$. The total number of cells, TE and ICM cells in the control+NC group was significantly more

than those in the PCOS+NC group ($P<0.001$, $P<0.001$, $P=0.011$). The number of apoptotic cells and the apoptosis rate were significantly lower than those in the PCOS+NC group (all $P<0.001$). The total number of cells, TE and ICM cells in the PCOS+miR-320-3p mimics group were also significantly more than those in the PCOS+NC group ($P<0.001$, $P<0.001$, $P=0.025$). The number of apoptotic cells and the apoptosis rate were significantly lower than those in the PCOS+NC group ($P=0.007$, $P<0.001$). There were no significant differences in the number of total cells, TE, ICM, apoptotic cells and apoptosis rate between the control+NC group and the PCOS+miR-320-3p mimics group (all $P>0.05$), and there was no significant difference in the ratio of TE/ICM among the three groups ($P>0.05$). 4) Compared with the control+NC group, the relative expressions of *Ulk1*, *Pbx3*, *Myc*, and *Dppa3* were down-regulated in the 4-cell embryos of the PCOS+NC group ($P=0.012$, $P=0.002$, $P<0.001$, $P=0.001$), and *Kdm5b* and *Satb2* were relatively down-regulated. Compared with the PCOS+miR-320-3p mimics group, the relative expressions of *Ulk1*, *Pbx3*, *Myc* and *Dppa3* were down-regulated in the 4-cell embryos of the PCOS+NC group ($P=0.005$, $P=0.001$, $P=0.001$, $P=0.004$), while the relative expressions of *Kdm5b* and *Satb2* were up-regulated ($P<0.001$, $P=0.001$). Compared with the control+NC group, the relative expression of *Wdr5* was up-regulated in the PCOS+NC group and the PCOS+miR-320-3p mimics group ($P=0.001$, $P=0.003$). There were no significant differences between PCOS+NC group and PCOS+miR-320-3p mimics group ($P>0.05$). There were no significant differences in *Pou5f1*, *Klf4*, *Ago2* among the three groups (all $P>0.05$).

Conclusion Low expression of miR-320-3p in PCOS mouse oocytes affects preimplantation blastocyst rate and blastocyst quality. Compensating miR-320-3p in PCOS oocytes improves embryonic developmental potential and improves embryo quality.

【Key words】 Polycystic ovary syndrome; Oocyte; Embryonic development; Mouse; miR-320-3p

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·临床报道·

辅助生殖技术助孕出生单胎新生儿第二性别比分析

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吴丽敏和高敏对本文有同等贡献

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【摘要】 目的 探究辅助生殖技术中出生单胎新生儿第二性别比(secondary sex ratio, SSR)的影响因素。方法 回顾性队列研究分析 2000 年 1 月至 2018 年 12 月期间在中国科学技术大学附属第一医院(安徽省立医院)生殖中心通过辅助生殖技术治疗出生的 7020 例单胎新生儿的临床资料, 分析新生儿的母亲年龄、授精方式、移植胚胎类型、移植胚胎期别等因素对单胎新生儿性别的影响。结果 在 7020 例新生儿中, 男婴 3730 例, 女婴 3290 例, 总 SSR 为 113 : 100。体外受精(*in vitro* fertilization, IVF)方式出生新生儿 SSR 明显高于卵胞质内单精子注射(intracytoplasmic sperm injection, ICSI)授精方式(121 : 100 比 95 : 100, $P < 0.001$), 其他因素对出生新生儿 SSR 无显著影响。分层分析中, 在 IVF 组和 ICSI 组间除了母亲年龄 ≥ 35 岁组、囊胚期胚胎移植组的 IVF 和 ICSI 出生的 SSR 差异无统计学意义($P > 0.05$)外, 其余各组的 IVF 出生新生儿的 SSR 都高于 ICSI(< 35 岁组: $P < 0.001$; 新鲜胚胎组: $P = 0.001$; 冻融胚胎组: $P = 0.003$; 卵裂期胚胎移植组: $P < 0.001$)。在 IVF 组内和 ICSI 组内分析显示各影响因素之间的 SSR 差异没有统计学意义($P > 0.05$)。单因素 logistic 回归分析显示, 单胎妊娠中授精方式对新生儿 SSR 产生的影响有统计学意义($OR = 0.792$, 95% $CI = 0.712 \sim 0.881$, $P < 0.001$)。去除混杂因素后 logistic 回归分析显示, 单胎妊娠中授精方式对新生儿 SSR 影响有统计学意义($aOR = 0.793$, 95% $CI = 0.713 \sim 0.883$, $P < 0.001$)。结论 授精方式是辅助生殖技术中影响出生单胎 SSR 的因素, IVF 较 ICSI 可提高 SSR 比值。

【关键词】 生殖技术, 辅助; 精子注射, 细胞质内; 常规体外受精; 第二性别比

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Secondary sex ratio analysis of singleton babies born following assisted reproductive technology

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【Abstract】 Objective To explore the influencing factors of the secondary sex ratio (SSR) of singleton babies born following assisted reproductive technology. **Methods** A total of 7020 single babies delivered by assisted reproductive technology at the Reproductive Medicine Center of the First Affiliated Hospital of USTC (Anhui Provincial Hospital) from January 2000 to December 2018 were collected in a retrospective cohort study. The effect of influencing factors, such as maternal age, fertilization method, embryo transfer type and embryo transfer period on the sex of singleton babies were analyzed. **Results** Among 7020 babies, 3730 were boys and 3290 were girls. The total SSR was 113 : 100. The SSR of *in vitro* fertilization (IVF) was significantly higher than that of intracytoplasmic sperm injection (ICSI) fertilization (121 : 100 vs. 95 : 100, $P < 0.001$), while other factors had no significant effect on the SSR of infants born. In the stratified analysis, there was no difference in SSR between IVF and ICSI in the blastocyst embryo transfer group with mother's age 35 years or older ($P < 0.05$), while the SSR of IVF in the other groups was higher than that of ICSI (<35 years old group: $P < 0.001$; fresh embryo group: $P = 0.001$; frozen-thawed embryo group: $P = 0.003$; cleavage embryo transfer group: $P < 0.001$). Univariate logistic regression analysis showed that the fertilization method in singleton pregnancy had a statistically significant effect on baby SSR ($OR = 0.792$, 95% $CI = 0.712 - 0.881$, $P < 0.001$). After removing confounding factors, logistic regression analysis showed that the fertilization method in singleton pregnancy had a statistically significant effect on neonatal SSR ($aOR = 0.793$, 95% $CI = 0.713 - 0.883$, $P < 0.001$). **Conclusion** The fertilization method of assisted reproductive technology can affect the SSR of singleton newborns. The SSR of IVF is significantly higher than that of ICSI and the difference was significant.

【 Key words 】 Reproductive technology, assisted; Sperm injection, intracytoplasmic; Conventional *in vitro* fertilization; Second sex ratio

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·个案报道·

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体外受精-胚胎移植中单角子宫并卵巢异位 2 例报道并文献复习

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【摘要】 目的 探讨体外受精-胚胎移植(*in vitro* fertilization-embryo transfer, IVF-ET) 中单角子宫并卵巢异位的临床处理策略。方法 回顾性分析 2 例罕见的行 IVF-ET 的单角子宫并卵巢异位患者的临床资料, 并进行相关文献复习。结果 2 例左侧单角子宫合并原发不孕患者阴道超声提示右侧卵巢未探及, 进一步行腹部核磁共振和腹部超声提示右侧卵巢腹腔异位。病例 1 在超促排卵过程中诉右侧腰部胀痛, 血清雌激素水平和阴道超声下左侧卵泡数量不一致, 继而阴道联合腹部超声同步监测卵泡发育, 给予经腹部及阴道联合采卵, 经冻胚移植后成功妊娠并于 36 周分娩。病例 2 亦在超促排卵过程中同步监测两侧卵巢卵泡发育, 经阴道联合腹部采卵后获得 2 枚囊胚冻存, 解冻单囊胚移植后自然流产。结论 卵巢异位多无明显临床表现, 极易被漏诊。对于单角子宫行辅助生殖技术助孕的患者, 如阴道超声未能探及单/双侧卵巢, 应进一步行腹部超声或核磁共振检查有无卵巢异位; 如确诊合并卵巢异位, 患者在超促排卵过程中应同步监测双侧卵巢卵泡发育, 采用经阴道联合腹部采卵, 最大程度增加患者的获卵率和妊娠机会。

【关键词】 卵巢异位; 单角子宫; 超促排卵; 取卵; 胚胎移植

Two cases of unicornuate uterus with ectopic ovary in IVF-ET and literature review

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【Abstract】 Objective To summarize the management of unicornuate uterus with ectopic ovary during *in vitro* fertilization and embryo transfer (IVF-ET). **Methods** The clinical data of 2 rare cases of uniangular uterus with ectopic ovary undergoing IVF-ET were retrospectively analyzed and the related literatures were

reviewed. **Results** Two patients were diagnosed as unicornuate uterus with unilateral ovary missing by vaginal ultrasound, subsequent abdominal ultrasound and magnetic resonance imaging (MRI) results indicated follicular structure in the peritoneal area, suggesting ectopic ovary. Case 1 showed flank pain as well as discrepancy between serum estradiol level and follicle numbers during ovarian hyperstimulation. The patient received trans-abdominal combined with trans-vaginal oocyte retrieval and successfully delivered a healthy baby at 36 weeks by transferring frozen blastocyst embryo. Case 2 was diagnosed as unicornuate uterus with lateral ectopic ovary by abdominal ultrasound before IVF treatment. We performed synchronized monitoring of bilateral ovarian follicular development and oocytes retrieval by transabdominal and transvaginal ultrasound, and then the two blastocysts were cryopreserved. However, the patient experienced spontaneous abortion following single frozen-thawed blastocyst transfer. **Conclusion** Ectopic ovaries present no obvious clinical manifestation and is easy to be ignored in diagnosis. For patients with unicornuate uterus treated by assisted reproductive technology, if vaginal ultrasound fails to detect ovary, we should further perform abdominal ultrasound or MRI to screen for ectopic ovary. If diagnosed with ectopic ovary, the patients should simultaneously be monitored the follicular development of bilateral ovaries during the process of ovarian hyperstimulation and adopt both transabdominal and transvaginal ultrasound-guided follicular aspiration to maximize the numbers of oocyte and pregnancy chance.

【 Key words 】 Ectopic ovary; Unicornuate uterus; Controlled ovarian stimulation; Oocyte pick up; Embryo transfer

·综述·

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miRNA-17~92 基因簇在多囊卵巢综合征发生 发展中的作用研究进展

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【摘要】 多囊卵巢综合征（polycystic ovary syndrome, PCOS）是育龄妇女最常见的内分泌紊乱疾病，以卵巢的多囊样改变、雄激素过多和排卵障碍为主要临床特征。已有大量研究证实，miRNAs 在 PCOS 的病理生理学中发挥重要作用。miRNA-17~92 基因簇是一个包含多顺反子簇的 miRNA 家族，最初被认为是癌基因，后来被证实可触发多种生理和病理过程。新近研究显示，miRNA-17~92 基因簇可通过调控卵巢颗粒细胞的功能而在 PCOS 的发生发展过程中发挥重要作用。本文就 miRNA-17~92 基因簇在 PCOS 发生发展中的作用及其分子途径进行综述。

【关键词】 多囊卵巢综合征； miRNA-17~92 基因簇； 颗粒细胞

Roles of miRNA-17-92 gene cluster in the pathogenesis of polycystic ovary syndrome

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【 Abstract 】 Polycystic ovary syndrome (PCOS) is the most common endocrine disease in reproductive-aged women, which is characterized by polycystic ovary changes, hyperandrogenism and anovulation. A large number of studies have confirmed that miRNAs play an important role in the pathophysiology of PCOS. The miRNA-17-92 gene cluster is a family of miRNAs containing multiple cistron clusters. It was initially considered to be an oncogene, but it can trigger a variety of physiological and pathological processes in many diseases. In recent years, more and more evidence has showed that miRNA-17-92 gene cluster plays an important role in the development of PCOS. In this study, we reviewed the roles of miRNA-17-92 gene cluster in the development of PCOS.

【 Key words 】 Polycystic ovary syndrome; miRNA-17-92 gene cluster; Granulosa cells

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·综述·

肠道微生物与子宫内膜异位症发病机制的研究进展

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【摘要】 子宫内膜异位症 (endometriosis, EMS) 是一种慢性炎症性疾病, 呈现雌激素依赖性。关于 EMS 的起源有很多学说, 但发病机制目前仍未明晰。近年来, 高通量测序的发展为肠道微生物与 EMS 之间的关系提供了新思路。对 EMS 患者与健康人粪便样本进行下一代测序分析比对, 确定其特定的肠道微生物群组成, 分析其对 EMS 潜在的病理生理机制的影响, 从而开发出新的 EMS 预防和治疗策略。本篇综述重点就肠道微生物参与 EMS 发病机制的研究进展进行论述。

【关键词】 子宫内膜异位症; 肠道微生物; 致病机制

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Advances in intestinal microorganisms and the pathogenesis of endometriosis

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【Abstract】 Endometriosis (EMS) is a chronic inflammatory disease that is estrogen-dependent. It was defined as endometrial tissue outside the uterus with clinical manifestations of chronic pelvic pain, abnormal menstruation and infertility. There are many theories about the origin of EMS, but the pathogenesis is still unclear. In recent years, the development of high-throughput sequencing has provided new ideas for the relationship between intestinal microorganisms and EMS. The next generation sequencing analysis and comparison of feces samples from patients with EMS and healthy persons were conducted to determine the composition of specific intestinal microflora and analyze the influence of potential pathophysiological mechanisms of EMS, so as to develop new prevention and treatment strategies for EMS. In this review, the research progress on the involvement of intestinal microorganisms in the pathogenesis of EMS was summarized.

【Key words】 Endometriosis; Intestinal microorganism; Pathogenic mechanism

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·综述·

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慢性子宫内膜炎的诊断及生育相关的发病机制 研究进展

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【摘要】 慢性子宫内膜炎（chronic endometritis, CE）是一种局部慢性炎症性疾病，其病理特征是子宫内膜间质浆细胞浸润。CE 主要的病因是微生物感染，然而，是否发生病理改变可能取决于子宫内膜免疫系统能否对微生物的感染进行适当的反应。CE 能够使子宫内膜免疫环境发生变化，子宫内膜容受性严重下降，并且与女性生殖预后密切相关，是反复种植失败及复发性流产的重要原因之一。本文就 CE 的诊断、微生物学及免疫学研究进展进行综述，以期为今后的研究、诊断及治疗提供依据。

【关键词】 慢性子宫内膜炎； 免疫组织化学； 宫腔镜检查； 子宫自然杀伤细胞

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Research progress in diagnosis and pathogenesis of chronic endometritis

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【Abstract】 Chronic endometritis (CE) is a local chronic inflammatory disease characterized by the infiltration of plasma cells into the endometrial stromal area. The main cause of CE is microbial infection. However, whether pathological changes occur may depend on whether the endometrial immune system can appropriately respond to microbial infection. CE can cause changes in the immune environment of the endometrium, decrease the endometrial receptivity severely, and is closely related to female reproductive prognosis. It is one of the important reasons for repeated implantation failure and recurrent miscarriage. In this review, we summarized the advances in the diagnosis, microbiology and immunology of CE, in order to provide the basis for future research, diagnosis and treatment.

【Key words】 Chronic endometritis; Immunohistochemistry; Hysteroscopy; Uterine natural killer cells

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·综述·

褪黑素在女性不孕相关疾病中的生殖调节研究

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【摘要】 褪黑素是一种主要由哺乳动物松果体分泌的神经胺类激素, 调控机体中枢和外周系统与昼夜节律和生殖有关的机制, 并具有强大的抗氧化、抗炎、抑制凋亡、抑制肿瘤、调节自噬和内分泌功能等作用。越来越多的研究表明, 褪黑素在防治女性生殖系统疾病中发挥重要作用, 从而改善由此导致的女性不孕症的结局。本文将对褪黑素的生殖调节以及在导致女性不孕的几种常见疾病中的作用研究进展进行总结。

【关键词】 褪黑素; 女性生殖; 不孕症

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Study on reproductive regulation of melatonin in female infertility related diseases

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【Abstract】 Melatonin is a neuroamine hormone secreted mainly by the pineal gland of mammals. It regulates the mechanisms related to circadian rhythm and reproduction in the central and peripheral systems of the body. Additionally, it also has powerful effects about antioxidant, anti-inflammatory, anti-apoptosis, anti-tumor, autophagy regulation, endocrine regulation and so on. An increasing number of researches suggest that melatonin plays an important role in the prevention and treatment of diseases of the female reproductive system, thus improving the outcome of female infertility. This review summarized the progress of the research on the reproductive regulation of melatonin and the role of melatonin in several common diseases that lead to female infertility.

【Key words】 Melatonin; Female reproduction; Infertility

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·综述·

胚胎植入前遗传学检测女性婚姻质量综述

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【摘要】 婚姻质量与个体健康有密切联系, 影响女性辅助生殖治疗效果, 是不少夫妻终止辅助生殖治疗的重要原因。随着胚胎植入前遗传学检测 (preimplantation genetic testing, PGT) 的发展和成熟, 未来辅助生殖技术势必有更广泛的适应人群。PGT 包含体外受精 (*in vitro* fertilization, IVF) 和遗传学检测两个主要的治疗过程, 适应证除了传统不孕夫妇外还包括不少遗传病高风险夫妇, 这意味着 PGT 女性婚姻质量相比不孕女性或 IVF 女性更加复杂。本文首先总结近年来国内外婚姻质量的研究方法, 接着在归纳 IVF 女性婚姻质量研究成果的基础上根据不同适应证提出 PGT 女性婚姻质量存在的潜在问题, 最后就国内婚姻质量的研究现状指出目前研究存在的局限性, 为日后更深入地开展 PGT 女性婚姻质量研究提供理论依据。

【关键词】 胚胎植入前遗传学检测; 受精, 体外; 婚姻质量; 女性; 不孕症

Marital quality of preimplantation genetic testing women: a literature review

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【Abstract】 Marital quality is closely related to individual health. It is the main reason for many couples to terminate assisted reproductive technology (ART) treatment, otherwise it also has been proved to be significantly related to curative effect of ART. With the development of preimplantation genetic testing (PGT), ART is bound to have a wider range of people to adapt in the future. PGT includes two main processes, *in vitro* fertilization (IVF) and genetic testing. In addition to traditional infertile couples, couples at high-risk of genetic diseases is also a common indication for PGT, which means that comparing to infertile women or IVF women, marital quality of PGT women is more complicated. Firstly, this review introduced the current methodology on marital quality, and basis of summarizing research results of marital quality of IVF women, according to different indications, we put forward potential problems of marital quality of PGT women. Finally, in the light of

domestic research status of marital quality, we referred to some research limitations, in order to provide a theoretical basis for further research on marital quality of PGT women.

【Key words】 Preimplantation genetic testing; Fertilization, *in vitro*; Marital quality; Female; Infertile

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·综述·

我国绝经后妇女宫内节育器取出问题综述

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【摘要】 目的 探讨国内围绝经期妇女宫内节育器 (intrauterine device, IUD) 滞留现状、可能造成的健康问题以及取出困难情况。方法 在 CNKI、万方、CBM、PubMed 等中外数据库中检索了迄今为止我国与围绝经期及绝经后 IUD 取出相关的公开发表文献, 获得了符合本综述纳入排除标准的 15 篇相关研究, 并对其进行质量评价和结果整理。结果 纳入研究普遍提到 IUD 滞留问题。IUD 取出难度及妇女的心理问题均随妇女绝经时间的增加而增大。围绝经期 IUD 滞留与腰部疼痛、小腹坠痛和绝经后出血有关。绝经后适时取出 IUD 有助于改善妇女腰背疼痛、心理问题的发生, 能够有效避免后期 IUD 取出困难问题。结论 围绝经期妇女存在 IUD 滞留问题, IUD 滞留可能造成取出困难, 同时可能造成妇女产生一系列生理、心理健康问题。因此, 绝经后适时取出 IUD 作为生殖健康和计划生育持续服务问题亟待解决。

【关键词】 宫内节育器; 围绝经期; 绝经后

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A review on removal of intrauterine device in postmenopausal women in China

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【Abstract】 Objective Explore the retention situation, possible health problems, and difficulties in removal of intrauterine device (IUD) in women who are perimenopausal in China. **Methods** We have searched published literature related to IUD removal of perimenopausal and postmenopausal women in China from databases including CNKI, WanFang data, CBM, PubMed and Other Chinese and foreign databases. Totally fifteen studies were included according the criteria of study inclusion and exclusion and these studies were assessed the quality and their results were summarized. **Results** The mentioned problems of IUD retention were the difficulty of IUD removal and psychological problems with the increase of women's menopause time. At the same time, perimenopausal IUD retention is associated with back pain, low abdominal pain and postmenopausal bleeding. Timely and safely removal of IUD after menopause can help to release the back pain and psychological problems in women, and can effectively avoid the difficulty of IUD removal in the later period. **Conclusion** Perimenopausal women may have IUD retention. This problem may not only cause difficulties of IUD removal, but also cause a series of women's mental health issues. Timely removal of IUD after menopause is a urgent needs f for reproductive health and family planning ongoing services.

【Key words】 Intrauterine device; Perimenopause; Menopause

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