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· MDT 专家视角专栏 ·

子宫腺肌病合并不孕的辅助生殖助孕策略

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【摘要】 子宫腺肌病是育龄妇女常见的疾病, 是导致不孕的重要原因之一。本文拟针对子宫腺肌病合并不孕患者的诊治难点, 基于子宫腺肌病与不孕的关系、子宫腺肌病对辅助生殖助孕结局的影响, 分别从子宫腺肌病合并不孕患者的辅助生殖助孕指征与时机、预处理方案、促排卵方案、胚胎移植策略等方面阐述观点。

【关键词】 生殖技术, 辅助; 子宫腺肌病; 不孕症

Assisted reproductive strategies for adenomyosis related infertility

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【Abstract】 Adenomyosis is a common disease in women of childbearing age, and is one of the important causes of infertility. Based on the relationship between adenomyosis and infertility, and the impact of adenomyosis on the outcome of assisted reproductive technology (ART), this article focused on the strategies of ART for patients with adenomyosis complicated with infertility, discussing the indications and timing of ART, pretreatment strategies, ovarian stimulation protocols and embryo transfer strategies.

【Key words】 Reproductive technology, assisted; Adenomyosis; Infertility

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· MDT 专家视角专栏 ·

如何提高子宫腺肌病合并不孕患者的助孕成功率？

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【摘要】 子宫腺肌病对育龄期女性生殖结局存在负面影响。探讨影响子宫腺肌病合并不孕患者生殖结局的潜在因素，有利于子宫腺肌病患者助孕成功率预测模型的构建。针对子宫腺肌病合并不孕患者，通过药物预处理、促排卵方案合理选择、保留生育功能的手术治疗、移植策略合理选择以及对患者妊娠后保胎处理等个体化措施优化辅助生殖助孕策略，可有效提高其助孕成功率，改善生殖结局。

【关键词】 子宫腺肌病； 不孕症； 辅助生殖

How to improve the success rate of assisted reproduction treatment in infertile patients with adenomyosis?

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【Abstract】 Adenomyosis has a negative impact on reproductive outcomes in women of reproductive age. This paper summarizes the potential factors affecting reproductive outcomes of adenomyosis patients with infertility, which is helpful to build a prediction model for the success rate of assisted pregnancy. For patients with adenomyosis-related infertility, effectively increasing the success rate could be achieved by optimizing and individualizing assisted reproductive strategies such as pharmacological pretreatment, proper controlled ovarian hyperstimulation protocol, fertility-sparing surgical treatment, rational selection of transplantation strategies, and prevention of miscarriage.

【Key words】 Adenomyosis; Infertility; Assisted reproduction

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·临床研究·

卵泡期长效长方案促排卵患者获得最佳卵巢反应的相关因素分析及预测模型建立

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【摘要】 目的 探索行辅助生殖技术卵泡期长效长方案超促排卵治疗的患者获取最佳卵巢反应的相关指标, 并建立卵巢反应性的诺曼预测模型。方法 本研究为回顾性队列研究, 分析 2018 年 7 月 1 日至 2019 年 7 月 30 日期间于福建省妇幼保健院生殖医学中心接受辅助生殖助孕治疗的 1289 例患者临床资料, 按照获卵数分为卵巢低反应组 (获卵数 ≤ 5 枚) 164 例, 卵巢正常反应组 (5 枚 $<$ 获卵数 ≤ 18 枚) 891 例, 卵巢高反应组 (获卵数 > 18 枚) 234 例。通过 logistic 回归筛选影响卵巢反应性的独立因素, 即为模型入组变量, 并依据模型中的回归系数建立诺曼预测模型。结果 三组患者的年龄、抗苗勒管激素 (anti-Müllerian hormone, AMH) 水平、基础窦卵泡计数 (antral follicle count, AFC) 差异均有统计学意义 [(32.43 \pm 3.99) 岁, (31.48 \pm 3.89) 岁, (29.91 \pm 3.73) 岁; (2.53 \pm 1.90) μ g/L, (3.79 \pm 2.20) μ g/L, (5.94 \pm 3.12) μ g/L; 10.24 \pm 3.10, 14.50 \pm 3.29, 19.81 \pm 3.44; 均 $P<0.001$]。而体质指数 (body mass index, BMI)、不孕年限及输卵管性不孕原因的差异均无统计学意义 (均 $P>0.05$)。三组患者行促排卵的促性腺激素 (gonadotropin, Gn) 起始剂量差异有统计学意义 [(182.62 \pm 53.96) U、(166.79 \pm 48.20) U、(159.13 \pm 43.92) U, $P<0.001$] , Gn 使用时间及临床妊娠率差异均无统计学意义 (均 $P>0.05$)。多因素逐步回归分析显示, 女方年龄 [0.93 (0.90~0.96), $P=0.007$]、AFC [1.07 (1.03~1.09), $P=0.001$]、AMH [1.29 (1.20~1.39), $P=0.001$]、基础卵泡刺激素 [0.79 (0.73~0.86), $P=0.001$]、黄体生成素 [1.11 (1.06~1.23), $P=0.010$]、Gn 起始剂量 [1.00 (1.00~1.01), $P=0.003$]、Gn 使用总量 [1.00 (0.99~1.00), $P=0.001$]、是否为子宫内膜异位症 [0.63 (0.47~0.86), $P=0.001$] 和多囊卵巢综合征 [0.30 (0.22~0.91), $P=0.030$] 是超促排卵过程中发生卵巢不同反应的独立因素。根据上述因素构建卵巢反应性的预测模型, 预测卵巢最佳反应状态的准确性

为 95%。用 2019 年 8 月 1 日至 2019 年 10 月 30 日期间该中心的 306 例同类患者数据对上述模型进行验证, 共 279 例患者的预测卵巢反应(获卵数)与实际相符, 符合度为 91.2%。模型的一致性指数是 0.71。结论 筛选出行卵泡期长效方案超促排卵中影响卵巢反应性的相关因素, 成功建立的诺曼模型能够有效、直观、可视化地预测超促排卵中的卵巢反应性。

【关键词】 卵泡期长效方案; 卵巢反应性; 诺曼模型

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Analysis of relative factors and prediction model for optimal ovarian response in patients with follicular phase long-acting long protocol

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【Abstract】 Objective To explore the relative factors for best ovarian response in patients undergoing assisted reproductive technology with follicular phase long-acting long protocol, and to establish a Nomogram prediction model of ovarian response. **Methods** This retrospective cohort study analyzed the clinical data of 1289 patients who received assisted reproductive treatment in the Center for Reproductive Medicine of Fujian Maternity and Child Health Hospital from July 1, 2018 to July 30, 2019. According to the number of oocytes retrieved, there were 164 cases in the low ovarian response group (≤ 5 oocytes retrieved), 891 cases in the normal ovarian response group (the number of retrieved oocytes was >5 , and ≤ 18), and 234 cases in the high ovarian response group (>18 oocytes retrieved). Independent factors affecting ovarian reactivity were screened by logistic regression, which were the model entry variables, and a Nomogram prediction model was established based on the regression coefficients in the model. **Results** There were statistically significant differences in age, anti-Müllerian hormone (AMH) level and antral follicle count (AFC) among the three groups [32.43 ± 3.99 , 31.48 ± 3.89 , 29.91 ± 3.73 ; (2.53 ± 1.90) $\mu\text{g/L}$, (3.79 ± 2.20) $\mu\text{g/L}$, (5.94 ± 3.12) $\mu\text{g/L}$; 10.24 ± 3.10 , 14.50 ± 3.29 , 19.81 ± 3.44 ; all $P < 0.001$]. There were no significant differences in body mass index (BMI), duration of infertility and causes of tubal infertility (all $P > 0.05$). The initial dosage of gonadotropin (Gn) used for ovarian hyperstimulation among the three groups was statistically different [(182.62 ± 53.96) U, (166.79 ± 48.20) U, (159.13 ± 43.92) U, $P < 0.001$], while the duration of Gn used and clinical pregnancy rate had no significant differences (all $P > 0.05$). Multifactorial stepwise aggression analysis showed that female age [$0.93(0.90-0.96)$, $P = 0.007$], AFC [$1.07(1.03-1.09)$, $P = 0.001$], AMH [$1.29(1.20-1.39)$, $P = 0.001$], basal follicle-stimulating hormone [$0.79(0.73-0.86)$, $P = 0.001$], luteinizing hormone value [$1.11(1.06-1.23)$, $P = 0.010$], initial dosage of Gn used [$1.00(1.00-1.01)$, $P = 0.003$], total dosage of Gn used

[1.00(0.99–1.00), $P=0.001$] and the presence or absence of diagnosis of endometriosis [0.63(0.47–0.86), $P=0.001$] and polycystic ovary syndrome [0.30(0.22–0.91), $P=0.030$] were independent factors for the occurrence of different ovarian responses during ovarian hyperstimulation. The prediction model of ovarian reactivity was constructed based on the above factors, and the accuracy of predicting the optimal ovarian response state was 95%. The above model was verified with 306 patients' data from August 1, 2019 to October 30, 2019 in this center, and the predicted ovarian response (number of oocytes obtained) of a total of 279 patients was consistent with the actual situation, with a coincidence degree of 91.2%. The consistency index of the model was 0.71. **Conclusion** We screened out the relevant factors affecting ovarian response in patients undergoing assisted reproductive technology with follicular phase long-acting long protocol, and established a Nomogram prediction model of ovarian response, which could effectively, intuitively and visually predict ovarian reactivity in hyperstimulation.

【Key words】 Follicular phase long-acting long protocol; Ovarian response; Nomogram prediction model

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·临床研究·

黄体期长效长方案促性腺激素释放 激素激动剂剂量对 IVF/ICSI 临床结 局的影响

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【摘要】 目的 探讨不同促性腺激素释放激素激动剂 (gonadotropin-releasing hormone agonist, GnRH-a) 剂量对体外受精/卵胞质内单精子注射-胚胎移植 (*in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer, IVF/ICSI-ET) 临床结局的影响。方法 采用前瞻性队列研究, 选择 2018 年 1 月至 2019 年 1 月期间在广州医科大学附属第三医院生殖医学中心接受 IVF/ICSI-ET 的患者为研究对象, 最终纳入 273 例。所有患者采用黄体期长方案促排卵, 根据 GnRH-a 剂量分为 1.0 mg、0.8 mg 和 0.5 mg 三组, 比较患者基础临床特征和控制性超促排卵、胚胎移植及子代数据。结果 三组患者基础临床特征及子代数据差异均无统计学意义 (均 $P>0.05$)。随降调节剂量的减少, 卵巢刺激时间明显下降, 0.5 mg 组最短, 为 (11.3 ± 1.4) d, 差异有统计学意义 ($P<0.001$); 促性腺激素 (gonadotropin, Gn) 使用总量有下降趋势, 胚胎丢失率降低, 活产率升高, 但差异均无统计学意义 (均 $P>0.05$)。在 1.0 mg 组, 受精率最低, 为 71.6% (768/1073), 三组间差异有统计学意义 ($P=0.005$), 早期流产率、无可利用胚胎周期取消率有升高趋势, 但差异均无统计学意义 (均 $P>0.05$)。结论 GnRH-a 0.5 mg 可减少促排卵时间并取得良好的临床结局, 是更优的降调节剂量。

【关键词】 生殖技术, 辅助; 超促排卵; 促性腺激素释放激素

Effect of GnRH-a dosage on IVF/ICSI clinical outcomes in luteal phase long protocol

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【Abstract】 Objective To investigate the effect of different dosages of gonadotropin-releasing hormone agonist (GnRH-a) on the clinical outcomes of *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET). **Methods** In this prospective cohort study, we recruited patients who received IVF/ICSI-ET in Center for Reproductive Medicine, the Third Affiliated Hospital of Guangzhou Medical University from January 2018 to January 2019. A total of 273 patients were finally enrolled in the study. We used the luteal phase long protocol in the controlled ovarian hyperstimulation program. Patients were divided into three groups according to the dosage of GnRH-a used: 1.0 mg, 0.8 mg and 0.5 mg. The basic clinical characteristics, controlled ovarian hyperstimulation, embryo transfer and offspring data were compared among the three groups. **Results** There were no significant differences in basal clinical characteristics and offspring data (all $P>0.05$). The lower dosage of GnRH-a, the fewer days of ovarian stimulation, 0.5 mg group showed the least days of ovarian stimulation $[(11.3\pm 1.4)$ d], which was

statistically significant from the other groups ($P<0.001$). In addition, we also found a decreasing trend of total gonadotropin (Gn), a lower loss rate of the embryo and a higher live birth rate in 0.5 mg group, although the difference did not reach statistically significant (all $P>0.05$). On the contrast, in 1.0 mg group, the fertilization rate [71.6% (768/1073)] significantly decreased ($P=0.005$), while the early abortion rate and the cancellation rate of the unavailable embryo cycles tended to increase but not statistically different (all $P>0.05$). **Conclusion** 0.5 mg GnRH-a can reduce the duration of ovarian stimulation and achieve good clinical outcomes, which may be a better dosage of down regulation.

【 Key words 】 Reproductive technology, assisted; Superovulations; Gonadotropin-releasing hormone

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·临床研究·

抗苗勒管激素水平对首次胚胎移植术后早期妊娠丢失的影响探讨

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【摘要】 目的 探讨抗苗勒管激素 (anti-Müllerian hormone, AMH) 水平对首次胚胎移植术后早期妊娠丢失结局的影响。方法 采用回顾性队列研究, 分析 2016 年 7 月至 2019 年 6 月期间在河南省人民医院生殖医学中心首次行体外受精/卵胞质内单精子注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 助孕且首次胚胎移植后人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 阳性的 3973 例患者的临床资料。按照 AMH 水平等分为四个亚组: A 组 ($AMH \leq 1.97 \mu\text{g/L}$)、B 组 ($1.97 \mu\text{g/L} < AMH \leq 3.31 \mu\text{g/L}$)、C 组 ($3.31 \mu\text{g/L} < AMH \leq 5.41 \mu\text{g/L}$) 和 D 组 ($AMH > 5.41 \mu\text{g/L}$), 通过单因素分析、分类多元 logistic 回归分析、曲线拟合及阈值效应等方法, 探讨 AMH 水平对行 IVF/ICSI 助孕首次胚胎移植术后早期妊娠丢失结局的影响。结果 ①纳入总人群的早期妊娠丢失率为 15.71% (624/3973)。四组间体质量指数、不孕类型、授精方式差异均无统计学意义 (均 $P>0.05$), AMH 水平 [$(1.21 \pm 0.50) \mu\text{g/L}$ 、 $(2.63 \pm 0.38) \mu\text{g/L}$ 、

(4.26 ± 0.60) $\mu\text{g/L}$ 、(8.26 ± 2.78) $\mu\text{g/L}$, $P < 0.001$]、年龄 [(32.35 ± 5.00) 岁、(30.77 ± 4.24) 岁、(29.90 ± 3.96) 岁、(29.35 ± 3.85) 岁, $P < 0.001$]、双侧窦卵泡计数 (8.01 ± 4.04 、 11.46 ± 4.40 、 13.55 ± 4.73 、 16.08 ± 5.08 , $P < 0.001$)、移植胚胎数 [(1.74 ± 0.44) 枚、(1.73 ± 0.45) 枚、(1.69 ± 0.46) 枚、(1.66 ± 0.47) 枚, $P < 0.001$]、移植胚胎发育时间 (卵裂期胚胎/囊胚比例) ($85.49\%/14.51\%$ 、 $76.42\%/23.58\%$ 、 $69.55\%/30.45\%$ 、 $65.79\%/34.21\%$, $P < 0.001$)、移植周期类型 (新鲜/冻融胚胎移植) ($75.08\%/24.92\%$ 、 $71.15\%/28.85\%$ 、 $57.79\%/42.21\%$ 、 $39.46\%/60.54\%$, $P < 0.001$) 及早期妊娠丢失率 (22.12% 、 12.25% 、 12.76% 、 15.64% , $P < 0.001$) 差异均有统计学意义。②调整混杂因素后, 分类多元 logistic 回归分析显示, B、C、D 三组的早期妊娠丢失率均低于 A 组, 其中总纳入人群中 B 组 (调整后 $OR=0.60$, 95% $CI=0.46 \sim 0.79$, $P < 0.001$)、C 组 (调整后 $OR=0.70$, 95% $CI=0.51 \sim 0.97$, $P=0.033$) 显著降低, 差异有统计学意义。<35 岁人群中 B 组 (调整后 $OR=0.46$, 95% $CI=0.30 \sim 0.71$, $P < 0.001$)、C 组 (调整后 $OR=0.62$, 95% $CI=0.39 \sim 0.98$, $P=0.041$)、D 组 (调整后 $OR=0.56$, 95% $CI=0.33 \sim 0.93$, $P=0.026$) 早期妊娠丢失率均显著降低, 差异有统计学意义; ≥ 35 岁人群中, 各组间早期妊娠丢失率差异均无统计学意义 (均 $P > 0.05$)。曲线拟合分析显示 AMH 与早期妊娠丢失呈曲线关系, 随着 AMH 水平增加, 早期妊娠丢失率逐渐下降后趋于平稳。结论 对于首次行胚胎移植术后 hCG 阳性的女性, AMH 水平对于 <35 岁人群的早期妊娠丢失结局有一定的影响。

【关键词】 抗苗勒管激素; 受精, 体外; 胚胎移植; 早期妊娠丢失

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Effect of anti-Müllerian hormone level on early pregnancy loss rate during the first embryo transfer in *in vitro* fertilization treatment

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【Abstract】 **Objective** To explore the effect of anti-Müllerian hormone (AMH) on early pregnancy loss after first embryo transfer during *in vitro* fertilization (IVF) treatment. **Methods** A total of 3973 women with positive human chorionic gonadotropin (hCG) after first embryo transfer from July 2016 to June 2019 in Reproductive Medical Center, Henan Provincial People's Hospital were studied retrospectively. All patients were categorized into four groups according to AMH levels: group A ($AMH \leq 1.97 \mu\text{g/L}$), group B ($1.97 \mu\text{g/L} < AMH \leq 3.31 \mu\text{g/L}$), group C ($3.31 \mu\text{g/L} < AMH \leq 5.41 \mu\text{g/L}$) and group D ($AMH > 5.41 \mu\text{g/L}$). Univariate analysis, multivariate logistic regression analysis and curve fitting analysis were used to investigate the effect of AMH level on early pregnancy loss rate. **Results** 1) The total early pregnancy loss rate of the first transfer cycle was 15.71% (624/3973). There were significant differences in AMH level [(1.21 ± 0.50) $\mu\text{g/L}$, (2.63 ± 0.38) $\mu\text{g/L}$, (4.26 ± 0.60) $\mu\text{g/L}$, (8.26 ± 2.78) $\mu\text{g/L}$, $P < 0.001$], age [(32.35 ± 5.00)

years, (30.77±4.24) years, (29.90±3.96) years, (29.35±3.85) years, $P<0.001$], antral follicular count of both ovaries (8.01±4.04, 11.46±4.40, 13.55±4.73, 16.08±5.08, $P<0.001$), number of transfer embryos (1.74±0.44, 1.73±0.45, 1.69±0.46, 1.66±0.47, $P<0.001$), developmental days of transfer embryos (cleavage embryos/blastocysts) (85.49%/14.51%, 76.42%/23.58%, 69.55%/30.45%, 65.79%/34.21%, $P<0.001$), type of transfer cycles (fresh transfer/frozen transfer) (75.08%/24.92%, 71.15%/28.85%, 57.79%/42.21%, 39.46%/60.54%, $P<0.001$) and early pregnancy loss rate (22.12%, 12.25%, 12.76%, 15.64%, $P<0.001$) among the four groups, while the body mass index, type of infertility and type of fertilization were comparable (all $P>0.05$). 2) After adjusting for confounding factors, group A was set as control group in multivariate logistic regression analysis, the early pregnancy loss rate was significantly lower in group B (adjusted $OR=0.60$, 95% $CI=0.46-0.79$, $P<0.001$) and group C (adjusted $OR=0.70$, 95% $CI=0.51-0.97$, $P=0.033$) for the total women. Further multivariate logistic regression analysis according to age sub-groups showed that the early pregnancy loss rates of group B (adjusted $OR=0.46$, 95% $CI=0.30-0.71$, $P<0.001$), group C (adjusted $OR=0.62$, 95% $CI=0.39-0.98$, $P=0.041$) and group D (adjusted $OR=0.56$, 95% $CI=0.33-0.93$, $P=0.026$) were significantly lower than those in group A for women no more than 35 years old, while the early pregnancy rates were comparable among the four groups for women aged 35 years or above (all $P>0.05$). The curve fitting analysis found that the relationship between AMH and early pregnancy loss was a curve line. The early pregnancy loss rate was decreased with the increasing of AMH level and gradually plateaued. **Conclusion** For the first embryo transfer cycles, AMH level has some effects on the early pregnancy loss for women no more than 35 years old.

【 Key words 】 Anti-Müllerian hormone; Fertilization *in vitro*; Embryo transfer; Early pregnancy loss

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·临床研究·

PCOS 患者胚胎质量以及解冻移植 周期妊娠结局的影响因素分析

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【摘要】 目的 探索多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 患者体外受精/卵胞质内单精子注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 周期胚胎质量以及冻融胚胎移植 (frozen-thawed embryo transfer, FET) 周期中妊娠结局的影响因素。方法 采用回顾性病例对照研究设计, 分析 2015 年 1 月至 2019 年 12 月期间于天津市中心妇产科医院生殖医学中心接受 IVF/ICSI 治疗, 行全胚冷冻治疗并第一次行 FET 的 1233 个周期, 根据是否为 PCOS 患者分为对照组 ($n=561$) 和 PCOS 组 ($n=672$)。比较两组之间患者一般临床资料、实验室相关指标、妊娠结局, 并通过多因素 logistic 回归分析晚期流产率的影响因素。结果 ①对照组和 PCOS 组的一般临床资料中不孕年限 [(3.95 ± 2.01) 年比 (4.84 ± 2.91) 年, $P=0.007$]、体质量指数 (body mass index, BMI) [(21.96 ± 2.52) kg/m^2 比 (23.96 ± 3.50) kg/m^2 , $P<0.001$]、基础黄体生成素 [(4.71 ± 2.38) mU/L 比 (8.18 ± 5.40) mU/L , $P<0.001$]、基础雌二醇 [(45.49 ± 31.80) ng/L 比 (56.67 ± 54.17) ng/L , $P=0.032$]、基础睾酮 [(42.80 ± 13.45) ng/L 比 (53.45 ± 38.67) ng/L , $P=0.001$]、促性腺激素起始量 [(230.80 ± 54.07) U 比 (192.11 ± 53.79) U , $P<0.001$] 差异均有统计学意义。FET 周期中内膜准备方案, PCOS 组中更多患者进行了激素替代周期 [64.1% ($431/672$) 比 26.6% ($149/561$)], 而对照组更多患者进行了自然周期移植 [73.4% ($412/561$) 比 35.9% ($241/672$)], 且差异均有统计学意义 (均 $P<0.001$)。②实验室相关指标中获卵数 PCOS 组大于对照组 [(23.36 ± 9.53) 枚比 (20.32 ± 8.81) 枚, $P=0.002$], PCOS 组的优质胚胎数 [(2.94 ± 3.13) 枚]、优质胚胎率 [33.3% ($2016/6048$)] 小于对照组 [(4.17 ± 3.65) 枚, $P=0.034$; 46.3% ($2339/5049$), $P<0.001$], 且差异均有统计学意义。③妊娠结局中, 优质胚胎移植率、生化妊娠率对照组大于 PCOS 组 [71.0% ($743/1046$) 比 59.3% ($761/1284$), $P<0.001$; 7.3% ($41/561$) 比 4.5% ($30/672$), $P=0.033$], 晚期流产率 PCOS 组大于对照组 [10.3% ($43/418$) 比 4.3% ($16/326$), $P=0.002$]。④进一步对晚期流产影响因素进行 logistic 回归分析, 在矫正混杂因素之后, PCOS ($OR=2.573$, 95% $CI=1.270\sim 5.212$, $P=0.009$) 以及母亲高 BMI ($OR=1.080$, 95% $CI=0.991\sim 1.176$, $P=0.031$) 为晚期流产的危险因素。结论 PCOS 患者优质胚胎数以及优质胚胎率均低于非 PCOS 患者, PCOS 以及高 BMI 是患者晚期流产的危险因素。在助孕治疗之前, 改善 PCOS 患者内分泌紊乱以及控制体质量对改善患者妊娠结局有积极意义。

【关键词】 多囊卵巢综合征; 胚胎质量; 冻融胚胎移植; 晚期流产率

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Analysis of the influencing factors of embryo quality and pregnancy outcomes in frozen-thawed embryo transfer cycle in polycystic ovary syndrome patients

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【Abstract】 Objective To explore the influencing factors of embryos quality during the cycle of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) and pregnancy outcomes of frozen-thawed embryo transfer (FET) in patients with polycystic ovary syndrome (PCOS). **Methods** A retrospective case-control study design was used to analyze patients who received IVF/ICSI treatment at the Reproductive Medicine Center of Tianjin Central Obstetrics and Gynecology Hospital from January 2015 to December 2019, underwent whole embryo cryopreserved and performed the first FET. The 1233 cycles included were divided into control group ($n=561$) and PCOS group ($n=672$) according to PCOS diagnosis. The general clinical characteristics, laboratory-related indicators and pregnancy outcomes of patients between the two groups were compared, and the affecting factors of the late miscarriage rate were analyzed by multivariate logistic regression. **Results** 1) In terms of the general clinical characteristics between the two groups, the differences of duration of infertility [(3.95±2.01) years vs. (4.84±2.91) years, $P=0.007$], body mass index (BMI) [(21.96±2.52) kg/m² vs. (23.96±3.50) kg/m², $P<0.001$], basal luteinizing hormone [(4.71±2.38) mU/L vs. (8.18±5.40) mU/L, $P<0.001$], basal estradiol [(45.49±31.80) ng/L vs. (56.67±54.17) ng/L, $P=0.032$], basal testosterone [(42.80±13.45) ng/L vs. (53.45±38.67) ng/L, $P=0.001$], gonadotropin initial used dosage [(230.80±54.07) U vs. (192.11±53.79) U, $P<0.001$] were statistically significant. The endometrium preparation plan in the FET cycle, more PCOS group patients received hormone replacement treatment [64.1% (431/672) vs. 26.6% (149/561)], while more patients in control group received natural cycle transplantation [73.4% (412/561) vs. 35.9% (241/672)], and the differences were statistically significant (all $P<0.001$). 2) In terms of the laboratory results, the number of oocytes retrieved in PCOS group (23.36±9.53) was higher than that in control group (20.32±8.81, $P=0.002$). The number of high-quality embryos and the rate of high-quality embryos in PCOS group [2.94±3.13; 33.3% (2016/6048)] were lower than those in control group [4.17±3.65, $P=0.034$; 46.3% (2339/5049), $P<0.001$], and the differences were statistically significant. 3) In the pregnancy outcomes, the high-quality embryo transfer rate and the biochemical pregnancy rate in control group were higher than those in PCOS group [71.0% (743/1046) vs. 59.3% (761/1284), $P<0.001$; 7.3% (41/561) vs. 4.5% (30/672), $P=0.033$], and the late miscarriage rate in PCOS group [10.3% (43/418)] was higher than that in control group [4.3% (16/326), $P=0.002$]. 4) Logistic regression analysis was performed on the influencing factors of late miscarriage. After correcting the confounding factors, PCOS ($OR=2.573$, 95% $CI=1.270-5.212$, $P=0.009$) and maternal high BMI ($OR=1.080$, 95% $CI=0.991-1.176$, $P=0.031$) were the risk factors for late miscarriage. **Conclusion** The number of high-quality embryos and the rate of high-quality

embryos in PCOS patients were lower than those in non-PCOS patients. PCOS and high BMI were risk factors for late miscarriage in patients. Improving endocrine disorders and weight control in PCOS patients before fertility treatment is of positive significance for improving the pregnancy outcome of patients.

【Key words】 Polycystic ovary syndrome; Embryo quality; Frozen-thawed embryo transfer; Late miscarriage rate

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·临床研究·

卵泡液 *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 水平与优质胚胎数的相关性及其预测不孕患者 IVF-ET 临床妊娠的效能研究

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【摘要】 目的 探讨卵泡液中叉头框转录因子 O 亚族 1 (Forkhead box transcription factor O1, *FoxO1*) mRNA、天冬氨酸蛋白水解酶-3 (*Caspase-3*) mRNA、生长分化因子-9 (growth differentiation factor-9, GDF-9) 水平与优质胚胎数的相关性及其预测不孕患者体外受精-胚胎移植 (*in vitro* fertilization-embryo transfer,

IVF-ET) 临床妊娠的效能。方法 选取 2017 年 2 月至 2020 年 1 月期间驻马店市中心医院收治的 468 例接受 IVF-ET 治疗的不孕患者进行病例对照研究, 根据是否妊娠分为妊娠组 ($n=248$)、未妊娠组 ($n=220$), 比较两组一般资料、取卵日性激素水平、卵泡液 *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 水平。采用 Pearson 分析卵泡液 *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 之间及其与优质胚胎数的相关性, 采用 logistic 回归方程分析 IVF-ET 临床妊娠的相关因素并以受试者工作特征 (receiver operating characteristic, ROC) 曲线分析卵泡液 *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 预测临床妊娠的效能。结果 妊娠组优质胚胎数多于未妊娠组 [(2.59 ± 0.68) 枚比 (1.78 ± 0.62) 枚, $P<0.001$], 基础卵泡刺激素 (follicle-stimulating hormone, FSH) 水平、基础黄体生成素 (luteinizing hormone, LH) 水平低于未妊娠组 [(7.16 ± 0.29) U/L 比 (6.21 ± 0.34) U/L, (8.72 ± 1.24) U/L 比 (10.65 ± 1.01) U/L, 均 $P<0.001$], 取卵日雌二醇高于未妊娠组 [(848.18 ± 50.68) ng/L 比 (605.35 ± 46.79) ng/L, $P<0.001$]。妊娠组 *FoxO1* mRNA、GDF-9 水平高于未妊娠组, *Caspase-3* mRNA 水平低于未妊娠组 (均 $P<0.001$); *FoxO1* mRNA 与 *Caspase-3* mRNA 呈负相关, 与 GDF-9 呈正相关 (均 $P<0.001$); *Caspase-3* mRNA 与 GDF-9 呈负相关 (均 $P<0.001$); *FoxO1* mRNA、GDF-9 与优质胚胎数呈正相关, *Caspase-3* mRNA 与优质胚胎数呈负相关 (均 $P<0.001$)。多元线性回归分析显示, 在排除混杂因素后, *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 水平与优质胚胎数相关 (均 $P<0.001$)。以 IVF-ET 临床妊娠为因变量, 纳入优质胚胎数、基础 FSH、基础 LH、取卵日雌二醇、*FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 为自变量进行 logistic 回归方程分析, 结果显示优质胚胎数、基础 FSH、基础 LH、取卵日雌二醇、*FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 均与临床妊娠结局显著相关 (均 $P<0.001$)。 *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 水平联合预测 IVF-ET 临床妊娠的曲线下面积 (area under curve, AUC) 值为 0.891, 大于 *FoxO1* mRNA 指标单独检测 (AUC=0.796, $P=0.012$)。结论 *FoxO1* mRNA、*Caspase-3* mRNA、GDF-9 水平与胚胎发育及性激素水平有关, 且 *FoxO1* mRNA、GDF-9 水平升高, *Caspase-3* mRNA 水平降低有利于临床妊娠, 三者联合检测可为评价 IVF-ET 临床妊娠提供参考。

【关键词】 受精, 体外; 胚胎移植; 优质胚胎数; 卵泡刺激素; 叉头框转录因子 O 亚族; 天冬氨酸蛋白水解酶-3; 生长分化因子-9

Correlation between *FoxO1* mRNA, *Caspase-3* mRNA, GDF-9 levels and the number of high-quality embryos and the efficacy of *in vitro* fertilization-embryo transfer in predicting clinical pregnancy in infertile patients

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【Abstract】 **Objective** To explore the correlation between Forkhead box transcription factor O1 (*FoxO1*) mRNA, *Caspase-3* mRNA, growth differentiation factor-9 (GDF-9) expression levels and the number of high-quality embryos and the efficacy of predicting *in vitro* fertilization-embryo transfer (IVF-ET) clinical

pregnancy in infertile patients. **Methods** A case-control study of 468 infertile patients who received IVF-ET treatment from February 2017 to January 2020 in Zhumadian Central Hospital was performed. According to whether pregnant, patients were divided into pregnancy group ($n=248$) and non-pregnancy group ($n=220$). We compared the general data, sex hormone levels on the day of egg retrieval, *FoxO1* mRNA, *caspase-3* mRNA, and GDF-9 levels in follicular fluid between the two groups. Pearson was used to analyze the relationship between *FoxO1* mRNA, *Caspase-3* mRNA, and GDF-9 in follicular fluid and the number of high-quality embryos. The logistic regression equation was used to analyze the related factors of IVF-ET clinical pregnancy. The receiver operating characteristic (ROC) curve was used to analyze the efficacy of follicular fluid *FoxO1* mRNA, *Caspase-3* mRNA, GDF-9 in predicting clinical pregnancy. **Results** The number of high-quality embryos in pregnancy group was higher than that in non-pregnancy group (2.59 ± 0.68 vs. 1.78 ± 0.62 , $P<0.001$), the basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were lower than those in non-pregnancy group [(7.16 ± 0.29) U/L vs. (6.21 ± 0.34) U/L, (8.72 ± 1.24) U/L vs. (10.65 ± 1.01) U/L, all $P<0.001$] and the estradiol on the day of oocytes retrieved was higher than that of non-pregnancy group [(848.18 ± 50.68) ng/L vs. (605.35 ± 46.79) ng/L, $P<0.001$]. *FoxO1* mRNA and GDF-9 in pregnancy group were higher than those in non-pregnancy group, *Caspase-3* mRNA was lower than that in non-pregnancy group ($P<0.001$). *FoxO1* mRNA was negatively correlated with *Caspase-3* mRNA and positively correlated with GDF-9 ($P<0.001$), *Caspase-3* mRNA was negatively correlated with GDF-9 ($P<0.001$). *FoxO1* mRNA and GDF-9 were positively correlated with the number of high-quality embryos, while *Caspase-3* mRNA was negatively correlated with the number of high-quality embryos (all $P<0.001$). Multiple linear regression analysis showed that after excluding confounding factors, the levels of *FoxO1* mRNA, *Caspase-3* mRNA, and GDF-9 were still correlated with the number of high-quality embryos (all $P<0.001$). IVF-ET clinical pregnancy was taken as a dependent variable and the number of high-quality embryos, basic FSH, basic LH, estradiol, *FoxO1* mRNA, *Caspase-3* mRNA, and GDF-9 were included as independent variables for logistic regression analysis. The number of high-quality embryos, basic FSH, basic LH, estradiol on the day of oocytes retrieved, *FoxO1* mRNA, *Caspase-3* mRNA and GDF-9 were significantly correlated with clinical pregnancy (all $P<0.001$). The area under curve (AUC) value of *FoxO1* mRNA, *Caspase-3* mRNA and GDF-9 mRNA combined to predict IVF-ET clinical pregnancy was 0.891, which was larger than *FoxO1* mRNA alone (AUC=0.796, $P=0.012$). **Conclusion** *FoxO1* mRNA, *Caspase-3* mRNA, and GDF-9 levels are related to embryonic development and sex hormone levels. Increased expression of *FoxO1* mRNA and GDF-9 and decreased expression of *Caspase-3* mRNA are beneficial to clinical pregnancy. Combined detection of *FoxO1*, *Caspase-3* and GDF-9 can evaluate IVF-ET clinical pregnancy.

【Key words】 Fertilization *in vitro*; Embryo transfer; Number of high-quality embryos; Follicle-stimulating hormone; Family O subgroup of fork-head frame transcription factor; Caspase-3; Growth differentiation factor-9

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·流行病学研究·

父母亲生育年龄等围孕期因素与儿童孤独症谱系障碍的关联性

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【摘要】 目的 分析父母亲生育年龄等围孕期因素与儿童孤独症谱系障碍 (autism spectrum disorder, ASD) 的关联性。方法 本研究采用病例对照研究, 选取 2018 年 6 月至 2019 年 2 月期间就诊于上海市精神卫生中心且被诊断为 ASD 的 2~6 岁儿童 (病例组, $n=104$), 对照为同期就诊于上海静安寺街道/上海彭浦新村街道社区卫生服务中心的 2~6 岁非 ASD 儿童 (对照组, $n=149$)。采用多因素 logistic 回归模型分析父母亲年龄等围孕期因素与儿童 ASD 间的关联性。结果 多因素 logistic 回归分析显示, 父亲生育年龄 ≥ 35 岁 ($OR=3.65$, 95% $CI=1.19\sim 11.15$, $P=0.023$)、父母亲孕前或孕期患病 ($OR=3.34$, 95% $CI=1.41\sim 7.94$, $P=0.006$) 以及儿童性别为男孩 ($OR=5.84$, 95% $CI=2.98\sim 11.44$, $P<0.001$) 与儿童 ASD 患病风险增加相关。父亲生育年龄 ≥ 35 岁的男童比父亲生育年龄 <35 岁的男童、父亲生育年龄 ≥ 35 岁的女童患 ASD 的风险高, 差异具有统计学意义 ($P=0.005$, $P=0.006$)。结论 父亲生育年龄与儿童 ASD 患病风险相关, 且男童中的作用可能更明显, 但需要前瞻性、大样本流行病学研究进行验证。

【关键词】 风险因素; 父亲年龄; 母亲年龄; 孤独症谱系障碍

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Association between parental characteristics during peri-conceptional period and risk of autism spectrum disorders in children

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【Abstract】 Objective To examine the association between parental characteristics and risk of autism spectrum disorder (ASD) in children. **Methods** In this case-control study, the cases were defined as children who were diagnosed with ASD and were recruited from June 2018 to February 2019 in Shanghai Mental Center ($n=104$). The controls were defined as children who did not have ASD and were recruited in the two community health centers in Jing-an District of Shanghai during the same period ($n=149$). All children recruited in this study were 2–6 years old. A multivariate logistic regression model was used to examine the association between parental characteristics and the risk of ASD in offspring, and further to estimate the interaction coefficient. **Results** According to multivariate regression analysis, the association between maternal age, previous pregnancy complication and the risk of ASD in children appeared to be not statistically significant. After adjusted, advanced paternal age (≥ 35 years old) ($OR=3.65$, 95% $CI=1.19-11.15$, $P=0.023$), parental disease before or during pregnancy ($OR=3.34$, 95% $CI=1.41-7.94$, $P=0.006$) and gender of child (male) ($OR=5.84$, 95% $CI=2.98-11.44$, $P<0.001$) were associated with increased risk of ASD. The results also showed that the boys whose father was 35 years old or more had a higher risk of ASD than the boys whose father was less than 35 years old and the girls whose father was 35 years old or more ($P=0.005$, $P=0.006$). **Conclusion** Advanced paternal age was associated with increased risk of ASD in offspring and this effect may be more pronounced in boys.

【Key words】 Risk factor; Paternal age; Maternal age; Autism spectrum disorder

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循证医学

卵巢低反应患者高孕激素状态下促排卵方案与拮抗剂方案临床应用效果对比的 meta 分析

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【摘要】 目的 比较高孕激素状态下促排卵 (progestin-primed ovarian stimulation, PPOS) 方案与拮抗剂方案对卵巢低反应 (poor ovarian response, POR) 患者的临床应用效果。方法 通过检索 Pubmed、The Cochrane Library、Embase、Web of Science、CNKI、Wanfang Data、CBM 数据库, 搜集 PPOS 方案与拮抗剂方案应用于 POR 患者的队列研究和随机对照试验 (randomized controlled trials, RCT), 检索时限从建库至 2020 年 5 月。严格筛选文献和提取资料后, 队列研究使用改良纽卡斯尔-渥太华量表 (Newcastle-Ottawa Scale, NOS) 系统评价方法、RCT 研究使用 Cochrane 系统评价方法对文献进行质量评价, 并使用 RevMan5.3 软件进行 meta 分析。结果 共纳入队列研究 7 篇, RCT 文献 3 篇, 包括 1977 例 POR 患者, 其中 PPOS 方案组 1053 例, 拮抗剂方案 924 例。Meta 分析结果显示, PPOS 方案的促性腺激素 (gonadotropin, Gn) 使用时间延长 ($P=0.02$), 但 Gn 总用量与拮抗剂方案相比差异无统计学意义 ($P>0.05$); PPOS 方案的直径 ≥ 14 mm 卵泡数和获卵数与拮抗剂方案相比差异无统计学意义 ($P>0.05$), M_{II} 卵率和受精率显著高于拮抗剂方案 ($P=0.04$, $P<0.001$), 但两组方案的优质胚胎率差异无统计学意义 ($P>0.05$); PPOS 方案的早发黄体生成素 (luteinizing hormone, LH) 峰发生率明显降低 ($P=0.04$), 扳机日雌二醇、孕酮、卵泡刺激素、LH 水平与拮抗剂方案相比差异均无统计学意义 (均 $P>0.05$); PPOS 方案的临床妊娠率高于拮抗剂方案, 而流产率低于拮抗剂方案 ($P=0.03$, $P<0.001$), 但周期取消率和出生率与拮抗剂方案相比差异均无统计学意义 (均 $P>0.05$)。结论 PPOS 方案可明显降低 POR 患者促排卵中 LH 峰发生率, 提高 M_{II} 卵率, 改善妊娠结局, 降低不良妊娠发生率, 可在 POR 患者中广泛安全使用。

【关键词】 高孕激素状态下促排卵; 促性腺激素释放激素拮抗剂; 控制性促排卵; 卵巢低反应; Meta 分析

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Comparison of the clinical efficacy of progestin-primed ovarian stimulation protocol and antagonist protocol in patients with poor ovarian response: a meta-analysis

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【 Abstract 】 Objective To compare the clinical efficacy of progestin-primed ovarian stimulation (PPOS) protocol and gonadotropin-releasing hormone (GnRH)-antagonist protocol in patients with poor ovarian response (POR). **Methods** By retrieving Pubmed, the Cochrane Library, Embase, Web of Science, CNKI, Wanfang Data, and CBM databases, the cohort studies and randomized controlled trials (RCTs) of PPOS and antagonist protocols applied to POR patients were collected and the retrieval time period was from establishment of the database to May 2020. After rigorous literature screening and data extraction, the cohort study used Newcastle Ottawa Scale (NOS) system evaluation method, the RCT used Cochrane system evaluation method to evaluate the literature quality, and the RevMan5.3 software was used for meta-analysis. **Results** A total of 7 cohort studies and 3 RCTs were included, totally 1977 POR patients, including 1053 in the PPOS protocol group and 924 in the antagonist protocol. Meta-analysis showed that the duration of gonadotropin (Gn) used in PPOS protocol group was extended ($P=0.02$), but there was no significant difference in the total dosage of Gn used compared with the antagonist protocol ($P>0.05$). There were no significant differences in the number of follicles with a diameter ≥ 14 mm and the number of retrieved oocytes between PPOS protocol group and antagonist protocol group (all $P>0.05$), the M_{II} oocyte rate and the fertilization rate were significantly higher than those of antagonist protocol ($P=0.04$, $P<0.001$), but there were no significant differences in the rate of high-quality embryos between the two groups ($P>0.05$). The incidence of early onset luteinizing hormone (LH) peak significantly reduced with PPOS protocol ($P=0.04$), the levels of estrogen, progesterone, follicle-stimulating hormone (FSH) and LH on trigger day were not significantly different from those of antagonist protocol (all $P>0.05$). The clinical pregnancy rate of PPOS protocol was higher than that of the antagonist protocol, but the abortion rate was lower than that of the antagonist protocol ($P=0.03$, $P<0.001$), and there were no significant differences in cycle cancellation rate and birth rate between the two protocols ($P>0.05$). **Conclusion** PPOS protocol can significantly reduce the incidence of premature LH surge in ovulation induction in POR patients, increase the M_{II} oocytes rate, improve the pregnancy outcome, reduce the incidence of adverse pregnancy, and can be widely and safely used in POR patients.

【 Key words 】 Progestin-primed ovarian stimulation; Gonadotropin-releasing hormone-antagonist; Controlled ovulation stimulation; Poor ovarian response; Meta-analysis

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·临床报道·

Y 染色体 AZFc 区不同部分缺失对严重少弱精子症患者 ICSI 结局的影响

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【摘要】 目的 探讨 Y 染色体无精子因子 (azoospermia factor, AZF) c 区不同部分缺失对严重少弱精子症患者卵胞质内单精子显微注射 (intracytoplasmic sperm injection, ICSI) 临床结局的影响。方法 本研究为回顾性队列研究, 分析在河南省人民医院生殖医学中心 2017 年 12 月至 2020 年 7 月期间经 Y 染色体 AZF 区高通量测序筛查、精子浓度 $<5 \times 10^6/\text{mL}$ 且行射精精子 ICSI 助孕的严重少弱精子症患者的临床资料, 根据筛查结果将携带 AZFc 缺失的患者纳入缺失组 ($n=108$), 无 AZFc 缺失的患者纳入对照组 ($n=445$), 同时按照缺失位点类型将 AZFc 缺失组分为 b2/b4 缺失 ($n=19$)、b2/b3 缺失 ($n=30$)、gr/gr 缺失 ($n=43$) 3 个亚组, 分别比较各组间及亚组间胚胎发育及妊娠结局情况。结果 存在 AZFc 缺失的患者第 3 日 (day 3, D3) 可利用胚胎率、优质胚胎率以及囊胚形成率均低于对照组, 差异均有统计学意义 [70.4% (556/790) 比 78.5% (2867/3651), $P<0.001$; 24.7% (199/807) 比 34.3% (1284/3747), $P<0.001$; 51.7% (277/536) 比 58.0% (1540/2592), $P=0.007$]; 种植率、临床妊娠率、移植周期活产率两组间比较差异均无统计学意义 (均 $P>0.05$)。AZFc 区域 b2/b3 缺失亚组 D3 可利用胚胎率、优质胚胎率、囊胚形成率、种植率、临床妊娠率及活产率与对照组比较, 差异均无统计学意义 (均 $P>0.05$); b2/b4 缺失亚组优质胚胎率 [23.2% (32/138)] 低于对照组 ($P=0.004$), 而 D3 可利用胚胎率、囊胚形成率、种植率、临床妊娠率及活产率与对照组相比, 差异均无统计学意义 (均 $P>0.05$); gr/gr 缺失亚组 D3 可利用胚胎率 [71.6% (280/391)]、优质胚胎率 [20.8% (84/403)] 以及囊胚形成率 [48.7% (133/273)] 均低于对照组 ($P=0.002$ 、 $P<0.001$ 、 $P<0.001$), 而种植率、临床妊娠率及活产率与对照组比较, 差异均无统计学意义 (均 $P>0.05$)。结论 Y 染色体 AZFc 区域

b2/b3 缺失和 b2/b4 缺失对严重少弱精子症患者 ICSI 胚胎发育及妊娠结局均无显著影响, gr/gr 缺失对胚胎发育不利影响最大, 但对妊娠结局无影响。

【关键词】 Y 染色体微缺失; 无精子因子 c 区; 严重少弱精子症; 精子注射, 细胞质内; 临床结局

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Effect of the different partial deletions in the AZFc locus of Y-chromosome on the ICSI outcome of severe oligoasthenozoospermia patients

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【Abstract】 Objective To investigate the effects of different partial deletions in azoospermia factor (AZF) locus of Y-chromosome on the clinical outcome of severe oligoasthenozoospermia patients by intracytoplasmic sperm injection (ICSI). **Methods** A retrospective cohort study was conducted on the patients undergoing high-throughput sequencing for Y chromosome microdeletion screening and ICSI treatment in Reproductive Medicine Center of Henan Provincial People's Hospital from December 2017 to July 2020. According to whether carrying AZFc microdeletions or not, the patients were divided into the AZFc-deletion group and control group. And AZFc-deletion group was divided into 3 subgroups, b2/b3 deletion, b2/b4 deletion and gr/gr deletions subgroup, by the types of partial deletion. **Results** The day 3 (D3) available embryo rate, the high-quality embryo rate, and the blastocyst formation rate in patients with AZFc deletion were statistically lower than those in control group [70.4% (556/790) vs. 78.5% (2867/3651), $P<0.001$; 24.7% (199/807) vs. 34.3% (1284/3747), $P<0.001$; 51.7% (277/536) vs. 58.0% (1540/2592), $P=0.007$], and there were no statistical differences in implantation rate, clinical pregnancy rate, live birth rate during transplantation cycle between the two groups (all $P>0.05$). The AZFc b2/b3 deletion subgroup had no significant differences in D3 available embryo rate, high-quality embryo rate, blastocyst formation rate, implantation rate, clinical pregnancy rate and live birth rate, compared with control group (all $P>0.05$). The rate of high-quality embryos in patients with the b2/b4 deletion subgroup [23.2% (32/138)] was lower than that of control group ($P=0.004$), but there were no statistical differences in D3 available embryo rate, blastocyst formation rate, implantation rate, clinical pregnancy rate and live birth rate (all $P>0.05$). The D3 available embryo rate [71.6% (280/391)], the high-quality embryo rate [20.8% (84/403)] and the blastocyst formation rate [48.7% (133/273)] in patients of gr/gr deletion subgroup were significantly lower than those in control group ($P=0.002$, $P<0.001$, $P<0.001$), but there were no statistical differences in implantation rate, clinical pregnancy rate and live birth rate (all $P>0.05$). **Conclusion** AZFc b2/b3 deletion and b2/b4 deletion in the AZFc locus of Y chromosome have no significant effect on embryonic development and pregnancy outcome in patients with severe

oligoasthenozoospermia undergoing ICSI. Gr/gr deletion has most adverse effect on embryonic development but no effect on pregnancy outcome.

【Key words】 Y chromosome microdeletion; Azoospermia factor c locus; Severe oligoasthenozoospermia; Sperm microinjection, intracytoplasmic; Clinical outcome

Fund program: Medical Science and Technology Research Plan of Henan Province, Project Co-built by Provincial Department (SBGJ202002003)

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·临床报道·

梗阻性无精子症再次精道显微重建术策略分析 ——附 21 例报道

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赵晶鹏和李朋对本文有同等贡献

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【摘要】 目的 探讨梗阻性无精子症患者初次输精管道显微吻合术失败后再次显微重建手术的有效性和安全性。方法 本研究为回顾性病例系列研究, 分析了因初次显微镜下输精管道重建手术失败, 2015 年 3 月至 2020 年 6 月期间于上海交通大学医学院附属第一人民医院泌尿外科临床医学中心男科行再次手术治疗的 21 例梗阻性无精子症患者的病例资料, 术后随访患者症状缓解或复通及妊娠情况。结果 21 例患者中, 8 例初次手术为输精管输精管吻合术, 8 例为输精管附睾吻合术, 5 例为交叉吻合术; 2 例因输精管结扎术后睾丸疼痛行手术治疗, 19 例因生育需求行手术治疗。再次手术探查发现 14 例原吻合口狭窄, 6 例吻合口有精子肉芽肿形

成, 1 例术中证实为非梗阻性无精子症。19 例成功行单侧或双侧输精管道吻合术, 1 例患者因原术区粘连严重而未能行再次吻合, 行睾丸取精术; 1 例术中证实为非梗阻性无精子症患者行睾丸显微取精术。术后随访(30.2±18.4)个月, 范围为3~58个月, 2 例失访。术后随访显示, 输精管结扎后睾丸疼痛患者 1 例阴囊症状完全缓解, 1 例部分缓解; 术后 11 例再通成功, 4 例自然妊娠, 2 例患者尚未复查精液。3 例患者通过辅助生殖技术成功妊娠(1 例使用新鲜精液精子, 2 例使用术中冻存睾丸精子)。所有患者术中、术后均未出现并发症。结论 对于初次显微重建手术失败的梗阻性无精子症患者, 再次输精管道重建手术安全可靠, 可获得满意的术后复通率和自然妊娠率。

【关键词】 梗阻性无精子症; 再次手术; 显微外科手术; 男性不育

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Reoperation strategies for obstructive azoospermia with initial microsurgical anastomosis failure (21 cases)

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【Abstract】 **Objective** To analyze the effectiveness and safety of reoperation for obstructive azoospermia (OA) with initial microsurgical anastomosis failure. **Methods** A retrospective case series was performed for OA patients who underwent reoperation after initial microsurgical anastomosis failure, in Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Institute of Urology, Urologic Medical Center from March 2015 to June 2020. Totally, 21 patients were enrolled in the study, and the clinical data, patency and pregnancy outcomes were reviewed. **Results** During the initial surgery, 8 cases underwent vasovasostomy and 8 cases underwent vasoepididymostomy, while the other 5 cases underwent crossover anastomosis; 19 cases underwent reoperation because of reproductive needs, and 2 for post-vasectomy chronic testicular pain. During the reoperation, anastomotic stricture was found in 14 cases, and sperm granuloma was found in 6 cases, while spermatogenic dysfunction was confirmed in 1 case. Unilateral or bilateral anastomosis was performed successfully in 19 cases. Testicular sperm extraction was performed for 1 case with non-obstructive azoospermia (NOA) and 1 case with severe adhesion respectively. Totally 19 cases was followed for 3 to 58 months [(30.21±18.43) months], and 2 cases were lost to follow-up. Chronic testicular pain was relieved completely in 1 of the 2 cases suffering from the post-vasectomy testicular pain. Overall, 11 cases achieved patency,

and 4 cases conceived naturally. Furthermore, 3 cases underwent *in vitro* fertilization cycle (1 case with semen sperm, and the other 2 cases with frozen testicular sperm). There were no severe post-operational complications in all cases.
Conclusion Microsurgical reoperation, which allows a favorable patency rate and natural pregnancy rate, is a valid option for the treatment of OA with initial microsurgical anastomosis failure.

【Key words】 Obstructive azoospermia; Reoperation; Microsurgery; Male infertility

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·个案报道·

IVF/ICSI 促排卵周期经阴道取卵联合经腹部取卵 1 例病例报道

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【摘要】 目的 探讨提高体外受精/卵胞质内单精子注射-胚胎移植 (*in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer, IVF/ICSI-ET) 周期中经阴道获卵困难患者的取卵技巧, 以降低 IVF/ICSI 周期取消率。方法 报道 1 例 IVF/ICSI 周期中经阴道取卵联合经腹部取卵的病例的临床资料。结果 1 例因男方因素行 ICSI 助孕的不孕患者在促排卵过程中阴道超声监测反复未探及右侧卵巢, 使用促性腺激素第 5 日后出现右下腹腹痛。结合既往阑尾切除手术史, 考虑存在因盆腔粘连所致卵巢位置高, 并随后经腹部超声予以证实。取卵术式采用超声引导下经阴道联合经腹部穿刺取卵, 左右卵巢分别获得成熟卵子各 2 枚, ICSI 授精后最终获胚 4 枚, 移植后生化妊娠。结论 经腹部超声引导下取卵, 相对安全、有效, 可以获得和常规经阴道超声引导下取卵类似的临床结局; 对于经阴道取卵困难的 IVF/ICSI 女性, 可以尝试选择经腹部超声取卵。在 IVF/ICSI 周期中, 需要提高病史询问、进周期前评估和促排卵监测、取卵及胚胎移植等各环节的质量。

【关键词】 受精, 体外; 胚胎移植; 取卵; 经腹部

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Transvaginal combined with transabdominal oocyte retrieval in IVF/ICSI cycle: a case report

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【Abstract】 Objective To improve the technique of oocyte retrieval in *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) cycles and reduce the cancellation rate of IVF/ICSI cycle. **Methods** The clinical data of a case of IVF/ICSI cycle using transvaginal combined with abdominal oocyte retrieval was reported. **Results** The right ovary of one infertile patient who received ICSI due to male factors was not detected repeatedly by transvaginal ultrasound during ovulation induction. The right lower abdominal pain occurred day 5 after using gonadotropin. We considered that the position of the right ovary was high due to pelvic adhesion after previous appendectomy, and was further confirmed by abdominal ultrasound. Two mature oocytes were obtained from the left and right ovaries respectively. Four embryos were obtained after ICSI insemination, and biochemical pregnancy occurred after transplantation. **Conclusion** Transabdominal ultrasound-guided oocyte retrieval is relatively safe and effective, and can obtain similar clinical outcomes as conventional transvaginal ultrasound-guided oocyte retrieval. For IVF/ICSI women with difficulty in obtaining oocytes through vagina, transabdominal ultrasound-guided oocyte retrieval can be tried. During IVF/ICSI treatment cycles, it is necessary to improve the quality of medical history inquiry, pre-cycle evaluation, ovulation induction monitoring, oocyte retrieval and embryo transfer.

【Key words】 Fertilization *in vitro*; Embryo transfer; Oocyte retrieval; Transabdominal

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·综述·

营养对女性生育能力的影响作用研究进展

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【摘要】 随着全球范围内不孕不育发病率的提高, 营养对生殖健康的影响越来越受到人们的重视。许多研究结果表明营养状况及日常营养物质的摄入对女性生育能力有着非常重要的影响。营养不良或营养过剩, 尤其是微量元素、维生素和三大类营养物质(包括糖类、脂类和蛋白质)在体内的均衡状况与女性生育功能密切相关, 并影响着女性卵巢储备、卵子发育、受精、胚胎发育、胚胎种植等整个生育过程。本文就营养状况与主要营养物质对女性生殖生育功能的影响及其作用进行综述。

【关键词】 女性生育; 卵巢储备; 胚胎发育; 营养物质; 营养状况
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Research progress on the effect of nutrition on female fertility

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【Abstract】 With the increasing incidence of infertility worldwide, the impact of nutrients on reproductive health has received increasing attention. Many research results indicate that nutritional status and daily nutrient intake have very important effects on female fertility. Malnutrition or excess nutrition, especially the balance of trace elements, vitamins and three nutrients including carbohydrates, lipids and proteins in the body are closely related to female reproductive function, affecting almost the whole reproductive process including female ovarian reserve, oocyte development, fertilization, embryo development and embryo implantation. This paper summarized the effects of nutrition status and main nutrients on female reproductive function.

【Key words】 Female fertility; Ovarian reserve; Embryo development; Nutrients; Nutrition status

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人类白细胞抗原-G 在母-胎免疫界面的功能和作用机制

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【摘要】 人类白细胞抗原-G (human leucocyte antigen G, HLA-G) 作为非经典的主要组织相容性复合物 I 类分子, 在母-胎界面的绒毛膜外滋养层细胞上特异性表达。妊娠期间, 胎儿同种异源的绒毛膜外滋养细胞侵入子宫黏膜, 却免于母体来源的免疫细胞攻击, 其中 HLA-G 起到极其关键的作用。关于 HLA-G 在母-胎界面特殊调控方式的研究, 特别是与各类免疫细胞及膜表面受体作用的分子机制, 引起学者的广泛关注。本文将着重对 HLA-G 在母-胎界面的表达、调节及与相关免疫细胞作用机制进行综述。

【关键词】 人类白细胞抗原-G; 母-胎界面; 母-胎免疫耐受; 绒毛外滋养细胞

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Mechanism and function of human leucocyte antigen G at the interface of maternal-fetal tolerance

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【Abstract】 Human leukocyte antigen G (HLA-G), one of the non-classical major histocompatibility complex class I molecules, is expressed uniquely on the extravillous trophoblast (EVT) cells at the maternal-fetal interface. Semi-allogeneic fetal EVT cells invade into the decidua during pregnancy without maternal immune cell attack, among which HLA-G plays an extremely important role. The special immune regulatory mechanisms of HLA-G at the interface of maternal-fetal tolerance, especially the possible molecular mechanisms interaction with immune cells and its membrane surface receptors, has been reentered into researchers' field. This review

focuses on the expression, regulatory mechanisms and function related immune cells of HLA-G in the interface of maternal-fetal.

【 Key words 】 Human leukocyte antigen G; Maternal-fetal interface; Maternal-fetal immunologic toleration; Extravillous trophoblast

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·综述·

蜕膜巨噬细胞在复发性流产中的研究进展

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【摘要】 复发性流产是临床难治性不育症, 其病因复杂, 近半数原因不明, 严重影响患者身心健康。蜕膜巨噬细胞在胚胎种植、胎盘形成及胎儿发育和分娩中发挥重要作用, 其数量、功能和表型与正常妊娠密切相关。本文就蜕膜巨噬细胞在复发性流产中的研究进展进行综述。

【关键词】 复发性流产; 蜕膜巨噬细胞; 免疫耐受

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Research advances of decidual macrophages in recurrent spontaneous abortion

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【Abstract】 Recurrent spontaneous abortion is a clinical refractory infertility with complex etiology and nearly half of the causes are unexplained, which seriously

affects the physical and mental health of patients. Decidual macrophages play an important role in embryo implantation, placenta formation, fetal development and delivery, and their number, function and phenotype are closely related to normal pregnancy. This article reviewed the research progress of decidual macrophages in recurrent spontaneous abortion.

【Key words】 Recurrent spontaneous abortion; Decidual macrophages; Immunological tolerance

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·综述·

性腺组织驻留巨噬细胞的研究进展

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【摘要】 组织驻留巨噬细胞 (tissue-resident macrophages, TRMs) 是一类存在于人体绝大多数组织器官、独立于外周循环且具有一定自我更新能力的固有免疫细胞。它们具有高度异质性, 在不同组织具有不同的起源、表型和功能。睾丸和卵巢作为机体的重要生殖器官, 其内具有复杂的生殖-内分泌-免疫调控网络。TRMs 可与性腺组织多种细胞相互作用, 性腺组织特异性微环境赋予 TRMs 独特的区域免疫特性与功能重塑; 同时, TRMs 也可参与调控性腺微环境稳态、配子发生发育及性激素合成等。本文综述了睾丸和卵巢中 TRMs 的起源、表型、极化、亚群分类等区域免疫特性, 并探讨其在维持性腺组织稳态和调控生殖内分泌功能中的重要作用。

【关键词】 巨噬细胞; 免疫; 性腺; 睾丸; 卵巢; 组织驻留巨噬细胞

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Research progress of gonad tissue-resident macrophages

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【Abstract】 Tissue-resident macrophages (TRMs) are innate immune cells located in most tissues and organs of the human body, and are independent of peripheral circulation and capable of self-renewal. They are highly heterogeneous, with different origins, phenotypes, and functions in different tissues. As the important reproductive organs in human, the testis and ovary contain a highly complicated reproductive-endocrine-immune regulatory network. TRMs can interact with a variety of cells in the gonadal tissue. The gonad-specific microenvironment could confer the tissue-specific regional immune identities and functional remodeling to TRMs. Meanwhile, the TRMs are adapted to maintain gonad homeostasis and regulate gametes development and steroidogenesis. In this review, we reviewed the origin, phenotype, polarization, subgroup classification, and other regional immune characteristics of TRMs in testis and ovary, and discussed the important role of TRMs in maintaining gonadal tissue homeostasis and regulating reproductive endocrine function.

【Key words】 Macrophages; Immunity; Gonad; Testis; Ovary; Tissue-resident macrophages

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·综述·

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父体慢性应激对生殖细胞重编程的影响及其机制

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【摘要】 父体慢性应激不仅可造成父体本身多脏器、多系统的损伤, 还可将危害传递至子代。而且, 父体慢性应激对子代的危害与生殖细胞重编程有关。当前

观点认为,生殖细胞命运的转变和发育潜能的维持源于表观遗传修饰。因此,一旦应激因素在特定时期导致父体生殖细胞发生表观遗传修饰改变,则可引起生殖细胞出现重编程,进而将危害传递至子代甚至多代。但是,父体慢性应激导致生殖细胞重编程的发生机制尚未完全阐明。本文综述了父体慢性应激对父体本身及其子代多代的危害,并结合最新研究进展探讨父体慢性应激影响生殖细胞重编程的发生机制,以期为父源性疾病提供更多理论依据。

【关键词】 慢性应激; 表观遗传修饰; 生殖细胞重编程

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Effect of chronic paternal stress on reproductive cell reprogramming and its mechanism

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【Abstract】 Paternal chronic stress can not only cause damage to multiple organs and systems of the paternal itself, but also transmit the harm to the offspring. Moreover, the harm caused by paternal chronic stress to the offspring is related to reprogramming of germ cells. The current views believe that the epigenetic modification is responsible for the transformation of germ cell fate and maintenance of developmental potential. Therefore, once the stress factors lead to epigenetic modification of the paternal germ cells in a certain period, it reprogram the germ cells, which can further transmit the harm to the offspring or even multiple generations. However, the mechanism of reprogramming of germ cells caused by chronic paternal stress has not been fully elucidated. This article reviewed the harm of paternal chronic stress to the paternal itself and its offspring for multiple generations, and combined the latest research progress to explore the mechanism by which paternal chronic stress affects reprogramming of reproductive cells, with a view to provide more theoretical basis for paternal-originated diseases.

【Key words】 Chronic stress; Epigenetic modification; Germ cells reprogramming

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·综述·

卵巢功能不全动物模型的研究进展

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【摘要】 卵巢功能不全 (premature ovarian insufficiency, POI) 是指女性在 40 岁前卵巢功能衰退的临床综合征, 以月经紊乱 (如停经或月经稀发) 伴有高促性腺激素和低雌激素为特征。虽已知的 POI 病因有卵巢手术、化疗、放疗以及染色体异常或环境因素, 但其发病机制尚未完全明确。目前 POI 动物模型种类较多主要包含两大类即啮齿类 POI 模型以及非啮齿类 POI 模型, 啮齿类 POI 模型中小鼠 POI 模型种类最多, 制备方法完善, 最常用于 POI 的相关研究; 大鼠的 POI 模型相较于小鼠 POI 模型使用频率低, 但对于 POI 的研究来说仍具有不可替代的价值。非啮齿类 POI 模型 (兔、猪和非人灵长类等) 卵巢形态及各阶段卵母细胞观察较容易, 其中非人灵长类 POI 模型与人类最为相似, 但由于实验成本高及饲养条件严格, 目前对于非啮齿类 POI 模型研究仍然较少, 需进一步深入研究从而建立完整的模型制备体系。本文拟对 POI 的动物模型进行综述, 为 POI 分子机制研究及新型诊疗措施提供参考。

【关键词】 卵巢功能不全; 啮齿类; 非啮齿类; 动物模型

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Research progress on animal models for the premature ovarian insufficiency

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【Abstract】 Premature ovarian insufficiency (POI) is a cause of infertility in women. It is characterized by menstrual disorders (such as menopause or sparse menstruation) with high gonadotropins and low estrogen levels in women younger than 40 years of age. Although some factors including ovarian surgery, chemotherapy, radiotherapy, chromosomal abnormalities or environmental have been reported to be involved in the development of POI, the underlying cause is not identified in the majority of cases. At present, there are mainly two kinds of POI animal models: rodent POI model and non-rodent POI model. Mouse POI model in rodent POI model has the most variety and mature method, and is most commonly used in POI related researches. Rat POI model is used less than mouse POI model,

but it still has irreplaceable value for POI research. The ovarian morphology and oocytes of non-rodent POI model (rabbit, pig and non-human primate, etc.) can be easily observed, among which the non-human primate POI model is the most similar to human. However, due to the high experimental cost and strict feeding conditions, there is still little research on non-rodent POI model. Further research is needed to establish a complete model establishment system. This review summarized the established animal models for the POI which provides valuable information regarding the selection of suitable animal model for the research in the pathogenesis of POI.

【 Key words 】 Premature ovarian insufficiency; Rodents; Non-rodents; Animal models

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