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·规范与标准·

基于 Delphi 法的辅助生殖技术治疗低预后人群诊疗中国专家意见

中国 ART 治疗低预后人群诊疗专家意见编写组

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【摘要】 目的 形成科学合理、规范实用的中国辅助生殖技术(ART)治疗低预后人群诊疗的专家意见。方法 运用 Delphi 法对中国 ART 治疗低预后人群的诊断、发病原因、治疗目标和治疗方法进行专家调查,并结合前期文献检索结果,编制第一轮问卷,征集辅助生殖领域专家意见;回收专家反馈意见,对问卷条目进行分析及修改后进入第二轮意见征集环节,经过两轮专家调研,通过专家意见赞成水平、专家参与调查研究的积极程度对本次专家调研结果进行评估。结果 第一轮问卷形成 30 个陈述,专家参与的积极程度为 87.0%,专家认可度均达到 70%以上。第二轮问卷为 26 条陈述,专家参与的积极程度为 95.7%,专家认可度均达到 70%以上,最终形成 26 条专家意见。结论 博洛尼亚低反应标准在某些方面存在欠缺,新的 POSEIDON 标准在一定程度上优化了低预后分类。通过对低预后的分类、病因、诊断及治疗方法进行充分的阐述并给予推荐性意见,希望能为临床改善低预后人群的成功率提供帮助。

【关键词】 生殖技术,辅助; 卵巢低反应; 低预后; Delphi 法; POSEIDON 标准

Delphi method-based Chinese experts' opinions on diagnosis and treatment of assisted reproductive technology in low-prognosis patients

Chinese Expert Suggestions Group on Diagnosis and Treatment of Assisted Reproductive Technology with Low-Prognosis Patients

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【Abstract】 Objective To form scientific, rational, standardized and practical expert opinions on the diagnosis and treatment of assisted reproductive technology (ART) in the low-prognosis population in China. **Methods** The diagnosis, causes or etiology, treatment targets, and treatment methods of ART were investigated by the Delphi method. The first round of the questionnaire was made by searching the literature and soliciting expert opinions in the field of ART. Then, the feedback from experts was collected, and the statements of the questionnaire were analyzed and revised for the second round of consultation by experts. The results of this expert survey were evaluated by the level of consistency of expert opinion and the degree of expert participation. **Results** The response rate of experts in the first and second rounds was 87.0% and 95.7%, respectively. After two rounds, all statements reached the target of 70% consensus. **Conclusion** The enthusiasm of experts was high, and their opinions were representative. The suggestions of Chinese experts on the diagnosis and treatment of ART with low-prognosis patients were made by expert consultation in the ART field using the Delphi survey technique.

【Key words】 Reproductive technology, assisted; Poor ovarian response; Low prognosis; Delphi method; POSEIDON criteria

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·临床研究·

波塞冬标准低预后患者的累积活产率分析

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【摘要】 目的 比较波塞冬标准分组各组患者的临床特征和累积活产率。方法 回顾性队列研究方法分析西北妇女儿童医院生殖中心在 2014 年 1 月 1 日至 2018 年 1 月 31 日期间接受体外受精-胚胎移植(IVF-ET)的低预后人群资料, 随访时间至少 1 年。经严格排除标准后, 共 4120 个新鲜完整周期纳入分析。这些患者按波塞冬标准分为 4 组 : A 组 (年龄<35 岁, 窦卵泡数≥5 枚, 前次标准刺激获卵数≤9 枚)共 1092 例, B 组(年龄≥35 岁, 窦卵泡数≥5 枚, 前次标准刺激获卵数≤9)共 480 例, C 组(年龄<35 岁, 窦卵泡数<5 枚)共 1132 例, D 组(年龄≥35 岁, 窦卵泡数<5 枚)共 1416 例。比较各组患者基本临床资料、胚胎发育及累积活产率等。结果 卵子输出率由高到低依次为 C 组 (149.47%)、D 组(112.06%)、B 组(85.39%)、A 组 (81.81%), 组间比较差异均有统计学意义(P 均=0.000 1)。无可移植胚胎率由高到低依次为 D 组(19.49%)、C 组(15.37%)、B 组(11.88%)、A 组 (10.90%), 组间比较差异均有统计学意义(P 均=0.000 1)。累积活产率由高到低依次为 A 组 (48.81%)、C 组(35.07%)、B 组(26.46%)及 D 组(14.55%), 组间比较差异均有统计学意义(P 均=0.000 1)。结论 波塞冬标准分组方法可以预测患者的累积活产率。年轻卵巢储备好的人群最高, 年轻卵巢储备差的人群次之, 高龄卵巢储备好的人群第三, 高龄卵巢储备差的人群最低。

【关键词】 卵巢低反应; 受精, 体外; 胚胎移植; 累积活产率; 低预后; 波塞冬标准

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Cumulative live birth rate of low prognosis patients based on POSEIDON criteria

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【Abstract】 Objective To investigate the characteristics and outcomes of low prognosis patients based on POSEIDON criteria undergoing *in vitro* fertilization and embryo transfer (IVF-ET) treatment. **Methods** A retrospective cohort study was conducted to analyze the data of low prognosis patients undergoing IVF-ET in Reproductive Medicine Centre, the Northwest Women's & Children's Hospital between January 1, 2014 to January 31, 2018. The follow-up lasted at least one year. After strict exclusion criteria, 4120 complete fresh cycles were included in the analysis. According to POSEIDON criteria, there were 1092 cases in group A [age<35 years, antral follicle count

(AFC)≥5, number of oocytes retrieved in previous standard stimulation≤9], 480 cases in group B (age≥35 years, AFC≥5, number of oocytes retrieved in previous standard stimulation≤9), 1132 cases in group C (age<35 years, AFC<5), and 1416 cases in group D (age≥35 years, AFC<5). The baseline characteristics, embryonic development and cumulative live birth rates were compared among the groups. **Results** The oocytes output rate ranked from high to low in order of group C (149.47%), group D (112.06%), group B (85.39%) and group A (81.81%) with significant differences (all $P=0.0001$). The non-usable embryo transplant rate ranked from high to low in order of group D (19.49%), group C (15.37%), group B (11.88%) and group A (10.90%) with significant differences (all $P=0.0001$). The cumulative live birth rate ranked from high to low in order of group A (48.81%), group C (35.07%), group B (26.46%) and group D (14.55%) with significant differences (all $P=0.0001$). **Conclusion** POSEIDON criteria grouping method can predict the cumulative live birth rate of patients. The cumulative live birth rate was the highest in the young women with good ovarian reserve, followed by the young women with diminished ovarian reserve, then the advanced age women with good ovarian reserve, and the lowest in the advanced age women with diminished ovarian reserve.

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

Fund program : National Nature Science Foundation of China (81771657) ; General Project of Science and Technology Department of Shaanxi Province-Social Development Field (2018SF-260)

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·临床研究·

不同降调节方案对子宫腺肌病患者体外受精/卵胞质内单精子显微注射治疗结局的效益分析

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【摘要】 目的 探讨不同降调节方案在子宫腺肌病患者体外受精(IVF)/卵胞质内单精子显微注射(ICSI)治疗中的应用及综合效益分析。方法 回顾性分析 2016 年 4 月 1 日至 2018 年 4 月 1 日期间于郑州大学第三附属医院生殖中心行新鲜胚胎移植的卵巢功能正常且合并子宫腺肌病的 307 例 IVF/ICSI 治疗周期, 根据不同的控制性超促排卵方案分为早卵泡期长效长方案组(A 组)、改良长方案组(B 组)和超长方案组(C 组)。比较各组的基本特征数据、IVF/ICSI 治疗数据及妊娠结局。结果 A 组的促性腺激素(Gn)使用总量 [(2 644.3±863.3) IU]、Gn 使用时间[(9.75±2.26) d]、获卵数

[(8.5±5.4) 枚]、可利用胚胎数 [(2.5±2.0) 枚] 均显著低于 B 组 [(3 008.4±1 047.3) IU, $P=0.044$; (10.74±2.45) d, $P=0.018$; (10.9±6.6) 枚, $P=0.025$; (3.6±2.7) 枚, $P=0.021$] 和 C 组 [(3 029.6±1 174.5) IU, $P=0.046$; (11.04±2.79) d, $P=0.003$; (11.2±7.2) 枚, $P=0.020$; (4.0±3.4) 枚, $P=0.002$] , B、C 两组差异均无统计学意义 ($P>0.05$) ; 胚胎种植率 C 组 (52.50%) 高于 A 组 (37.89%) 和 B 组 (39.64%) , 3 组间差异有统计学意义 ($P=0.045$) , A 组和 B 组间差异无统计学意义 ($P>0.05$) ; A、B、C 3 组的到达活产时间 [(316.6±9.9) d, (346.3±9.6) d, (381.9±22.2) d] 逐渐增加且组间差异有统计学意义 ($P<0.001$) ; Spearman 相关分析及二元逻辑回归分析显示促性腺激素释放激素激动剂 (GnRH-a) 降调节可能是获卵数 ($r=0.123, P=0.031$) 及胚胎种植 ($OR=1.599$, 95% $CI=1.078-1.616, P=0.041$) 的保护因素。结论 GnRH-a 降调节 2 个周期的改良长方案可能给予子宫腺肌病患者 IVF/ICSI 助孕周期带来最大效益。

【关键词】 子宫腺肌病；不孕症；降调节；受精，体外；胚胎移植；卵胞质内单精子注射；到达活产时间

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Benefits analysis of different down-regulation protocols for *in vitro* fertilization/intracytoplasmic sperm injection treatment outcomes in females with adenomyosis

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【Abstract】 Objective To explore the application and comprehensive benefit analysis of different down-regulation protocols in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) in females with adenomyosis. **Methods** A retrospective analysis of the 307 IVF/ICSI cycles with normal ovarian function and adenomyosis who underwent fresh embryo transfer from April 1, 2016 to April 1, 2018. According to the controlled ovarian hyperstimulation protocols, the patients were divided into the early follicular long-term protocol group (group A), the modified long-term protocol group (group B) and the super-long-term protocol group (group C). The general characteristics, treatment data of IVF/ICSI and pregnancy outcomes of each group were compared. **Results** The total dosage of gonadotropin (Gn) used [(2 644.3±863.3) IU], the duration of Gn used [(9.75±2.26) d], the number of oocytes retrieved (8.5±5.4) and available embryos (2.5±2.0) in group A were significantly lower than those in group B [(3 008.4±1 047.3) IU, $P=0.044$; (10.74±2.45) d, $P=0.018$; 10.9±6.6, $P=0.025$; 3.6±2.7, $P=0.021$] and group C [(3 029.6±1 174.5) IU, $P=0.046$; (11.04±2.79) d, $P=0.003$; 11.2±7.2, $P=0.020$; 4.0±3.4, $P=0.002$], there were no significant differences between group B and group C ($P>0.05$). The embryo implantation rate in group C (52.50%) was higher than that in group A (37.89%) and group B (39.64%) , the difference among the three groups was statistically significant ($P=0.045$), there was no significant difference between group A and group B ($P>0.05$). The time to live birth of group A [(316.6±9.9) d], group B [(346.3±9.6) d], and group C [(381.9±22.2) d] increased gradually and the difference among the three groups was significant ($P<0.001$). Spearman correlation analysis and binary logistic regression analysis respectively showed that the gonadotropin-releasing hormone agonist (GnRH-a) down-regulation may be the protection factors of the number of oocytes retrieved ($r=0.123, P=0.031$) and embryo implantation ($OR=1.599$, 95% $CI=1.078-1.616, P=0.041$). **Conclusion** The modified long-term protocol with GnRH-a 2-cycle down-regulation may maximize the benefits of IVF/ICSI cycles in women with adenomyosis.

【Key words】 Adenomyosis ; Infertility ; Down-regulation ; Fertilization *in vitro* ; Embryo transfer ; Intracytoplasmic sperm injection ; Time to live birth

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·临床研究·

钙离子载体 A23187 激活卵母细胞在卵胞质内单精子注射中的应用

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【摘要】 目的 分析 Ca^{2+} 载体 A23187 对卵胞质内单精子注射(ICSI)受精失败或受精低下患者受精及胚胎发育的影响。方法 回顾性自身对照研究分析 2010 年 1 月至 2018 年 1 月期间在中山大学附属第六医院生殖医学研究中心, 因前次 ICSI 受精失败或低下[双原核(2PN)受精率 $\leq 30\%$], 再次行 ICSI 助孕时采用 Ca^{2+} 载体 A23187 激活的 43 名患者资料。根据前次受精情况将患者分为受精失败和受精低下组、射出精子组和睾丸精子组, 激活周期与既往 ICSI 周期自身对照。结果 受精失败、受精低下、睾丸精子和射出精子各组激活周期的 2PN 受精率显著高于既往 ICSI 周期(分别为 41.9%比 0, $P < 0.001$; 44.3%比 16.5%, $P < 0.001$; 36.5%比 13.5%, $P = 0.004$; 43.1%比 11.1%, $P < 0.001$); 受精低下组和射出精子组激活周期每周期可移植胚胎数和优质胚胎数较既往周期提高 (P 均 < 0.05); 激活周期最终获得 9 例健康活产婴儿。结论 Ca^{2+} 载体 A23187 辅助激活能够提高既往 ICSI 受精失败或低下患者的受精率, 并能改善使用射出精子 ICSI 患者的胚胎情况及临床结局。

【关键词】 卵胞质内单精子注射; Ca^{2+} 载体 A23187; 卵母细胞激活; 受精

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Artificial oocyte activation with calcium ionophore A23187 in intracytoplasmic sperm injection cycles

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【Abstract】 Objective To analyze the effect of calcium ionophore A23187 on fertilization and embryonic development of mature oocytes in patients with intracytoplasmic sperm injection (ICSI) failure history or poor fertilization rate. **Methods** A total of 43 patients who were conducted artificial oocyte activation with calcium ionophore A23187 due to total fertilization failure or poor fertilization rate [two pronucleus (2PN) rate $\leq 30\%$] in previous ICSI cycles, from January 2010 to January 2018 in Reproductive Medicine Research Center, the Sixth Affiliated Hospital of Sun Yat-sen University were included in this retrospective self-control research. Fertilization rate, embryo development and pregnancy outcomes were compared between activation cycles and ICSI cycles, respectively in fertilization failure group, poor fertilization group, ejaculated spermatozoa group and

extracted-testicular spermatozoa group. **Results** In fertilization failure group, poor fertilization group, extracted-testicular spermatozoa group and ejaculated spermatozoa group, the 2PN fertilization rate of activation cycles significantly increased compared with standard ICSI cycles (41.9% vs. 0, $P<0.001$; 44.3% vs. 16.5%, $P<0.001$; 36.5% vs. 13.5%, $P=0.004$; 43.1% vs. 11.1%, $P<0.001$). In poor fertilization group and ejaculated spermatozoa group, the average number of transplanting embryos and high-quality embryos in activation cycles were significantly higher than those in ICSI cycles ($P<0.05$). Nine healthy neonates were delivered after oocyte activation in 43 patients. **Conclusion** Calcium ionophore A23187 activation can improve fertilization rate in patients with failed or poor fertilization rate of ICSI cycles, and improve embryonic development and pregnancy outcomes of ICSI cycles using ejaculated spermatozoa.

【Key words】 Intracytoplasmic sperm injection ; Calcium ionophore A23187 ; Oocyte activation ; Fertilization

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·临床研究·

卵巢早衰初诊患者改良 Kupperman 评分 与确诊年龄、生命质量的多重线性回归分 析

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【摘要】 目的 探究卵巢早衰(POF)初诊患者绝经相关症状与确诊年龄、各维度生命质量是否存在相关性。方法 采用横断面研究, 用改良 Kupperman 评分表和 SF-36 生命质量调查量表对 2015 年 1 月至 2018 年 12 月期间就诊于浙江大学医学院附属妇产科医院妇科内分泌门诊的 POF 初诊患者进行问卷调查, 并收集研究对象年龄、性激素水平、社会人口学因素等信息, 多重线性回归分析 POF 患者改良 Kupperman 评分与确诊年龄、生命质量各维度间的线性关系。结果 共有 170 名 POF 患者完成调查, 其中 122 人(71.76%)有绝经相关症状。有绝经相关症状者的确诊年龄 [37(33, 39)岁]较无症状者大 [35(29, 38)岁, $P=0.042$]。除生理功能外, 生命质量中生理职能维度 ($P=0.006$)、躯体疼痛维度 ($P=0.025$)、总体健康维度 ($P<0.000 1$)、活力维度 ($P<0.000 1$)、社会功

能维度($P=0.006$)、情感职能维度($P=0.004$)、精神健康维度($P=0.005$)得分均低于无症状者,差异均具有统计学意义。多重线性回归分析结果显示 POF 患者确诊年龄、总体健康、情感职能和活力得分与改良 Kupperman 总评分相关,回归系数分别为 0.158、-0.219、-0.222 和-0.226(P 均 <0.05)。结论 有绝经相关症状的 POF 初诊患者生命质量明显降低,确诊年龄、生命质量维度总体健康、情感职能和活力得分与绝经相关症状发生存在相关性。

【关键词】 卵巢早衰; 早发性卵巢功能不全; 绝经相关症状; 生命质量; 多重线性回归

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Multiple linear regression analysis of modified Kupperman index score in newly diagnosed patients with early ovarian failure and the age of diagnosis and quality of life

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【Abstract】 Objective To analyze the correlation between menopausal symptoms of newly diagnosed patients with premature ovarian failure (POF) and age of diagnosis and quality of life in all dimensions. **Methods** A cross-sectional study was used. The modified Kupperman index and quality of life scale (Short Form 36 Health Survey Profile, SF-36) were used to assess the patients with POF who were treated for the first time in the Gynecologic Endocrine Outpatient Clinics of Women's Hospital, Zhejiang University School of Medicine from January 2015 to December 2018. The correlation was analyzed by the multiple linear regression analysis method. **Results** A total of 170 patients completed the survey, among which 122 women (71.76%) had menopausal symptoms. The age of diagnosis for patients with menopausal symptoms [(34.9±5.1) years] was older than that for patients without symptoms [(32.7±6.2) years, $P=0.042$]. Except the physiological function domain, POF patients with menopausal symptoms had impaired quality of life in domains of role-physiological ($P=0.006$), bodily pain ($P=0.025$), general health ($P<0.0001$), vitality ($P<0.0001$), social functioning ($P=0.006$), role-emotional ($P=0.004$) and mental health ($P=0.005$) compared with patients with no symptom. The results of multiple linear regression analysis showed that the diagnosed age, scores of general health, role-emotional, and vitality of POF patients were correlated with the total scores of modified Kupperman index, with regression coefficients of 0.158, -0.219, -0.222 and -0.226, respectively ($P<0.05$ for all). **Conclusion** The life quality of POF patients with menopausal symptoms was significantly impaired. The age of diagnosis, quality of life in dimensions of general health, role-emotional and vitality were correlated with the occurrence of menopausal symptoms.

【Key words】 Premature ovarian failure; Primary ovarian insufficiency; Menopausal symptom; Quality of life; Multiple linear regression

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·临床研究·

不同宫腔内装置方法用于预防宫腔粘连分离术后再粘连的临床疗效研究

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【摘要】 目的 探讨不同宫腔内装置方法预防宫腔粘连分离术(TCRA)后再粘连的临床疗效。方法 回顾性分析 2016 年 8 月至 2018 年 8 月期间在河南省人民医院治疗中重度宫腔粘连并成功分离 98 例患者的临床资料, 根据术后宫腔内放置的装置不同分成 3 组, A 组放置金属元宫环(IUD)(30 例); B 组放置宫腔支撑球囊(30 例); C 组放置金属元宫环+防粘连膜(38 例)。对比 3 组患者术后宫腔恢复情况、术后宫腔粘连评分改善率、临床疗效及月经改善情况。结果 对于中重度宫腔粘连患者成功分离宫腔粘连后 3 组患者治疗前后宫腔粘连评分差值, C 组较 A、B 组均有显著改善(A 组: 9.50 ± 8.00 , B 组: 11.00 ± 7.00 , C 组: 14.50 ± 9.00 ; A、C 组比较, $P < 0.001$; B、C 组比较, $P < 0.001$)。3 组治疗前后子宫内膜厚度差值, C 组较 A、B 组均有显著改善[A 组: (2.34 ± 1.43) mm, B 组: (2.53 ± 1.72) mm, C 组: (3.82 ± 3.00) mm; A、C 组比较, $P = 0.003$; B、C 组比较, $P = 0.005$]。3 组治疗后月经量比较, C 组较 A、B 组均有显著改善(A、C 组比较, $\chi^2 = 8.420$, $P = 0.015$; B、C 组比较, $\chi^2 = 8.678$, $P = 0.013$)。术后 1、3 个月常规行宫腔镜检查, 根据 2015 年中国宫腔粘连分级评分标准再次进行评分, 3 组间比较差异均有统计学意义(P 均 < 0.01), C 组效果最佳。结论 TCRA 宫腔内放置金属元宫环联合防粘连膜在预防中重度 TCRA 后再粘连有较好的效果。

【关键词】 宫腔粘连; 子宫球囊支架; 金属元宫环; 防粘连膜; 宫腔粘连分离术
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Clinical efficacy of different intrauterine device methods for preventing re-adhesion after intrauterine adhesion separation

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【Abstract】 Objective To investigate the therapeutic effect of anti-adhesion membrane, intrauterine device and intrauterine balloon stent on intrauterine adhesion. **Methods** Ninety patients with moderate to severe intrauterine adhesions treated in Henan Provincial People's Hospital from August 2016 to June 2018 were divided into three groups according to the treatment of different intrauterine devices: group A (30 cases) with intrauterine device (IUD), group B (30 cases) with intrauterine balloon stent and group C (38 cases) with metal intrauterine device plus anti-adhesion membrane. Improvement rate of intrauterine adhesion score, clinical efficacy and menstrual improvement of the three groups were compared among these groups. **Results** For patients with moderate to severe intrauterine adhesions, the difference between the intrauterine adhesion scores before and after treatment was significantly improved in group C compared with groups A and B (group A: 9.50 ± 8.00 , group B: 11.00 ± 7.00 , group C: 14.50 ± 9.00 , comparison of groups A and C: $P < 0.001$, comparison of groups B and C: $P < 0.001$). The difference between endometrial thickness before and after treatment was significantly improved in group C compared with groups A and B [group A: (2.34 ± 1.43) mm, group B: (2.53 ± 1.72) mm, group C: (3.82 ± 3.00) mm, comparison of groups A and C: $P = 0.003$, comparison of groups B and C: $P = 0.005$]. The menstrual volume after treatment was significantly improved in group C compared with groups A and B (comparison of groups A and C, $\chi^2 = 8.420$, $P = 0.015$; comparison of groups B and C, $\chi^2 = 8.678$, $P = 0.013$). Hysteroscopy was routinely performed at 1 and 3 months after surgery, and re-scoring was performed according to the 2015 Chinese uterine adhesion rating scale. The differences among the three groups were statistically significant ($P < 0.01$). **Conclusion** Operation with metal intrauterine device plus anti-adhesion membrane has a good therapeutic effect on moderate and severe intrauterine adhesions.

【Key words】 Uterine adhesion ; Uterine balloon stent ; Anti-adhesion membrane ; Uteral adhesion separation

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·临床研究·

天然孕酮阴道环的有效性与安全性评价

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【摘要】 目的 评价天然孕酮阴道环(PVR)对哺乳期妇女避孕的有效性和安全性。方法 收集复旦大学附属妇产科医院 2014 年 6 月至 2015 年 2 月期间年龄在 20~40 周岁的产后 6~10 周内的健康哺乳期妇女共 48 例, 采用随机数字表法进行分段随机分为 2 组, 分别使用 PVR(PVR 组)和避孕套(避孕套组), 连续观察 9 个月, 观察 PVR 的有效性和安全性。结果 疗效评价结果显示 : PVR 组与避孕套组避孕有效率差异无统计学意义($P>0.05$), 全分析集(FAS)统计结果与符合方案分析集(PPS)统计结果一致。次要疗效评价结果显示 : 两组受试者在第 270 日比较婴儿身高与体质量增长变化, 组间比较差异均无统计学意义(P 均 >0.05) ; 两组受试者给药后的阴道出血次数、每次阴道出血时间、每次平均每日阴道流血量、哺乳期闭经时间差异均无统计学意义(P 均 >0.05)。安全性评价结果显示 : PVR 组受试者给药后月经经期、月经周期、月经血量与避孕套组比较, 差异均无统计学意义(P 均 >0.05)。两组受试者给药后每日哺乳次数比较差异有统计学意义, PVR 组哺乳次数略多于避孕套组($P=0.0319$), 但在母乳喂养时间上组间差异无统计学意义($P>0.05$)。PVR 组受试者给药后阴道分泌物明显增多, 在给药后 30 d、90 d、180 d、270 d 与避孕套组比较, 差异均有统计学意义(P 值分别为 0.0046、0.0001、0.0004、0.0219)。结论 PVR 与避孕套避孕效果相当, 是哺乳期避孕的有效安全的选择。

【关键词】 阴道环 ; 哺乳期 ; 避孕 ; 天然孕酮

Evaluation of effect and safety of the vaginal ring with natural progesterone

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【Abstract】 Objective To investigate the effect and safety of vaginal ring with natural progesterone (PVR) on the contraception in lactating women. **Methods** Totally 48 cases of healthy postnatal lactating women aged 20–40 years were enrolled at 6–10 weeks after childbirth during June 2014 to February 2015 in Obstetrics and Gynecology Hospital of Fudan University, and were divided into PVR group and condom group in accordance with the random number table. The effectiveness and safety of PVR which has been observed for 9 months continuously were investigated. **Results** Primary efficacy evaluation index outcomes: there were no statistically significant differences between the two groups in effective rates of contraceptives ($P>0.05$), full analysis set (FAS) was consistent with per protocol set (PPS). Secondary efficacy evaluation index outcomes: the increments in infant weight and height on 270th day after birth were not significantly different between the two groups ($P>0.05$). No statistically significant differences were observed in the frequency, duration and amount of vaginal bleeding, as well as the amenorrhea period between PVR and condom groups. The duration and periodicity of menstruation and amount of menstrual blood loss of PVR group showed no differences with condom group. Although there was no statistically significant difference between the two groups in total days of breast-feeding ($P>0.05$), PVR group presented a significantly higher frequency of daily breastfeeding than condom group ($P=0.0319$). Compared with condom group, women in PVR group presented significant increased volume of vaginal discharge during 30 d ($P=0.0046$), 90 d ($P=0.0001$), 180 d ($P=0.0004$), 270 d ($P=0.0219$) of postpartum after PVR treatment. **Conclusion** PVR has an equal effect as condoms, and is an effective and safe choice of contraception during lactation.

【Key words】 Vaginal ring ; Lactation ; Contraception ; Natural progesterone

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·实验研究·

全外显子组测序研究卵巢早衰特异性变异 关联的生物学过程

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【摘要】 目的 研究卵巢早衰(POF)特异性变异关联的生物学过程。方法 通过对来自 2 个家系的 3 个 POF 患者和 7 个健康对照的全外显子组测序数据进行生物信息学分析。对筛选获得的 POF 特异性单核苷酸变异 (SNVs) 以及对应的基因进行生物学功能富集与蛋白互作分析。结果 262 个疾病特异性变异对应基因显著富集在多个 GO 功能条目下 , 如在生物学过程集合中的嗜同性

细胞黏附($P=1.28E-3$)、细胞黏附($P=3.56E-3$)、转录的正调节($P=9.41E-3$)、消化道发育($P=0.011$)、Notch 信号通路($P=0.018$)、钙离子跨膜转运($P=0.021$)、细胞对氧气水平降低的反应($P=0.026$)等, 在细胞组分集合中的质膜($P=2.58E-4$)、细胞前缘($P=0.014$)、中心粒($P=0.016$)、动力蛋白复合物($P=0.033$)、突触后致密区($P=0.035$), 在分子功能集合中的转录因子活性($P=5.04E-3$)、肌动蛋白结合($P=6.03E-3$)、钙离子结合($P=0.008$)、核小体组蛋白结合($P=0.039$)、碳水化合物结合($P=0.048$)等。其次 262 个基因显著富集在多个 KEGG 生物信号通路中, 如背腹轴形成($P=4.09E-4$)、甲状腺激素信号通路($P=0.017$)、血管加压素调节的水重吸收($P=0.020$)、Notch 信号通路($P=0.025$)、亨廷顿病($P=0.042$)。另外对 262 个基因编码的蛋白进行蛋白互作网络分析, 结果显示 *MYC*、*FOXO1*、*CREBBP*、*NOTCH2* 及 *HES1* 等包含在互作网络中的核心基因组成的较强网络簇中。结论 POF 特异性的遗传学变化可能通过导致卵巢发育生物学过程及卵巢发育相关的信号通路的活性改变, 从而促进 POF 的发生。这些证据可以为 POF 的遗传发病机制进一步研究提供坚实的理论依据。

【关键词】 全外显子测序; 卵巢早衰; 功能富集; 信号通路; 蛋白互作

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Whole exome sequencing to study the biological processes associated with specific mutations in premature ovarian failure

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【Abstract】 Objective To study the biological processes associated with the premature ovarian failure (POF)-specific variants from the genome level. **Methods** Bioinformatics analysis was performed by whole exome sequencing data from 3 POF patients and 7 healthy controls from 2 families. POF-specific single nucleotide variants (SNVs) and corresponding genes were used to execute biological function enrichment and protein interaction analysis. **Results** Totally 262 disease-specific mutations were significantly enriched in multiple GO functional items, such as homophilic cell adhesion ($P=1.28E-3$), cell adhesion ($P=3.56E-3$), positive regulation of transcription ($P=9.41E-3$), digestive tract development ($P=0.011$), Notch signaling pathway ($P=0.018$), calcium ion transmembrane transport ($P=0.021$) and cellular response to decreased oxygen levels ($P=0.026$) in the set of biological processes; plasma membrane ($P=2.58E-4$), cell leading edge ($P=0.014$), centriole ($P=0.016$), dynein complex ($P=0.033$), postsynaptic density ($P=0.035$) in the set of cell component; transcription factor activity ($P=5.04E-3$), profilin binding ($P=6.03E-3$), calcium ion binding ($P=0.008$), nucleosomal histone binding ($P=0.039$), carbohydrate binding ($P=0.048$) in the set of molecular function. A total of 262 genes were significantly enriched in multiple KEGG biological signaling pathways, such as dorso-ventral axis formation ($P=4.09E-4$), thyroid hormone signaling pathway ($P=0.017$), vasopressin-regulated water reabsorption ($P=0.020$), Notch signaling pathway ($P=0.025$) and Huntington's disease ($P=0.042$). In addition, 262 genes encode proteins sets were performed to protein interaction network analysis, the result showed that *MYC*, *FOXO1*, *CREBBP*, *NOTCH2*, and *HES1* were involved in the strong network clusters composed of core genes in the interaction network. **Conclusion** POF-specific genetic changes may contribute to the development of POF by causing changes in the biological processes and activity of the signaling pathway of ovarian development. These evidence can provide a solid theoretical basis for further research on the heredity pathogenesis of premature ovarian failure.

【Key words】 Whole exome sequencing; Premature ovarian failure; Functional enrichment; Signaling pathway; Protein-protein interaction

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·流行病学研究·

中国育龄妇女产后月经恢复时间及其影响因素:15 省市现况调查

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【摘要】 目的 研究中国育龄妇女产后月经恢复时间及其影响因素。方法 在我国东、中、西部地区 15 个省市自治区 60 家医院, 随机抽取 2015 年 7 月至 2016 年 6 月期间 1 个月, 于 2017 年 7 月至 12 月, 按照分娩时间顺序依次通过电话调查这 1 个月期间分娩孕妇 300 名, 了解其月经恢复时间、母乳喂养、再次妊娠以及避孕药具使用等情况。采用 SPSS21.0 统计学软件进行分析, 平均产后月经恢复时间用算术均数, 累积月经恢复率用寿命表法计算, 影响因素分析采用 2 水平 Cox 模型分析。结果 截止至调查日, 98.18% (17 488/17 813) 的调查对象已恢复月经, 产后月经恢复时间为(6.13±3.87)个月。产后 3、6、7、12 个月累积月经恢复率分别为 17.88%、47.68%、62.95%和 88.45%。Cox 回归分析结果显示: 25~39 岁妇女产后月经恢复时间均晚于≤24 岁妇女 ($HR=0.944$, 95% $CI=0.895\sim0.995$; $HR=0.896$, 95% $CI=0.847\sim0.949$; $HR=0.904$, 95% $CI=0.844\sim0.968$); 相比于产次为 1、非纯母乳喂养、产后避孕的妇女, 产次≥3、纯母乳喂养、未避孕的妇女产后月经恢复时间均延迟 ($HR=0.896$, 95% $CI=0.817\sim0.981$; $HR=0.564$, 95% $CI=0.537\sim0.593$; $HR=0.676$, 95% $CI=0.643\sim0.711$); 少数民族妇女产后月经恢复时间早于汉族妇女 ($HR=1.132$, 95% $CI=1.069\sim1.198$)。结论 我国妇女产后平均月经恢复时间约 6 个月, 年龄、产次、纯母乳喂养、采取避孕措施、民族是产后月经恢复的影响因素。

【关键词】 产后; 月经恢复; 影响因素

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Timing and determinants of resumption of postpartum menstruation in Chinese women: a cross-sectional study in 15 provinces

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【 Abstract 】 Objective To investigate the timing and determinants of postpartum menstruation in Chinese women of child-bearing age. **Methods** This study was conducted at 60 hospitals in 15 provinces in China. Around 300 postpartum women who gave a birth between July 2015 to June 2016 were randomly selected and investigated at each participating hospital. Information on resumption of postpartum menstruation, breastfeeding, subsequent pregnancy after childbirth, contraceptive use, etc. were collected by telephone interviews during July and December 2017. SPSS21.0 software was used in data analysis. Arithmetical mean and life table were used to calculate the average timing of resumption of postpartum menstruation and probabilities of the return to postpartum menses within one year after childbirth. A 2 level Cox regression model was used to identify determinants of resumption of postpartum menstruation. **Results** Among the 17 813 postpartum women who were investigated in this study, 98.18% (17 488/17 813) reported return of menses after childbirth. The timing between childbirth and return of menses was (6.13±3.87) months. The cumulative probabilities of resumption of postpartum menstruation at 3, 6, 7 and 12 months after childbirth were 17.88%, 47.68%, 62.95% and 88.45%, respectively. Results of Cox regression analysis showed that resumption of postpartum menstruation in the 25-29, 30-34 and 35-39 age groups of women was later than that of those under 24-year old ($HR=0.944$, 95% $CI=0.895-0.995$; $HR=0.896$, 95% $CI=0.847-0.949$; $HR=0.904$, 95% $CI=0.844-0.968$). Postpartum women who had 3 births or more, exclusive breastfeeding and no use of contraception after childbirth were associated significantly longer timing of the first postpartum menstruation ($HR=0.896$, 95% $CI=0.817-0.981$; $HR=0.564$, 95% $CI=0.537-0.593$; $HR=0.676$, 95% $CI=0.643-0.711$). The Han nationality was significantly more likely to have a longer timing of resumption of postpartum menstruation than their counterparts ($HR=1.132$, 95% $CI=1.069-1.198$). **Conclusion** The average timing of resumption of postpartum menstruation in Chinese women is about 6 months. Age, parity, exclusive breastfeeding, contraceptive use and nationality are significantly associated with resumption of postpartum menstruation.

【Key words】 Postpartum ; Resumption of menstruation ; Determinants

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·个案报道·

重复宫颈、阴道穹窿部息肉样子宫内膜异位症手术病例 1 例并文献复习

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【摘要】 目的 介绍重复宫颈、阴道穹窿部息肉样子宫内膜异位症手术病例 1 例。方法 分析 1 例发生于宫颈、阴道穹窿部的息肉样子宫内膜异位症的临床资料 , 并进行相关文献回顾。结果

患者因经期延长伴反复发现宫颈、阴道赘生物 3 年余入院，宫颈、宫颈-阴道穹窿部赘生物经病理诊断为息肉样子宫内膜异位症，诊断及及时、准确。结论 对于反复宫颈、阴道处赘生物生长及阴道反复流血的患者应注重妇科专科查体，必要时行病理活检以明确诊断，从而降低误诊、漏诊率。

【关键词】 子宫内膜异位症； 息肉样子宫内膜异位症； 诊断

A case report of a repeated operation of polypoid endometriosis in the cervix and vaginal canal and a review of the literature

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【Abstract】 Objective To report a rare case of repeated operation of polypoid endometriosis (PEM) in the cervix and vaginal canal. **Methods** The clinical materials of a case that PEM occurred in the cervix and vaginal canal was retrospectively analyzed and related literature review was conducted. **Results** The patient was admitted to the hospital for prolonged menstruation with repeated discovery of cervical and vaginal neoplasm for more than 3 years. The diagnosis of cervical and cervix-vaginal neoplasm was pathologically diagnosed as PEM. The diagnosis was timely and accurate. **Conclusion** For patients with repeated cervix, vaginal neoplasm growth and repeated vaginal bleeding should be paid attention to gynecological specialist examination, if necessary, pathological biopsy was used to confirm the diagnosis, and to reduce the rate of misdiagnosis and missed diagnosis.

【Key words】 Endometriosis ; Polypoid endometriosis ; Diagnosis

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·个案报道·

基于二代测序胚胎植入前遗传学检测在三方重排复杂染色体易位携带者助孕中的应用

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【摘要】 目的 讨论基于二代测序 (NGS) 的胚胎植入前遗传学检测(PGT)在三方重排复杂染色体易位携带者助孕中的应用。 **方法** 应用卵胞质内单精子显微注射、单细胞基因扩增、NGS 等方法对 2 例三方重排复杂染色体易位携带者夫妇行 PGT 助孕。 **结果** 2 对夫妇中男方均为三方重排复杂染色体易位，共进行了 3 个 PGT 周期。例 1 夫妇获卵 10 枚，第 3 日(D3)胚胎共 4 枚，第

5/6 日(D5/6)形成了 3 枚囊胚，活检 2 枚囊胚，经过 NGS 检测，诊断异常的胚胎 1 枚，诊断正常/平衡的胚胎 1 枚，解冻移植后未临床妊娠。例 2 夫妇进行了 2 个周期 PGT，第 1 周期获卵 11 枚，D3 胚胎共 6 枚，D5/6 形成了 5 枚囊胚，活检囊胚 4 枚，第 2 周期获卵 14 枚，D3 胚胎共 6 枚，D5/6 形成了 3 枚囊胚，活检囊胚 3 枚，经过 NGS 检测，第 1 周期 4 枚胚胎诊断异常，第 2 周期 1 枚胚胎诊断异常，诊断正常/平衡的胚胎 2 枚，解冻移植 1 枚囊胚后临床妊娠成功。于孕 16 周羊水穿刺 G 显带提示为 46,XN, t(8,13,10)(q21;q31;p15)，孕 40 周活产一健康男婴。结论 虽然复杂染色体重排携带者夫妇正常胚胎的概率很低，但 NGS-PGT 是其降低流产率、获得有血缘关系的后代的重要方法。

【关键词】 复杂染色体重排； 胚胎植入前遗传学检测； 生殖技术，辅助

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Application of preimplantation genetic testing based on next generation sequencing in three-way complex chromosome rearrangements for assisting reproduction

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【Abstract】 Objective To detect the availability of the preimplantation genetic testing (PGT) based on next generation sequencing (NGS) in three-way complex chromosome rearrangements for assisting reproduction. **Methods** Two couples with three-way complex chromosome rearrangements were treated by intracytoplasmic sperm injection, single-cell gene amplification, NGS for assisting reproduction. **Results** The male partners were the three-way complex chromosome rearrangements carriers, and a total of 3 PGT cycles were performed. In case 1, 10 oocytes were obtained in the only PGT cycle and 4 embryos were formed on day 3. And 3 blastocysts were formed on day 5/6, and 2 blastocysts were suitable for biopsy. After NGS, 1 blastocyst was diagnosed as abnormal, and 1 blastocyst was diagnosed as normal/balanced, which was used in frozen-thawed embryo transfer. The outcome was unpregnancy. In case 2, 25 oocytes were obtained in two PGT cycles and 8 embryos were formed on day 3. And 8 blastocysts were formed in day 5/6, and 7 blastocysts were suitable for biopsy. After NGS, all of 4 blastocysts were diagnosed as abnormal in the first cycle, and 1 blastocyst was diagnosed as abnormal, and 2 blastocysts were diagnosed as normal/balanced in the second cycle. One of the 2 normal/balanced blastocysts was used in frozen-thawed embryo transfer. Fortunately, the outcome was clinical pregnant. The prenatal diagnosis that used G-band and SNP array analysis at 16 weeks of pregnancy showed 46,XN, and a healthy baby was born at full-term normal delivery. **Conclusion** Although the probability of normal embryos in couples with CCRs is very low, PGT based on NGS is an important method to reduce the miscarriage rate and obtain related offspring.

【Key words】 Complex chromosome rearrangements ; Preimplantation genetic testing ; Reproductive technique, assisted

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· 综 述 ·

多囊卵巢综合征对子代发育影响的研究进展

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【摘要】 多囊卵巢综合征 (polycystic ovary syndrome , PCOS) 是育龄期女性最常见的生殖内分泌疾病, 其特征表现为稀发排卵、高雄激素血症、卵巢多囊样改变。近年来越来越多的研究证实, PCOS 影响子代生长发育以及代谢、神经精神、生殖等系统的发育。现对国内外最新发表文献进行综述, 研究 PCOS 对子代发育的影响, 以期对 PCOS 的治疗和 PCOS 母婴的健康提供理论依据。

【关键词】 多囊卵巢综合征; 子代; 发育

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Research progress on the effect of polycystic ovarian syndrome on the development of the offspring

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【Abstract】 Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder in women of reproductive age. PCOS is characterized by the presence of oligoovulation or anovulation (OA), hyperandrogenism (HA) and polycystic ovary morphology. More and more studies show that PCOS affects the offspring's development in growth, metabolic, nervous and reproductive system. This paper collects recent published papers to review the effect of PCOS on the offspring's development and provide a theoretical basis for the treatment of PCOS.

【Key words】 Polycystic ovary syndrome ; Offspring ; Development

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· 综 述 ·

高通量遗传检测技术在早发性卵巢功能不全遗传学病因研究中的应用

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【摘要】 早发性卵巢功能不全(premature ovarian insufficiency, POI)是一类临床较常见的严重危害女性生殖健康的疾病,其病因复杂,遗传因素被认为是其重要致病因素之一。随着高通量遗传检测技术的应用,POI的遗传学病因鉴定迎来新的契机和挑战。染色体微阵列芯片分析(chromosome microarray analysis,CMA)用于鉴别基因组拷贝数变异(copy number variation,CNV)和POI的关系。全基因组关联研究(genome-wide association studies, GWAS)用于POI的遗传致病或易感位点的鉴定。目前CMA和GWAS在POI中的研究相对较少、样本量小,没有发现明确高度相关的、可重复的CNV或遗传易感位点。全外显子组测序(whole exome sequencing,WES)对于鉴定POI新致病基因具有独特优势。靶向二代测序(targeted next generation sequencing,targeted NGS)通过捕获多个靶向基因(panel)制备文库,可以同时已知POI致病基因进行快速、高通量的筛查,具有更高临床应用价值,有望提高POI基因诊断率。本文就高通量遗传检测技术在POI病因研究中的应用进行综述。

【关键词】 高通量核苷酸测序; 微阵列分析; 全基因组关联研究; 全外显子组测序; 早发性卵巢功能不全

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Application of high-throughput genetic technology in genetic etiology of premature ovarian insufficiency

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【Abstract】 Premature ovarian insufficiency (POI) is a common disease that seriously endangers women's reproductive health. Its etiology is complex, and genetic factors are considered as one of its important pathogenic factors. With the application of high-throughput genetic testing technology, the genetic etiology of POI will face new opportunities and challenges. Chromosomal microarray analysis (CMA) is used to identify the relationship between genomic copy number variation (CNV) and POI. Genome wide association studies (GWAS) are used for the identification of genetic pathogenic or susceptible sites of POI. Up to date, no highly correlated, reproducible CNV and genetic susceptibility loci have been found in POI by the technology of CMA and GWAS, due to few studies and small sample size. Whole exome sequencing (WES) has unique advantages for identifying

novel pathogenic genes of POI. Targeted next generation sequencing (targeted NGS) allows for rapid, high-throughput screening of known POI-causing genes by capturing multiple targeted genes. So, it is expected to be valuable to improve the genetic diagnostic rate of POI. This article reviews the application of high-throughput genetic testing in the study of POI etiology.

【Key words】 High-throughput nucleotide sequencing ; Microarray analysis ; Genome-wide association study ; Whole exome sequencing ; Premature ovarian insufficiency

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· 综 述 ·

端粒和端粒酶在生殖领域的研究进展

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【摘要】 端粒是染色体末端的 DNA-蛋白质复合物, 端粒的长度决定了细胞的寿命; 端粒酶是具有延长端粒长度的逆转录酶。外周血白细胞及人类生殖系细胞中都有端粒及端粒酶活性的表达。研究显示端粒及端粒酶活性与胚胎发育异常及不孕不育有关, 明确端粒、端粒酶与不孕不育的关系可为一些疾病的治疗带来指导意义。本文就端粒及端粒酶在生殖领域研究进展方面作一综述。

【关键词】 端粒; 端粒酶; 人类生殖系细胞; 外周血白细胞; 不孕不育

Application of telomere and telomerase in reproduction

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【Abstract】 Telomeres are DNA-protein complexes at the ends of chromosomes. Telomerase is a reverse transcriptase that can prolong the length of telomeres. Telomere and telomerase activity are found to be expressed in peripheral blood leukocytes and human germline cells. Moreover, they have been found to be associated with infertility related diseases and abnormal embryonic development. It is of guiding significance to clarify the relationship between telomerase and infertility for the treatment of some diseases. We reviewed the research progress of telomeres and telomerase in the field of human reproduction.

【Key words】 Telomere ; Telomerase ; Human germ cells ; Peripheral blood cells ; Infertility