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单基因病胚胎着床前遗传学检测专家共识

中国医师协会生殖医学专业委员会,中国医师协会医学遗传医师分会

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【摘要】 随着分子生物学技术、遗传诊断技术的发展以及相关术语的更新,单基因病胚胎着床前遗传学检测(preimplantation genetic testing for monogenic/single gene disorders, PGT-M)技术不断进步和更新,广泛应用于临床以避免遗传病患儿的出生和阻断致病基因的家族传递。目前,关于PGT-M的共识还很少,为了规范PGT-M的应用,中国医师协会生殖医学专业委员会精准辅助生殖研究学组及中国医师协会医学遗传医师分会部分专家,包括生殖医学、遗传学和心血管医学专家,共同制定了这一共识。共识包括PGT-M的适应证、禁忌证、诊断策略、遗传和生殖咨询、报告形式、结果解释、知情同意和患者随访等。这一共识将使更多相关的临床工作者和研究人员获益,供临床及实验室参考使用。

【关键词】 着床前遗传学检测; 单基因病; 专家共识

基金项目:国家重点研发计划(2018YFC1003104、2019YFA0801400、2018YFC1004000)

A Chinese experts' consensus on preimplantation genetic testing for monogenic disorders

Professional Committee on Reproductive Medicine, Chinese Medical Doctor Association;
The Society of Medical Geneticists, Chinese Medical Doctor Association

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【Abstract】 Upon the recent advances in molecular biological techniques and genetic diagnostic strategies, along with the updates on relevant terminologies, new methods of preimplantation genetic testing for monogenic/single gene disorders (PGT-M) are developed to prevent transmissions of inherited diseases. However, few

consensuses on PGT-M have been published. In order to properly regulate the application of PGT-M, experts from the field of reproductive medicine and genetics jointly drafted this consensus, which includes indications for patient selection, diagnostic strategy, genetic and reproductive counseling, report generation, result interpretation, informed consent and patient follow-ups, etc. This consensus serves to benefit everyone interested in PGT-M in establishing evidence-based clinical and laboratory practices.

【Key words】 Preimplantation genetic testing; Monogenic disorders; Expert consensus

Fund program: National Key Research and Development Program (2018YFC1003104, 2019YFA0801400, 2018YFC1004000)

·特约专论·

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“5G+区块链”赋能植入前遗传学检测技术用于罕见病的精准防控

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【摘要】 罕见遗传病作为出生缺陷的重要组成, 是我国乃至全球所面临的严峻挑战。联合诊断单基因病和染色体病非整倍体高通量测序与连锁分析 (mutated allele revealed by sequencing with aneuploidy and linkage analyses,

MARSALA)新策略下,以下一代测序(next generation sequencing, NGS)为核心技术的胚胎植入前遗传学检测(preimplantation genetic testing, PGT)作为一种经济且有效的一级防控措施在阻断罕见遗传病的发生上发挥重要作用。随着第五代移动通信技术(5th generation mobile networks, 5G)商业化时代的到来,5G结合区块链技术给PGT精准控制罕见遗传病带来了新的发展方向。本文总结目前PGT技术用于控制罕见病的发展现状,基于5G和区块链技术,提出建设基于“5G+区块链”的基因诊断云服务平台、远程协同诊疗平台、中国人群基因组突变数据库的设想,试图把握5G时代红利使我国罕见遗传病的精准防控走在国际前沿水平。

【关键词】 第五代移动通信技术; 区块链; 胚胎植入前遗传学检测; 防控; 遗传; 罕见病; 下一代测序

"5G + Blockchain"—enabled preimplantation genetic testing for precise prevention and control of rare disease

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【Abstract】 Based on next generation sequencing, preimplantation genetic testing (PGT), with novel strategy of mutated allele revealed by sequencing with aneuploidy and linkage analyses (MARSALA) is an economic and effective primary measure to control rare diseases by helping patients to select embryo free of monogenic diseases and aneuploidy (chromosome abnormality). With the commercialization of 5th generation mobile networks (5G) technology, "5G+blockchain" has brought a new development trend to PGT in the field of accurately control rare diseases. Therefore, in the present study, we summarize the current status of PGT and the characteristics of 5G and blockchain, then propose a plan to build a genetic diagnosis cloud service platform, a collaborative diagnosis and treatment platform for rare diseases, and a gene mutation database of Chinese population genetic disease, based on technology of 5G and blockchain in order to grasp the bonus of 5G era and promote the development of prevention and control of rare disease.

【Key words】 5th generation mobile networks; Blockchain; Preimplantation genetic testing; Prevention and control; Heredity; Rare disease; Next generation sequencing

·临床研究·

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卵泡期长效长方案改善子宫内膜异位症患者 IVF/ICSI 的临床结局

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【摘要】 目的 探讨卵泡期长效长方案在子宫内膜异位症患者体外受精 (*in vitro* fertilization, IVF) / 卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI) 助孕过程中的作用。方法 回顾性队列研究分析 2015 年 7 月 1 日至 2019 年 6 月 30 日期间在青岛大学附属烟台毓璜顶医院生殖医学中心第一次行 IVF/ICSI 助孕的 383 例子宫内膜异位症患者的临床资料。根据促排卵方案将患者分为卵泡期长效方案组 (A 组)、长方案组 (B 组) 和拮抗剂方案组 (C 组), 采用单因素分析和多因素 logistic 回归分析比较各组患者的临床结局。结果 A 组与 B 组和 C 组相比, 促性腺激素 (gonadotropin, Gn) 启动日和人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 注射日的血清促黄体生成素 (luteinizing hormone, LH) 水平 [0.64 (0.35, 0.99) IU/L 比 1.78 (1.42, 2.05) IU/L 比 5.00 (3.63, 6.46) IU/L; 0.89 (0.37, 1.33) IU/L 比 2.48 (1.76, 3.25) IU/L 比 2.46 (1.66, 3.67) IU/L] 和雌二醇水平 [6.70 (5.00, 16.90) μ g/L 比 7.93 (6.50, 7.93) μ g/L 比 34.05 (22.99, 45.58) μ g/L; 1.82 (1.11, 2.75) μ g/L 比 2.97 (2.16, 4.24) μ g/L 比 2.03 (1.49, 2.96) μ g/L] 显著降低 (P 均 <0.001); Gn 使用总量 [2700 (2250, 3200) IU 比 1875 (1575, 2250) IU 比 1800 (1425, 2250) IU] 和 Gn 使用时间 [11 (9, 13) d、9 (8, 10) d 和 8 (8, 9) d] 显著增加 (P 均 <0.001); 临床妊娠率 [76.53% (75/98)、61.39% (62/101) 和 54.39% (31/57), $P=0.010$]、胚胎种植率 [54.10% (99/183)、42.63% (81/190) 和 40.19% (43/107), $P=0.029$] 和活产率 [66.33% (65/98)、53.47% (54/101) 和 47.37% (27/57), $P=0.046$] 显著提高。结论 与长方案和拮抗剂方案相比, 卵泡期长效长方案能改善子宫内膜异位症患者 IVF/ICSI 的临床结局。

【关键词】 子宫内膜异位症; 受精, 体外; 长效促性腺激素释放激素激动剂; 临床妊娠率

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Follicular phase long-acting gonadotropin-releasing hormone agonist long protocol could improve IVF/ICSI outcomes of patients with endometriosis

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【Abstract】 Objective To investigate the effect of follicular phase long-acting gonadotropin-releasing hormone (GnRH) agonist long protocol on *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcomes of patients with endometriosis (EMS). **Methods** This retrospective cohort study was carried out from July 1st 2015 to June 30th 2019 and enrolled 383 young patients with EMS who underwent the first IVF/ICSI. According to the controlled ovarian hyperstimulation protocols, patients were classified into three groups: follicular phase long-acting GnRH agonist long protocol group (group A), short-acting GnRH agonist long protocol group (group B) and GnRH antagonist protocol group (group C). The clinical outcomes of IVF/ICSI were compared among the groups by using univariate and multivariate logistic regression analyses. **Results** The patients with EMS in group A had significantly higher duration of stimulation and total dosage of gonadotrophin (Gn) used [11 (9,13) d, 2700 (2250, 3200) IU] than those in group B and group C [9 (8,10) d, 1875 (1575, 2250) IU; 8 (8,9) d, 1800 (1425, 2250) IU] (all $P<0.001$). Serum levels of luteinizing hormone (LH) [0.64 (0.35, 0.99) IU/L vs. 1.78 (1.42, 2.05) IU/L vs. 5.00 (3.63, 6.46) IU/L; 0.89 (0.37, 1.33) IU/L vs. 2.48 (1.76, 3.25) IU/L vs. 2.46 (1.66, 3.67) IU/L] and estradiol [6.70 (5.00,16.90) $\mu\text{g/L}$ vs. 7.93 (6.50, 7.93) $\mu\text{g/L}$ vs. 34.05 (22.99, 45.58) $\mu\text{g/L}$; 1.82 (1.11, 2.75) $\mu\text{g/L}$ vs. 2.97 (2.16,4.24) $\mu\text{g/L}$ vs. 2.03 (1.49, 2.96) $\mu\text{g/L}$] on Gn initiation day and human chorionic gonadotropin (hCG) injection day were significantly lower in group A (all $P<0.001$). Group A had significantly higher clinical pregnancy rate [76.53% (75/98)], implantation rate [54.10% (99/183)] and live birth rate [66.33% (65/98)] compared with those in group B and group C [61.39% (62/101) and 54.39% (31/57), $P=0.010$; 42.63% (81/190), and 40.19% (43/107), $P=0.029$; 53.47% (54/101), and 47.37% (27/57), $P=0.046$]. **Conclusion** Follicular phase long-acting GnRH agonist protocol could improve IVF/ICSI outcomes of patients with EMS compared with short-acting GnRH agonist long protocol and GnRH antagonist protocol.

【 Key words 】 Endometriosis; Fertilization *in vitro*; Long-acting gonadotropin-releasing hormone agonist; Clinical pregnancy rate

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单胚胎移植周期临床结局的影响因素分析

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【摘要】 目的 探讨影响体外受精-胚胎移植 (*in vitro* fertilization-embryo transfer, IVF-ET) 中单胚胎移植 (single embryo transfer, SET) 妊娠结局的因素。方法 回顾性队列分析南方医科大学南方医院妇产科生殖医学中心 2013 年 9 月 1 日至 2019 年 12 月 31 日期间行 SET 共 2734 个周期的患者资料, 根据胚胎移植时机的不同, 分为第 3 日 (day 3, D3) 移植组 (D3 组)、第 4 日 (day 4, D4) 移植组 (D4 组)、第 5 日 (day 5, D5) 移植组 (D5 组)、第 6 日 (day 6, D6) 移植组 (D6 组)。分析对比患者不同年龄段、不同移植时机、不同胚胎评分的 SET 临床妊娠情况。结果 SET 周期总临床妊娠率为 39.8% (1098/2734), 总活产率为 30.5% (842/2734)。D3 组、D4 组、D5 组、D6 组的临床妊娠率分别为 33.3% (264/793)、36.4% (142/390)、52.5% (492/937)、32.6% (200/614), 活产率为 25.6% (203/793)、30.5% (119/390)、40.9% (383/937)、22.3% (137/614), 组间比较差异均有统计学意义 (P 均 <0.001)。D3 组形态学评分 8-细胞 I 级、7-细胞 I 级、8-细胞 II 级的胚胎总临床妊娠率 [41.7% (207/496)] 和总活产率 [32.1% (159/496)] 均高于其他非优质卵裂期胚胎 [19.2% (57/297), $P<0.001$; 14.8% (441/297), $P<0.001$]; D4 组发生融合 (融合期及早期囊胚) 的胚胎的临床妊娠率 [40.4% (134/332)] 和活产率 [34.0% (113/332)] 均高于未发生融合的胚胎 [13.8% (8/58), $P<0.001$; 10.3% (113/332), $P=0.001$]; 对于发育缓慢的囊胚, 将其培养至 D6 囊胚移植和在 D5 移植 2 期囊胚的临床妊娠率 [32.6% (200/614) 比 30.6% (22/72)] 和活产率 [22.3% (137/614) 比 27.8% (20/72)] 相比差异均无统计学意义 (P 均 >0.05)。结论 选择 D5 优质囊胚和 D4 融合期以上的桑椹胚进行单胚胎移植能在获得最佳妊娠结局的同时降低多胎妊娠发生率; 对于整体 D5 发育缓慢的胚胎, 继续培养至 D6 完全扩张囊胚再行移植, 可能是一种改善妊娠结局的策略; 对于卵裂期胚胎, 采用 8-细胞 I 级、7-细胞 I 级和 8-细胞 II 级的优质胚胎移植标准更能确保 D3 单胚胎移植的成功率, 获得满意的妊娠结局。

【关键词】 受精，体外； 单胚胎移植； 胚胎质量； 卵裂期胚胎； 桑椹胚； 囊胚

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Factors influencing clinical pregnancy outcomes after single embryo transfer

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【 Abstract 】 Objective To analyze the factors influencing clinical pregnancy outcomes after single embryo transfer (SET) undergoing *in vitro* fertilization-embryo transfer (IVF-ET) treatment cycles. **Methods** A retrospective cohort analysis was carried out on SET cycles of Center for Reproductive Medicine in Nanfang Hospital from September 1st, 2013 to December 31st, 2019. Totally 2734 SET cycles were assigned to day 3 (D3) group, day 4 (D4) group, day 5 (D5) group, day 6 (D6) group according to the different stages of embryo development and analyzed for the relation of clinical pregnancy outcomes to ages, different embryo stages and quality. **Results** The total clinical pregnancy rate (CPR) was 39.8% (1098/2734) and the live birth rate (LBR) was 30.5% (842/2734) in the 2761 SET cycles. The significant differences were observed among four groups in CPR [D3 group, D4 group, D5 group and D6 group: 33.3% (264/793), 36.4% (142/390), 52.5% (492/937) and 32.6% (200/614), respectively, $P<0.001$] and LBR [24.8% (203/793), 30.5% (119/390), 40.9% (383/937) and 22.3% (137/614), respectively, $P<0.001$]. In D3 group, significantly higher CPR and LBR were observed after transfer of top-quality cleavage embryos (8-cell I, 7-cell I, 8-cell II) than those in other cleavage embryos [CPR: 41.7% (207/496) vs. 19.2% (57/297), $P<0.001$; LBR: 32.1% (159/496) vs. 14.8% (441/297), $P<0.001$]. In D4 group, significantly higher CPR and LBR were observed after transfer of embryo with entirely compaction than partial compaction [CPR: 40.4% (134/332) vs. 13.8% (8/58), $P<0.001$; LBR: 34.0% (113/332) vs. 10.3% (113/332), $P=0.001$]. In slow-growing blastocysts group, fresh transfer of embryos which began blastulation but did not reach Gardner stage III by D5 resulted in similar outcomes to the transfer of fully expanded blastocysts by D6 [CPR: 30.6% (22/72) vs. 32.6% (200/614), $P>0.05$; LBR: 27.8% (20/72) vs. 22.3% (137/614), $P>0.05$]. **Conclusion** SET of a top-quality D5 blastocyst or D4 morula can reduce the incidence of multiple pregnancies and obtain the best pregnancy

outcome. For slow-growing D5 blastocysts, it may be a strategy to improve pregnancy outcome to continue culture until D6 fully expanded blastocysts and then perform subsequent frozen-thawed embryo transfer. For cleavage embryo, SET of top-quality cleavage embryos (8-cell I, 7-cell I, 8-cell II) also achieved satisfactory pregnancy outcome.

【Key words】 Fertilization *in vitro*; Single embryo transfer; Embryo quality; Cleavage embryo; Morula; Blastocyst

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子宫内膜异位症患者异位内膜组织中差异表达 microRNA 的筛选

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【摘要】 目的 探讨微小 RNA (microRNA, miRNA) 在子宫内膜异位症 (endometriosis, EMS) 患者异位内膜组织中的表达特征。方法 收集 2018 年 4 月至 2019 年 10 月期间于厦门大学附属第一医院妇产科就诊 EMS 患者异位内膜组织和对照组在位内膜组织开展实验。利用 Illumina 平台的 miRNA 测序检测内膜组织中 miRNA 的表达情况。通过生物信息学分析差异表达的 miRNAs 及其潜在靶基因在 EMS 发生、发展中的作用。结合文献挑选 6 个具有显著差异的 miRNAs (miR-98-5p、let-7c-5p、miR-495-3p、miR-200b-3p、miR-200c-3p、miR-148b-3p), 应用实时荧光定量逆转录聚合酶链反应 (quantitative real-time

polymerase chain reaction, qRT-PCR) 进行验证, 并在构建 miRNA-基因调控网络后初步验证其潜在靶基因。结果 测序结果显示, 相比对照组, EMS 患者异位内膜组织中有 69 个 miRNAs 出现差异表达 (差异倍数 >1.5 , $P<0.05$), 其中表达上调 22 个, 表达下调 47 个。基因本体分析显示, 差异表达的 miRNAs 所调控的靶基因在生物学过程中集中在与蛋白质修饰、发育调控、细胞代谢和形态结构等相关。KEGG pathway 分析显示, 靶基因富集于蛋白质功能、自噬、AGE-RAGE 及 MAPK 信号通路中。qRT-PCR 结果显示 miR-98-5p、let-7c-5p、miR-200b-3p、miR-200c-3p 的表达情况与测序结果一致。miRNA-基因共表达网络显示 miRNAs 与所预测的靶基因间的相互关系。miRNAs 潜在靶基因的 qRT-PCR 验证结果显示, miR-200b-3p、miR-200c-3p 与 *ZEB2* 呈负相关, miR-98-5p 与 *PGRMC1* 呈负相关, miR-98-5p、let-7c-5p 与 *ADIPOR2* 呈正相关。结论 miR-98-5p、let-7c-5p、miR-200b-3p 和 miR-200c-3p 在 EMS 患者异位内膜组织中存在显著差异表达, 可能参与 EMS 的发生、发展。

【关键词】 子宫内位异位症; 微小 RNA; 异位内膜; 在位内膜; 差异表达

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Screening for differentially expressed microRNAs in ectopic endometrial tissue of endometriosis patients

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【Abstract】 **Objective** To investigate the microRNA (miRNA) expression features in ectopic endometrial tissues of endometriosis (EMS) patients. **Methods** From April 2018 to October 2019, ectopic endometrial tissues from EMS patients and eutopic endometrial tissues from control women who received treatment in the Department of Obstetrics and Gynecology of The First Affiliated Hospital of Xiamen University were used in subsequent experiments. Differentially expressed miRNAs were screened out in ectopic endometrial tissues by detecting miRNA sequence from Illumina. The potential roles of these differentially expressed miRNAs and their potential targeted genes in pathogenesis of EMS were analyzed by bioinformatics, and the differential expression levels of 6 miRNAs (miR-98-5p, miR-495-3p, let-7c-5p, miR-200b-3p, miR-200c-3p, miR-148b-3p) were validated by quantitative real-time polymerase chain reaction (qRT-PCR) and subsequently used to build the miRNA-gene regulatory network, then we verified its potential target gene. **Results** The microarray results showed that 69 miRNAs might be differentially expressed in ectopic endometrial tissues compared with those in eutopic endometrial tissues (fold change >1.5 , $P<0.05$), including 22 up-regulated miRNAs and 47 down-

regulated miRNAs. Gene ontology (GO) analysis showed that the target genes of these differentially expressed miRNAs mainly participated in the protein modification, regulation of development, cell metabolism and morphological structure. KEGG pathway analysis showed that these targeted genes were involved in protein function, autophagy, AGE-RAGE and MAPK signaling pathways. The expression levels of miR-98-5p, let-7c-5p, miR-200b-3p and miR-200c-3p were validated to be significantly altered in ectopic endometrial tissues. The miRNA-gene co-expression network revealed the correlation between the 4 miRNAs and their predicted target genes. qRT-PCR validated results showed that the expression of miR-200b-3p and miR-200c-3p were significantly negatively correlated with *ZEB2*, while miR-98-5p was negatively correlated with *PGRMC1*, miR-98-5p and let-7c-5p were positively correlated with *ADIPOR2*. **Conclusion** MiR-98-5p, let-7c-5p, miR-200b-3p and miR-200c-3p were significantly differentially expressed in the ectopic endometrial tissues of EMS patients, which may be involved in the development of EMS.

【 Key words 】 Endometriosis; MicroRNA; Ectopic endometrial tissue; Eutopic endometrial tissue; Differential expression

Fund program: National Nature Science Foundation of China (81701419, 81871145); Natural Science Foundation of Fujian Province (2019J01566); The Key Medical and Health Program of Xiamen (3502Z20209001)

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胚胎形态学参数与整倍体状态的相关性分析

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【摘要】 目的 研究胚胎植入前遗传学检测 (preimplantation genetic testing, PGT) 周期中, 卵裂期 (第 3 日) 胚胎质量、囊胚活检时间、囊胚扩张程度、囊胚内细胞团(inner cell mass, ICM)评分及囊胚滋养层(trophectoderm, TE) 评分对其整倍体状态的影响。方法 回顾性病例对照分析郑州大学第三附属医院生殖医学科 2017 年 1 月至 2019 年 10 月期间 255 个行 PGT 助孕周期的患者临床资料, 分析囊胚相关形态学参数与整倍体状态的相关性。结果 ①977 枚囊胚进行活检, 共 937 枚囊胚成功获得染色体结果 (95.9%), 其中整倍体 396 枚 (42.3%), 非整倍体 541 枚 (57.7%)。②在夫妻双方有染色体异常的周期中, 633 枚囊胚整倍体率与女方年龄未呈现明显相关趋势, 无染色体异常的周期中 304 枚囊胚整倍体率随着女方年龄的增加呈显著下降趋势 ($P=0.0001$)。③校正女方年龄及不同周期的影响后, 第 6 日、第 7 日活检囊胚整倍体率显著低于第 5 日活检囊胚 ($OR=0.7$, 95% $CI=0.5\sim0.9$, $P=0.0091$; $OR=0.4$, 95% $CI=0.1\sim0.6$, $P=0.0012$); ICM 级别为 B 的活检囊胚整倍体率显著低于级别为 A 的囊胚 ($OR=0.4$, 95% $CI=0.3\sim0.7$, $P=0.0001$); TE 级别为 C 的活检囊胚整倍体率显著低于级别为 A 的囊胚 ($OR=0.4$, 95% $CI=0.2\sim0.7$, $P=0.0004$)。但囊胚扩张程度及已经形成囊胚后第 3 日胚胎质量对囊胚整倍体率无显著影响。结论 形成囊胚后第 3 日胚胎质量、囊胚扩张程度与囊胚整倍体状态无关, 活检时间、ICM 级别及 TE 级别与整倍体状态显著相关。

【关键词】 囊胚; 整倍体; 胚胎植入前遗传学检测; 活检时间

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Association between morphological parameters and ploidy status of the blastocysts

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【Abstract】 Objective To investigate the correlation between the human Day 3 embryo quality, blastocyst biopsy time, degree of expansion of the blastocysts, inner cell mass (ICM) morphology, trophectoderm (TE) morphology and their ploidy status. **Methods** This was a retrospective case-control study for patients who underwent *in vitro* fertilization with preimplantation genetic testing (PGT) at the Reproductive Medicine Center of the Third Affiliated Hospital of Zhengzhou University from January 2017 to October 2019. A total of 977 blastocysts were biopsied in 255 cycles of PGT, and the correlation between relevant morphological parameters and euploidy rate was analyzed. **Results** 1) A total of 977 blastocysts from 255 cycles were biopsied, and 937 blastocysts (95.9%) successfully obtained chromosome results, including 396 (42.3%) euploidy and 541 (57.7%) aneuploidy. 2) There was no significant correlation between the euploidy rate of blastocysts and the maternal age in the preimplantation genetic testing for chromosomal structural rearrangements (PGT-SR) cycles (633 blastocysts), while in the preimplantation

genetic testing for aneuploidy (PGT-A) cycles (304 blastocysts) the euploidy rate of blastocysts showed a significant downward trend with the increase of the maternal age ($P=0.000\ 1$). 3) The euploidy rate of blastocysts biopsy on day 6 and day 7 was significantly lower than that on the day 5 ($OR=0.7$, 95% $CI=0.5-0.9$, $P=0.009\ 1$; $OR=0.4$, 95% $CI=0.1-0.6$, $P=0.001\ 2$), the euploidy rate of the blastocysts with ICM grade B was significantly lower than that of the blastocysts with ICM grade A ($OR=0.4$, 95% $CI=0.3-0.7$, $P=0.000\ 1$), the rate of euploidy of the blastocysts with TE grade C was significantly lower than that with TE grade A ($OR=0.4$, 95% $CI=0.2-0.7$, $P=0.000\ 4$) adjusting for maternal age and cycle difference, while day 3 embryo quality, degree of expansion of the blastocysts were not associated with blastocysts ploidy.

Conclusion Day 3 embryo quality and expansion of the blastocysts have no correlation with euploidy, while the blastocyst biopsy time, ICM morphology, TE morphology are significantly correlated with their ploidy status.

【Key words】 Blastocysts; Euploid; Preimplantation genetic testing; Biopsy time

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小鼠不同阶段卵泡同步分离方法的初步建立及评估

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【摘要】 目的 建立并评估同步分离卵巢内不同发育阶段卵泡的方法——酶消化后滤网过滤法。方法 运用混合有胶原酶 I 和脱氧核糖核酸酶 I 的消化酶来消化小鼠卵巢预切组织，然后依次通过不同孔径（100 μm 、40 μm 、20 μm ）的滤网以实现不同发育阶段卵泡同步分离的目的，将翻转冲洗 100 μm 滤网得到的卵泡记为 A 组（>100 μm ），翻转冲洗 40 μm 滤网得到的卵泡记为 B 组（40~100 μm ），翻转冲洗 20 μm 滤网得到的卵泡记为 C 组（20~40 μm ）。评估并比较经不同孔径滤网筛选获得的卵泡群的数量、大小、形态、活力和发育潜能。结果 数量上，C 组获得的卵泡数目最多，A 组次之，B 组最少；形态上，C 组卵泡基底膜完整率高于 A 组和 B 组（ $P<0.001$ ， $P<0.001$ ）。活力上，A 组卵泡的存活率 70.59%（120/170）高于 B 组 51.79%（58/112）和 C 组 35.90%（28/78）（ $P=0.0016$ ， $P<0.001$ ）。发育潜能上，经过 96 h 体外培养，A 组卵泡直径由（113.64 \pm 9.57） μm 增长至（150.95 \pm 45.90） μm （ $P=0.0024$ ），B 组卵泡直径由（88.12 \pm 9.12） μm 增长至（120.61 \pm 18.00） μm （ $P<0.001$ ），C 组卵泡在培养第 24 h 内出现单层颗粒细胞贴壁，卵母细胞与颗粒细胞之间失去连接结构，卵母细胞完全裸露，未能培养成功。结论 酶消化后多重滤网过滤法能快速有效获得大量形态完整、有活力和发育潜能良好的卵泡，且能达到不同发育阶段卵泡同步分离的目的。

【关键词】 小鼠； 卵泡； 过滤； 活力； 体外培养； 同步分离

基金项目：国家自然科学基金（81701460）；浙江省医药卫生科技计划（2019KY033、2020KY414、2020KY448）

Preliminary establishment and evaluation of a method for synchronized isolation of mouse follicles across different developmental stages

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【Abstract】 Objective To establish and evaluate a follicle isolation method, combination of enzymatically digestion with strainer filtration, for synchronously collecting mouse follicles across different developmental stages. **Methods** Pre-cutted ovarian tissue blocks were digested with enzymes mixed by Collagenase I and DNase I, and then filtered through three different pore size cell strainers to synchronously separate the follicles at developmental stages. The follicles obtained by turning over and washing the 100 μm strainer were recorded as group A (>100 μm), as same as the follicles obtained by turning over and washing the 40 μm strainer were recorded as group B (40–100 μm), and the follicles obtained by turning over and washing the 20 μm strainer were recorded as group C (20–40 μm). The quantity, morphology, viability and developmental potency were examined among these harvested follicles. **Results** In terms of quantity, follicles in group C accounted for most, followed by follicles in group A, and the follicles in group B were the least. Morphologically, the basal membrane integrity rate of follicles in group C was higher than that of groups B and A ($P<0.001$ and $P<0.001$, respectively). As for viability, the survival rate of follicles in group A was 70.59% (120/170), which was higher than that in group B (51.79%, 58/112) and group C (35.90%, 28/78)

($P=0.0016$ and $P<0.001$, respectively). In terms of developmental potency, after 96 h of *in vitro* culture, the diameter of follicles in group A increased from $(113.64\pm 9.57)\mu\text{m}$ to $(150.95\pm 45.90)\mu\text{m}$ ($P=0.0024$), and the diameter of follicles in group B increased from $(88.12\pm 9.12)\mu\text{m}$ to $(120.61\pm 18.00)\mu\text{m}$ ($P<0.001$). In group C, monolayer-layer granulosa cells were attached to the follicles within 24 h of culture, and the connection structure between oocytes and granulosa cells was lost. The oocytes were completely exposed and failed to be cultured successfully. **Conclusion** Combining enzymatically digestion with multiple strainers filtration is a rapid and effective method for follicle collecting, which is capable to isolate different developmental stage mouse follicles synchronously with morphological integrity, favorable viability and good developmental potency.

【 Key words 】 Mice; Follicle; Filtration; Viability; Culture *in vitro*; Synchronized isolation

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辅助生殖技术助孕女性稽留流产绒毛组织各型染色体异常发生率的研究

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【摘要】 目的 研究辅助生殖技术 (assisted reproductive technology, ART) 与自然妊娠 (natural conception, NC) 受孕稽留流产患者绒毛组织各型

染色体异常发生率及分类情况。方法 采用回顾性队列研究,共收集 2016 年 1 月至 2020 年 1 月期间在郑州大学第三附属医院生殖中心就诊的 637 例稽留流产患者的绒毛组织,根据受孕方式将患者分为 ART 组和 NC 组,再根据采用不同的 ART 助孕方式进一步将 ART 组分为夫精人工授精(artificial insemination by husband, AIH)、体外授精(*in vitro* fertilization, IVF)、卵胞质内单精子显微注射(intracytoplasmic sperm injection, ICSI)三组。通过高通量测序(next generation sequencing, NGS)技术检测稽留流产患者绒毛组织的染色体拷贝数变异(copy number variations, CNVs)和染色体数目的异常。结果 637 例稽留流产患者的绒毛组织染色体检测结果中,染色体 CNVs 和数目正常的绒毛组织占样本总例数的 45.2%(288/637),染色体 CNVs 和数目异常的绒毛组织占样本总例数的 54.8%(349/637)。其中 CNVs 占比 3.8%(14/637),染色体数目异常占比 52.5%(335/637)。ART 组与 NC 组绒毛组织染色体异常率分别为 59.2%(226/382)、51.0%(130/255),差异无统计学意义($P>0.05$);其中 AIH 组、IVF 组、ICSI 组绒毛组织染色体异常率分别为 52.1%(25/48)、58.9%(146/248)、64.0%(55/86),与 NC 组相比,IVF 组和 ICSI 组绒毛组织染色体异常有升高趋势,四组间两两比较差异均无统计学意义($P>0.008$)。结论 总体 ART 助孕不增加女性稽留流产绒毛组织染色体异常的发生率,但 IVF/ICSI 助孕较自然受孕及 AIH 助孕,稽留流产绒毛染色体异常率有增高趋势。

【关键词】 生殖技术,辅助; 稽留流产; 绒毛染色体; 非整倍体; 染色体拷贝数变异

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The incidence of chromosomal abnormalities in the villus tissue of women with missed abortion by assisted reproductive technology

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【Abstract】 **Objective** To study the incidence and classification of chromosomal abnormalities in villi of missed abortion patients with assisted reproductive technology (ART) and natural conception (NC). **Methods** Totally 637 patients with missed abortion villi from the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University during January 2016 and January 2020 were collected and divided into ART group and NC group according to the mode of pregnancy in this retrospective cohort study. The ART group was further divided into artificial insemination by husband (AIH), *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Next generation sequencing (NGS) was used to detect the copy number variations (CNVs) and chromosome number abnormalities of chorionic villi of missed abortion. **Results** Among 637 missed abortion chorionic villi, 45.2% (288/637) of the samples had normal chromosome and 54.8% (349/637) had abnormal chromosome. CNVs accounted for 3.8%

(14/637) of the total samples, and chromosome number abnormalities accounted for 52.5% (335/637) of the total samples. The abnormal rates of villi chromosome in ART group and NC group were 59.2% (226/382) and 51.0% (130/255), respectively, and there was no significant difference between ART group and NC group ($P>0.05$). The abnormal rates of villus chromosome in AIH group, IVF group and ICSI group were 52.1% (25/48), 58.9% (146/248) and 64.0% (55/86), respectively. Compared with NC group, the abnormal rate of villus chromosome in IVF group and ICSI group was increased, but there was no significant difference ($P>0.008$). **Conclusion** In general, ART did not increase the incidence of chromosomal abnormalities in missed abortion villi. However, compared with natural pregnancy and AIH assisted pregnancy, IVF/ICSI had a higher chromosomal abnormality in missed abortion villi.

【Key words】 Reproductive technology, assisted; Missed abortion; Villus chromosome; Aneuploidy; Copy number variations

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宫腔粘连患者生殖预后影响因素分析

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【摘要】 目的 探讨宫腔粘连患者生殖预后影响因素。方法 本研究为前瞻性队列研究, 选择 2017 年 1 月至 2018 年 2 月期间就诊于重庆市妇幼保健院的宫腔粘连患者 178 例, 分别统计患者病史 (年龄、病程、有无不孕史及复发性流产史、术前宫腔操作次数、术前月经类型、术前增殖晚期子宫内膜厚度)、宫腔形态学指标 (包括输卵管开口是否可见、粘连范围、粘连性质)、二探宫腔恢复情况,

并与术后妊娠进行单因素及多因素分析。结果 术后妊娠率为 59.6%(106/178), 活产率为 45.5% (81/178), 宫腔恢复有效率为 88.8% (158/178)。不同病程 ($P=0.007$)、粘连性质 ($P=0.001$)、粘连范围 ($P=0.001$)、二探宫腔恢复情况 ($P=0.037$) 的妊娠率差异均具有统计学意义。多因素 logistic 回归分析结果显示, 病程、粘连性质是影响宫腔粘连患者术后妊娠的独立危险因素 ($P=0.012$, $P=0.003$)。结论 病程、粘连性质与宫腔粘连患者的生殖结局密切相关。

【关键词】 宫腔粘连; 妊娠率; 生殖预后; 影响因素

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Analysis of influencing factors for reproductive outcome of the patients with intrauterine adhesions

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【Abstract】 Objective To analyze the influencing factors for reproductive outcome of the patients with intrauterine adhesions (IUA). **Methods** Totally 178 cases were selected as the subjects in prospective cohort study from those diagnosed with IUA and underwent surgery in Chongqing Health Center for Women and Children from January 2017 to February 2018. The relationships of pregnancy with medical history (including age, course of disease, past history of infertility and recurrent abortion, operation times of uterine cavity, preoperative menstruation, endometrial thickness), morphological index of uterine cavity (including opening of oviduct, adhesion range, adhesion properties) and recovery of uterine cavity were analyzed. **Results** The overall pregnancy rate was 59.6% (106/178), the live birth rate was 45.5% (81/178), and the effective rate of uterine cavity recovery was 88.8% (158/178). There were statistical differences in the pregnancy rate of different courses of disease ($P=0.007$), adhesion properties ($P=0.001$), adhesion range ($P=0.001$) and the recovery of uterine cavity ($P=0.037$). The logistic statistics showed that course of disease and adhesion properties were independent factors ($P=0.012, P=0.003$). **Conclusion** The course of disease and adhesion properties were independent factors which influence reproductive outcome of the patients with IUA.

【Key words】 Intrauterine adhesion; Pregnancy rate; Reproductive outcome; Influencing factor

Fund program: Foundation of the Science and Technology Commission of Yuzhong District, Chongqing City (20180134)

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早期卵巢交界性肿瘤患者行保留生育功能手术的临床分析

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【摘要】 目的 探讨早期 (FIGO I 期) 卵巢交界性肿瘤患者行保留生育功能手术对生育和预后的影响。方法 回顾性分析 2009 年 10 月至 2019 年 10 月期间在南方医科大学附属衡阳医院和铜仁市人民医院行保留生育功能手术的 FIGO I 期卵巢交界性肿瘤患者的临床资料, 并随访至 2020 年 3 月, 记录其生存及妊娠情况。结果 本研究共纳入 30 例卵巢交界性肿瘤患者 (Ia 期 18 例, Ic 期 12 例)。30 例患者中, 病理类型浆液性 18 例, 黏液性 10 例, 子宫内膜样 2 例。中位随访时间 42 个月, 3 例 (10.0%) 患者出现复发。随访结束时, 所有患者均无瘤生存。计划妊娠 22 例, 13 例 (59.1%) 自然妊娠并成功分娩, 子代健康无畸形。结论 对年轻有强烈生育要求的早期卵巢交界性肿瘤患者行保留生育功能手术可能是安全而可行的。

【关键词】 卵巢交界性肿瘤; 手术; 预后

Clinical analysis of fertility-sparing surgery for patients with early-stage borderline ovarian tumor

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【Abstract】 Objective To evaluate the effects of fertility-sparing surgery on fertility and prognosis in patients with early-stage (stage FIGO I) borderline ovarian tumor. **Methods** The clinical files of patients who were diagnosed with stage FIGO I borderline ovarian tumor and underwent fertility-sparing surgery

from October 2009 to October 2019 at Affiliated Hengyang Hospital of Southern Medical University and Tongren People's Hospital were retrospectively analyzed. The patients were followed up to March 2020 to record their survival and pregnancy. **Results** A total of 30 patients with borderline ovarian tumor were included in this study (18 cases were stage I a, 12 cases were stage I c). The pathological diagnoses of the tumors were serous in 18, mucinous in 10 and endometrioid in 2. The median follow-up time was 42 months, and 3 patients (10.0%) experienced recurrence. At the end of the follow-up, all the patients were survival without tumor. There were 22 planned pregnancies and 13 (59.1%) spontaneous pregnancies with successful delivery. The offspring were healthy without deformity. **Conclusion** For the patients with stage FIGO I borderline ovarian tumor who want to retain fertility, fertility-sparing surgery may be safe and feasible.

【Key words】 Borderline ovarian tumor; Surgery; Prognosis

·现场调查·

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四川地区 850 例自体精液保存患者 支原体感染现状及药敏分析

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【摘要】 目的 分析自体精液保存患者支原体感染现状及其药敏试验,为临床合理用药提供参考。方法 采用横断面调查研究,分析自 2013 年 11 月至 2020 年 3 月期间于四川大学华西第二医院人类精子库进行自体精液保存的 850 例患者的临床资料,分析其支原体感染情况及药敏试验。据患者年龄将患者分为 13~20 岁、21~30 岁、31~40 岁、41~50 岁和>50 岁 5 个年龄段,比较其支原体感染情况;据患者婚姻状况将患者分为已婚及未婚,比较其支原体感染情况。结果 ①自体精液保存患者支原体感染例数为 167 例,阳性率 19.65%。各年龄段支原体阳性率差异有显著统计学意义($P=0.001$),其中以>50 岁阳性率最高[35.29%(6/17)],其次为 31~40 岁年龄段[26.23%(80/307)],支原体感染率最低的年龄段为 13~20 岁[2.86%(2/70)];已婚人群的支原体感染率[23.51%(91/387)]明显高于未婚人群[16.41%(76/463)]($P=0.009$)。②167 名支原体阳性患者药敏试验结果显示,对交沙霉素敏感性最高,其次为罗红霉素、阿奇霉素、强力霉素及克拉霉素;对环丙沙星耐药性最高,其次为司帕沙星、左氧氟沙星及氧氟沙星。支原体药敏试验结果提示,对喹诺酮类抗菌药耐药性最强,且不同年份间喹诺酮类抗菌药耐药性差异有统计学意义($P=0.001$)。结论 自体精液保存患者支原体感染率较高,已婚患者及育龄期患者支原体感染率较高。建议支原体感染阳性患者进行自体精液保存前应治疗,转阴后再进行精子冻存,临床治疗时应根据药敏试验选择相应的抗生素,避免产生耐药反应。

【关键词】 支原体感染; 药敏分析; 自体精液保存

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Mycoplasma and ureaplasma infection and drug sensitivity analysis on 850 sperm cryopreservation patients in Sichuan area

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【Abstract】 Objective To analyze the mycoplasma and ureaplasma infection and drug sensitivity analysis on sperm cryopreservation patients in Sichuan area, in order to provide reference for clinical rational use of the drug. **Methods** A cross-sectional study was conducted from November 2013 to March 2020, 850 patients who came to human sperm bank of West China Second University Hospital, Sichuan University for sperm cryopreservation participated in this study. Sensitivity analysis of the mycoplasma and ureaplasma were performed. All the patients were classified into 5 groups to compare the mycoplasma and ureaplasma statuses according to the age: 13–20 years old, 21–30 years old, 31–40 years old, 41–50 years old, >50 years old; according to the marital status of the patients, the patients were divided into married and unmarried to compare the mycoplasma and

ureaplasma infection. **Results** 1) There were 167 cases of the mycoplasma and ureaplasma infection in sperm cryopreservation patients, the positive rate was 19.65%. The positive rate of mycoplasma and ureaplasma infection in all age groups had a significant difference ($P<0.001$), among which the group of >50 years old had the highest positive rate [35.29% (6/17)], followed by 31–40 years old group [26.23% (80/307)], and the 13–20 years old group had the lowest positive rate of mycoplasma and ureaplasma infection [2.86% (2/70)]. The mycoplasma and ureaplasma infection rate of married people [23.51% (91/387)] was significantly higher than that of unmarried people [16.41% (76/463)] ($P=0.009$). 2) The antimicrobial susceptibility test (AST) in 167 mycoplasma and ureaplasma-positive patients showed that the most sensitive drugs for mycoplasma and ureaplasma were josamycin, followed by roxithromycin, azithromycin, doxycycline and clarithromycin; the most resistance drugs for mycoplasma and ureaplasma were ciprofloxacin, followed by sparfloxacin, levofloxacin and oxygen ofloxacin. AST showed that the most resistance drugs for mycoplasma and ureaplasma were quinolone antimicrobials, and there was significant differences in the resistance of quinolone antimicrobials in different years ($P=0.001$). **Conclusion** The mycoplasma and ureaplasma infection rate of sperm cryopreservation patient was at a high level, married patients and reproductive-age patients had a higher rate of mycoplasma and ureaplasma infection. It is recommended that patients with positive mycoplasma and ureaplasma infection should be treated before self-sperm preservation, and the semen should be frozen after mycoplasma and ureaplasma infection become negative. During clinical treatment, antibiotics should be selected according to drug sensitivity experiments to avoid drug resistance.

【 Key words 】 Mycoplasma and ureaplasma infections; Antimicrobial susceptibility test; Sperm cryopreservation

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·综述·

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干细胞在早发性卵巢功能不全中的应用

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【摘要】 早发性卵巢功能不全是当今不孕症的重要病因之一, 且发病率呈逐年上升趋势。其病因多种, 大部分为特发性, 临床上尚无根治办法, 严重影响了女性及其家庭的生活质量。干细胞具有自我更新、多向分化的特征, 是再生医学领域的种子细胞, 为早发性卵巢功能不全的治疗提供了新思路。本文将干细胞在临床前实验研究和临床试验中的研究成果, 及近年来兴起的通过体外诱导多能干细胞(induced pluripotent stem cell, iPSC)分化形成卵母细胞的研究进展作一综述。

【关键词】 早发性卵巢功能不全; 干细胞; 配子形成

Application of stem cells in premature ovarian insufficiency

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【Abstract】 Premature ovarian insufficiency (POI) is the major cause of infertility with increasing morbidity currently. It is a heterogeneous disorder of multiple etiologies and there is presently no proven cure, which impairs the life quality of female and their families. Stem cells, with the self-renewing and multi-direction differentiation abilities, are the seed cells in regenerative medicine and provide novel and promising therapy for POI. Here, we summarize the progress of preclinical researches, clinical trials and the emerging trend to induce differentiation of stem cells into oocytes.

【Key words】 Premature ovarian insufficiency; Stem cells; Gametogenesis

·综述·

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泛素-蛋白酶体系统在精子发生及受精过程中的作用

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【摘要】 泛素-蛋白酶体系统（ubiquitin-proteasome system, UPS）是真核细胞内除自噬-溶酶体外的另一种蛋白质降解系统。UPS 可以清除错误折叠的蛋白，减少因错误折叠蛋白堆积而导致的衰老疾病发生。UPS 选择性的蛋白质降解和调节功能作用于精原细胞的有丝分裂、减数分裂和精子细胞的变形过程，在精子发生中扮演重要角色。另外，精子的获能、顶体反应、透明带穿透、受精后精子线粒体的消除等重要生殖过程也与 UPS 紧密相关。本文就近年来 UPS 在精子发生和受精过程中的作用及其与不孕症关系研究进行文献综述。

【关键词】 泛素-蛋白酶体系统；泛素化；精子发生；受精；不孕症
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Role of ubiquitin-proteasome system in spermatogenesis and fertilization

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【Abstract】 The ubiquitin-proteasome system (UPS) is a protein degradation system in addition to lysosomal system in eukaryotic cells. UPS can eliminate misfolded proteins and reduce the occurrence of aging diseases caused by the accumulation of misfolded proteins. The selective protein degradation of UPS acts on the mitosis and meiosis process of spermatogonia, which is very important for spermatogenesis. In addition, important reproductive processes such as sperm capacitation, acrosome reaction, penetrating zona pellucida and elimination of sperm mitochondria after fertilization are also closely related to UPS. This article reviews the recent literatures on the role of UPS in spermatogenesis, fertilization and its relationship with infertility.

【 Key words 】 Ubiquitin-proteasome system; Ubiquitination; Spermatogenesis; Fertilization; Infertility

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网络药理学促进中药在生殖健康领域的应用

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【摘要】 网络药理学是以系统生物学理论为基础对生物系统进行网络分析, 选取特定信号节点开展多靶点药物分子设计、系统地阐述机体与药物相互作用的原理和规律的新兴学科。受生殖系统和中药本身固有特点的限制, 生殖相关疾病治疗过程的中药应用发展缓慢。网络药理学相关技术手段的引入, 有助于综合找寻潜在的疾病药物新靶点和相关信号通路, 也以更加系统和广泛的视角加深了对药物作用机制的了解, 在新药的探索和现有药物的再利用中具有极大的价值。本文就网络药理学促进中药在生殖相关疾病中的应用进行综述, 为促进中药研发提供参考。

【关键词】 中药; 网络药理学; 生殖健康; 药物研发

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Network pharmacology promotes the application of Traditional Chinese Medicine in the field of reproductive health

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【Abstract】 Network pharmacology is a new discipline which is based on the theory of system biology to analyze the network of biological systems, select specific signal nodes to carry out multi-target drug molecular design, and systematically elaborate the principle and law of the interaction between organism and drug. Limited by the inherent characteristics of the reproductive system and Traditional Chinese Medicine, the application of Traditional Chinese Medicine in the reproductive diseases develops slowly. The introduction of network pharmacology-related technologies helps to comprehensively search for potential new drug targets for diseases and related signaling pathways, and deepens the understanding of the mechanism of drug action from a more systematic and extensive perspective. It is of great value in the exploration of new drugs and the reuse of existing drugs. In this

paper, the application of network pharmacology in promoting Traditional Chinese Medicine in reproductive diseases is reviewed to provide reference for the research and development of Traditional Chinese Medicine.

【 Key words 】 Traditional Chinese Medicine; Network pharmacology; Reproductive health; Drug development

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