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本期责任编辑王黎茜 本期责任编辑宋培培 本期责任编辑宋培培

高龄女性不孕诊治指南

中国医师协会生殖医学专业委员会

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【摘要】 随着越来越多的育龄夫妇推迟其生育计划, 以及我国“二孩政策”全面放开, 高龄希望生育父母的比例逐渐增加。然而, 随着女性年龄增加, 卵巢功能逐渐下降, 且子宫肌瘤、瘢痕子宫、盆腔炎等发生率显著增加, 不孕症的发生率逐渐增加。高龄女性即使通过辅助生殖技术(ART)获得成功妊娠, 妊娠并发症风险和内、外科合并症的发生风险亦会随年龄增大而增加, 如流产、胎死宫内、低出生体质量、早产以及妊娠期糖尿病和高血压疾病等。对于高龄不孕患者的诊治策略目前尚缺乏一致性, 患者的诊疗疗效更是参差不齐。基于以上情况, 中国医师协会生殖医学专业委员会组织生殖内分泌及 ART 专家编写了本“高龄女性不孕诊治指南”, 希望本指南可以规范我国高龄不孕女性患者的诊治流程。本指南从高龄女性的生育状况、需要进行的相关生育力评估及指标解读以及高龄女性孕前身体和营养准备、咨询、相关妊娠风险评估等入手进行深入探讨, 分析了目前临床、实验室的热点问题: 高龄女性子代遗传学特征及评估、咨询以及相应的实验室筛查、诊断方法和操作规范。另外, 对于高龄女性妇产科及内外科合并症发生率高的状况, 针对不同合并症状况探讨了相应的诊疗规范。最后, 综合各方面情况制定了高龄女性不孕症的助孕策略, 为高龄不孕女性的诊治提供依据和指导。

【关键词】 高龄; 不孕症; 并发症; 助孕策略

基金项目: 国家卫生科研专项项目(201402004)

Guideline for diagnosis and treatment of infertility in advanced age women

Chinese Medical Doctor Association Reproductive Medicine Specialized Committee

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【Abstract】 As more and more couples postponing their childbearing plan, as well as China's two-child policy fully liberalized, the proportion of advanced age parents gradually increased. In addition, with the age in women, ovary function gradually descend and the incidence of uterine fibroids, scarred uterus and pelvic inflammation disease significantly increased, which increased the risk of infertility. Even advanced age women succeeded get pregnancy through assisted reproductive technology (ART), they also have increased risk of miscarriage, gestational diabetes, gestational hypertension, intrauterine fetal death, low birth weight of newborn, or premature birth. The strategy of diagnosis and treatment of elderly patients with infertility is still lack of uniformity. In the light of the above situation, the specialized committee organized experts of reproductive endocrinology and ART to compose this guideline, with the intent of standardizing the process of diagnosis and treatment of advanced aged infertile patients. This guideline interpreted reproductive status and related fertility evaluation of advanced age infertile women, and discussed pre-pregnancy body and nutrition preparation and consultation, and related risk assessment of pregnancy of these patients. It also analyzed current clinical and laboratory hot issues: the genetic characteristics and evaluation, counseling, and corresponding laboratory screening, diagnostic methods and operating norms of advanced age women. In addition, for elderly women with high incidence of internal and surgical medicine complications, this guideline gave us norms of diagnosis and treatment of different complications. Finally, strategies of treatment were provided for advanced age infertile women.

【Key words】 Advanced age; Infertility; Complication; Strategy of assisted reproductive technology (ART)

Fund program: Research Fund of National Health and Family Planning Commission of China (201402004)

供精人工授精 10 690 个周期妊娠结局的多因素分析

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【摘要】目的 分析探讨多种因素对供精人工授精(AID)妊娠结局的影响。**方法** 回顾性分析 2013 年 1 月-2015 年 12 月期间在本中心治疗的 10 690 个 AID 周期, 对女方年龄、不孕年限、治疗方案、输卵管通畅程度、子宫内膜厚度、每周期排卵数、每周期 AID 授精次数、精子冻融复苏后浓度、精子冻融复苏后活动率、精子冻融复苏后前向运动精子总数与术后妊娠结局进行 χ^2 和多因素 Logistic 回归分析。**结果** 年龄 ≤ 30 岁妇女的妊娠机会是年龄 >35 岁者的 1.934 倍($OR=1.934, P<0.001$)、年龄 31~35 岁妇女的妊娠机会是 >35 岁者的 1.511 倍($OR=1.511, P<0.001$), 自然周期妇女妊娠机会是促排卵周期者的 1.307 倍($OR=1.307, P<0.001$), 每周期 AID 授精 2 次的妇女妊娠机会是 1 次组的 1.486 倍($OR=1.486, P=0.001$), 每周期 AID 授精 3 次的妇女妊娠机会是 1 次组的 1.338 倍($OR=1.338, P=0.020$), 每周期排卵 2 个的妇女妊娠机会是排 1 个卵组的 1.362 倍($OR=1.362, P=0.001$), 每周期排卵 3 个的妇女妊娠机会是排卵 1 个组的 1.499 倍($OR=1.499, P=0.004$), 精子冻融复苏后活动率 $>60\%$ 的妇女妊娠机会是 $\leq 60\%$ 组的 1.211 倍($OR=1.211, P=0.038$), 精子冻融复苏后前向运动精子总数 $\geq 35 \times 10^6$ 的妇女妊娠机会是 $\leq 25 \times 10^6$ 组的 1.319 倍($OR=1.319, P=0.011$)。**结论** 女方年龄 ≤ 35 岁、每周期排卵 2~3 个、每周期 AID 授精 2~3 次、精子冻融复苏后活动率 $>60\%$ 和精子冻融复苏后前向运动精子总数 $\geq 35 \times 10^6$ 能提高授精妇女的妊娠几率; 在患者无明显排卵障碍的情况下, 应首选自然周期。

【关键词】 供精人工授精(AID); 妊娠; Logistic 回归

基金项目: 广东省人口和计划生育委员会项目(20132010); 广东省医学科研基金项目(A2014195)

· 临床研究 ·

Analysis of the clinical outcome of 10 690 artificial insemination cycles with donor sperma Zhang Qingjian, Song Ge, Zhong Xiaoying, Lu Yanhua, Zheng Weiwei, Zhu Xiaoli, Tan Yumei, Li Minru, Zhan Zehu, Zhang Zhijian
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【Abstract】Objective To analyze the effects of various factors on the clinical outcome of artificial insemination with donor sperm (AID). **Methods** A total of 10 690 AID cycles were analyzed between 2013 and 2015 in our center. The relationship between the clinical outcome and the factors, such as woman's age, duration of infertility, therapeutic regimen, fallopian tube patency, endometrial thickness, number of eggs ovulated per cycle, number of insemination per cycle, sperm concentration after thawing, sperm activity ratio after thawing and the total number of progressively motile sperm was analyzed by χ^2 and multiple factor Logistic regression. **Results** The pregnancy opportunity was 1.934 times of women who were younger than or equal to 30 years ($OR=1.934, P<0.001$) and 1.511 times of women aged 31–35 years ($OR=1.511, P<0.001$) as high as those who were older than 35 years. It was 1.307 times of women received the natural cycle as high as that of women received ovulation induction cycle ($OR=1.307, P<0.001$). It was 1.486 times of women received double inseminations per cycle ($OR=1.486, P=0.001$), and 1.338 times of women received three inseminations per cycle ($OR=1.338, P=0.020$) as high as that of women received one insemination per cycle. It was 1.362 times of women with 2 eggs ovulated per cycle ($OR=1.362, P=0.001$), and 1.499 times of women with 3 eggs ovulated per cycle ($OR=1.499, P=0.004$) as high as that of women with one egg ovulated per cycle. It was 1.211 times of women received sperm with sperm activity ratio more than 60% after thawing as high as that of women received sperm with sperm activity ratio less than or equal to 60% after thawing ($OR=1.211, P=0.038$). It was 1.319 times of women received the progressively motile sperm more than or equal to 35×10^6 after thawing as high as that of women received the progressively motile sperm less than or equal to 25×10^6 after thawing ($OR=1.319, P=0.011$). **Conclusion** Many factors such as woman's age less than or equal to 35 years, double or three inseminations per cycle, 2 or 3 eggs ovulated per cycle, sperm activity ratio more than 60% after thawing and the progressively motile sperm more than or equal to 35×10^6 after thawing can improve the pregnancy rate. In the case of patients with no obvious ovulation disorders, natural cycle should be preferred.

【Key words】 Artificial insemination with donor sperm (AID); Pregnancy; Logistic regression

Fund program: Program of Guangdong Provincial Population and Family Planning Commission (20132010); Program of Guangdong Provincial Medical Research Foundation (A2014195)

乙肝病毒携带对不同卵巢储备功能女性体外受精 - 胚胎移植结局的影响

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【摘要】目的 探讨乙肝病毒携带对不同卵巢储备功能女性进行体外受精 - 胚胎移植(IVF-ET)助孕胚胎发育及妊娠结局的影响。**方法** 回顾性分析接受 IVF-ET 助孕的 1 310 例不孕症患者资料, 按照血清抗苗勒管激素(AMH)水平, 分为三组: 卵巢储备低下组(A 组)AMH<2 $\mu\text{g/L}$, 正常卵巢储备组(B 组)AMH 2~7 $\mu\text{g/L}$, 卵巢高储备组(C 组)AMH>7 $\mu\text{g/L}$, 每组按 HBsAg 检测结果分为女方乙肝病毒携带组和正常对照组, 比较两组的正常受精率、卵裂率、优质胚胎率、着床率、临床妊娠率及流产率有无差异。**结果** A 组及 C 组中, 乙肝病毒携带组与正常对照组的正常受精率、卵裂率、优质胚胎率、着床率及临床妊娠率差异无统计学意义($P>0.05$), 但 A 组中乙肝病毒携带组的无可移植胚胎率(14.6%)高于正常对照组(5.9%)($P<0.05$); B 组中乙肝病毒携带组的正常受精率(69.8%)、卵裂率(96.97%)、优质胚胎率(21.8%)、着床率(31.3%)及临床妊娠率(44.1%)均低于正常对照组(73.6%, 98.6%, 26.2%, 41.3%, 59.8%)($P<0.05$), 差异有统计学意义。3 组中乙肝病毒携带组的流产率均高于正常对照组($P<0.05$), 差异有统计学意义。**结论** 乙肝病毒携带可能干扰了卵巢储备低下及正常卵巢储备女性的卵子质量及胚胎的发育, 最终影响妊娠结局。

【关键词】 乙型肝炎病毒; 卵巢储备; 体外受精 - 胚胎移植(IVF-ET)

基金项目: 福建省科技计划项目(2015D018)

Effects of hepatitis B virus infection in women with different ovarian reserve on outcomes of *in vitro* fertilization and embryo transfer Lin Jin, Sha Yanwei, Qiu Pingping, Zhang Ling, He Xuemei, Shi Yingying, Ye Yaping, Su Zhiying, Li Ping

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【Abstract】 Objective To investigate the effects of hepatitis B virus (HBV) in women with different ovarian reserve on outcomes of *in vitro* fertilization and embryo transfer (IVF-ET). **Methods** The clinical data of 1 310 patients were retrospectively analyzed, who were divided into three groups according to serum anti-Müllerian hormone (AMH) level: low ovarian reserve group (group A, AMH<2 μg/L), normal ovarian reserve group (group B, AMH 2–7 μg/L), high ovarian reserve group (group C, AMH>7 μg/L). Each group was divided into two groups: HBV carrier group and control group. The normal fertilization rate, the cleavage rate, the rate of good-quality embryos, the implantation rate, the clinical pregnancy rate and the abortion rate were compared. **Results** There was no significant difference between the HBV carrier group and control group in normal fertilization rate, the cleavage rate, the rate of good-quality embryos, the implantation rate and the clinical pregnancy rate ($P>0.05$). But in group A, the rate of no transferrable embryos of HBV carrier group was higher than that of control group with significant difference ($P<0.05$). In group B, the normal fertilization rate (69.8%), the cleavage rate (96.97%), the rate of good-quality embryos (21.8%), the implantation rate (31.3%), and the clinical pregnancy rate (44.1%) of HBV carrier group were all lower than those of control group (73.6%, 98.6%, 26.2%, 41.3%, 59.8%) with significant difference ($P<0.05$). In three groups, the abortion rate of HBV carrier group was all higher than that of control group with significant difference ($P<0.05$). **Conclusion** HBV carrier in women of low ovarian reserve and normal ovarian reserve group could affect the outcomes of IVF-ET treatment.

【Key words】 Hepatitis B virus; Ovarian reserve; *In vitro* fertilization and embryo transfer (IVF-ET)

Fund program: Fujian Science and Technology Project (2015D018)

超促排卵过程中抗苗勒管激素动态变化及其与临床结局的相关性

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【摘要】目的 探讨血清及卵泡液(follicular fluid, FF)中抗苗勒管激素(AMH)在控制性超促排卵(COH)过程中的动态变化及其与 COH 结局的相关性分析。**方法** 选取因输卵管因素和/或男方因素行体外受精/卵胞质内单精子注射-胚胎移植(IVF/ICSI-ET)的周期, 随机分为长方案组($n=38$)和非降调节组($n=38$)。长方案组和非降调节组分别于前一个月经周期第2或第3日(基础日)、降调节期间月经第2或第3日、促性腺激素(Gn)启动日、Gn启动第5日(Gn5)、诱发排卵日(hCG注射日)、取卵前1日和取卵后3d抽取外周静脉血。取卵日收集直径 ≥ 18 mm(大)、14~17 mm(中)、 <14 mm(小)的FF。**结果** 降调节后血清AMH水平在Gn启动日较基础日显著升高, 2种COH方案随外源性Gn使用时间的增加血清AMH降低; 随卵泡直径增大, FF中AMH降低。Gn5血清AMH与获卵数、M_{II}卵数和可利用胚胎数相关性最强, 中FF的AMH与窦卵泡数(AFC)、Gn用量和可利用胚胎相关性较好。**结论** 降调节显著升高AMH水平, 增加可募集AFC及改善卵泡发育同步化, 提示可依此调整Gn用量, 外源性Gn使用后AMH水平逐渐降低; Gn5血清AMH水平可预测IVF/ICSI-ET结局。

【关键词】 抗苗勒管激素(AMH); 非垂体降调节; 卵泡液; 控制性超促排卵(COH)

Anti-Müllerian hormone dynamics during controlled ovarian hyperstimulation and its correlation with clinical outcomes Wang Dongxue, Wu Xiaohua

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【Abstract】 Objective To evaluate the dynamics of anti-Müllerian hormone (AMH) of serum and follicular fluid (FF) during controlled ovarian hyperstimulation (COH) and to analyze the relationship between AMH and outcomes of COH. **Methods** A total of 76 eligible IVF/ICSI-ET cycles owing to the tubal or male factors were studied, which were randomly grouped into GnRH-a long protocol and non pituitary down regulation protocol. Serum AMH levels were measured at day 2/3 of previous menstrual cycle (baseline), day 2/3 of menstrual during down regulation, the day of Gn starting, day 5 of Gn stimulation (Gn5), day of hCG administration (dhCG), the day before oocyte retrieval and 3 d after oocyte retrieval. FF was grouped into huge (≥ 18 mm), middle (14-17 mm) and small (<14 mm) depending on diameters. **Results** Serum AMH level was significantly higher on the day of Gn starting compared with baseline after the GnRH-a. AMH was gradually decreased with exogenous Gn administration during COH. AMH in FF was gradually decreased with follicles' diameter increasing. There was the strongest correlation between AMH of Gn5 and number of retrieved oocytes, the number of M_{II} and embryos' conditions during COH. AMH in middle FF was significantly related with antral follicle count (AFC), Gn used dosage and number of available embryos. **Conclusions** AMH level is significantly elevated after pituitary down regulation, and this augments the number of recruited follicles and improves follicle synchronization. In addition, we can adjust Gn used dosage depending on AMH level of Gn starting. AMH is gradually decreased with exogenous Gn using. At Gn5 serum AMH level may be a better predictive marker of the outcomes of IVF.

【Key words】 Anti-Müllerian hormone (AMH); Non pituitary down regulation; Follicular fluid (FF); Controlled ovarian hyperstimulation (COH)

基于“治未病”思想观察中药补肾调冲方对卵巢早衰大鼠 2 种相关生长因子表达的影响

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【摘要】目的 探讨中药补肾调冲方对卵巢早衰(POF)大鼠的防治作用及通过调控血管内皮生长因子(VEGF)、碱性纤维母细胞生长因子(bFGF)的表达调节卵巢功能及预防机制。**方法** 随机选取 SD 雌性大鼠 60 只, 分别设空白、模型、中药低、中、高剂量组和西药组, 每组 10 只。空白组自由饮水; 模型组给予雷公藤多苷片造模 14 d; 中药组先给予低、中、高不同剂量补肾调冲中药 36 d, 再给予雷公藤多苷片造模 14 d; 西药组先给予结合雌激素 36 d, 再给予雷公藤多苷片造模 14 d。实验结束后观察大鼠的卵巢指数、子宫指数; 光学显微镜下计数各组大鼠卵巢内各级卵泡数目; ELISA 检测血清卵泡刺激素(FSH)、黄体生成素(LH)、雌二醇(E₂)、抗苗勒管激素(AMH)的水平; 免疫组织化学法检测 VEGF 及 bFGF 蛋白的表达; 实时荧光 PCR 法检测 *VEGF*、*bFGF* mRNA 的表达。**结果** 模型组大鼠卵巢指数、子宫指数明显低于空白组、各给药组($P<0.01$); 中药低剂量组卵巢指数与西药组比较有统计学差异($P<0.05$); 与模型组比较, 各给药组及空白组大鼠始基卵泡、窦前卵泡及窦状卵泡数目明显增多, 闭锁卵泡的数目明显减少($P<0.01$); 中药低剂量组与西药组比较大鼠始基卵泡、窦前卵泡及窦状卵泡数目明显减少, 闭锁卵泡的数目明显增多($P<0.05$); 与模型组比较, 各给药组及空白组血清 FSH、LH 水平明显降低($P<0.01$), 血清 E₂、AMH 水平明显升高($P<0.01$); 与模型组比较, 各给药组及空白组 VEGF、bFGF 蛋白及 mRNA 表达明显降低($P<0.01$), 中药低剂量组与西药组比较 bFGF 蛋白表达及 mRNA 明显降低($P<0.05$)。**结论** 中药补肾调冲方对卵巢具有一定的保护作用, 预防效果明显, 其作用机制可能与补肾调冲方中某些中药能够上调 VEGF、bFGF 的表达, 为卵泡发育提供基础, 复苏即将凋亡的卵泡, 增强卵巢功能有关。

【关键词】 中药补肾调冲方; 卵巢早衰(POF); 卵巢指数; 子宫指数; 卵泡; 血管内皮生长因子(VEGF); 碱性纤维母细胞生长因子(bFGF)

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· 实验研究 ·

Effect of Bushen Tiaochong Recipe on expression of two related growth factors in premature ovarian failure rats based on the theory of “treating disease without disease”

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【Abstract】Objective To investigate the preventive effect of traditional Chinese medicine Bushen Tiaochong Recipe in premature ovarian failure rats on the regulation of ovarian function and prevention mechanism through regulating the expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

Methods A total of 60 female rats were randomly selected to set up a blank, model and prevent the low-, medium- and high-dose groups and Western medicine group. Ten rats in each group. The rats in blank group were given free drinking water, and then given Tripterygium model for 14 d. Three Chinese medicine groups were given low-, medium- and high-dose Bushen Tiaochong Recipe for 36 d, and then given Tripterygium model for 14 d; Western medicine group was given estrogen for 36 d, then given tripterygium glycosides tablet for 14 d. The ovarian index and rat uterus index were observed after the end of the experiment; the number of the rats ovarian follicles was observed in light microscopy. Serum follicular stimulation hormone (FSH), luteinizing hormone (LH), estrogen (E₂), anti-Müllerian hormone (AMH) were detected by ELISA. Expressions of VEGF and bFGF protein were detected by immunohistochemistry; expressions of *VEGF* and *bFGF* mRNA were detected by real-time fluorescence PCR method.

Results The ovarian index and uterus index of rat were significantly lower than those in the control and the treatment group ($P < 0.01$). Ovarian indexes in low-dose Chinese medicine group and Western medicine group were significantly different ($P < 0.05$). Compared with the model group, the number of rat primordial follicles, preantral and antral follicles in each treatment group and blank control group increased significantly, while the number of atretic follicles significantly reduced ($P < 0.01$). The number of rat primordial follicles, preantral and antral follicle in low-dose Chinese medicine group and Western medicine group significantly reduced, while the number of atretic follicles increased significantly ($P < 0.05$). Compared with the model group, the levels of serum FSH and LH in each treatment group and blank control group decreased significantly ($P < 0.01$), while serum E₂ and AMH levels increased significantly ($P < 0.01$). Compared with the model group, VEGF and bFGF protein and mRNA expression in each treatment group and blank control group were significantly decreased ($P < 0.01$), the expressions of bFGF protein and mRNA in low-dose Chinese medicine group and Western medicine group were decreased significantly ($P < 0.05$). **Conclusion** Bushen Tiaochong Recipe has an obvious protective effect on ovary. Its mechanism may relate with some of the traditional Chinese medicine of Bushen Tiaochong Recipe which can increase the expression of VEGF and bFGF. Bushen Tiaochong Recipe can provide a basis for follicular development, the recovery of follicles before apoptosis and enhance the function of ovary.

【Key words】 Bushen Tiaochong Recipe; Premature ovarian failure (POF); Vascular endothelial growth factor (VEGF); Basic fibroblast growth factor (bFGF)

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· 实验研究 ·

一种高效分离原代人子宫内膜间质和上皮细胞的方法

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【摘要】目的 建立一种高效分离子宫内膜上皮细胞与间质细胞的方法。**方法** 收集全子宫切除患者的健康子宫内膜组织, 将子宫内膜组织剪碎后, 采用二次酶消化-二次过滤-差时贴壁的方法将人子宫内膜间质细胞(HUSC)与上皮细胞(HUEC)分离。采用流式细胞仪鉴定分离所得人子宫内膜基质和上皮细胞; 并进一步对原代子宫内膜间质细胞进行诱导蜕膜化。**结果** 流式细胞术检测分离的间质细胞波形蛋白阳性率为(97.0 ± 2.5)%, 上皮细胞角蛋白阳性率为(90.0 ± 4.1)%。此外, 使用环磷酸腺苷(cAMP)联合醋酸甲羟孕酮(MPA)体外诱导子宫内膜间质细胞产生了良好的蜕膜化反应。**结论** 成功建立了一种高效分离原代人子宫内膜基质和上皮细胞的方法。

【关键词】 人子宫内膜间质细胞; 人子宫内膜上皮细胞; 分离方法; 标志分子; 蜕膜化

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· 实验研究 ·

Method for efficiently separating primary human endometrial stromal and epithelial cells Lyu Fang, Wang Lili, Guo Yong, Gu Fengle, Li Xueli, Zhang Shucheng, He Bin, Wang Jiedong, Chen Fang, Zhang Xiaomei
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【Abstract】 Objective To establish an efficient method for isolating primary human endometrium stromal and epithelial cells *in vitro*. **Methods** Health endometrial tissue of hysterectomy patient was obtained, and was cut into a small piece. Firstly, the human endometrial stromal cells (HUSC) and human endometrial epithelial cells (HUEC) were isolated by the twice enzymatic digestion, twice separation and different adherent time of the two types of cells. And then HUSC and HUEC were identified and the percentage of vimentin (Vim)-positive and cytokeratin (CK)-positive ones were determined by flow cytometry. After that, primary HUSC were stimulated by cyclic adenosine monophosphate (cAMP)+medroxyprogesterone acetate (MPA) for 4 d and 7 d. **Results** The HUSC purity was $(97.0 \pm 2.5)\%$ and the HUEC purity was $(90.0 \pm 4.1)\%$ determined by flow cytometry, indicating that we had highly purified cultures of HUSC and HUEC *in vitro*. After cAMP+MPA induction for 4 d and 7 d, the HUSC showed more obvious changes in cell morphology and prolactin (PRL) level. **Conclusion** We successfully established an efficient method of isolation and characterization of primary human endometrium stromal and epithelial cells *in vitro*.

【Key words】 Human endometrium stromal cells; Human endometrium epithelial cells; Isolation method; Molecular markers; Decidualization

Fund program: The Ministry of Science and Technology Infrastructure Work Projects (2013FY110521); National Science Foundation of China (81601343); The Science Foundation of Yangzhou (1026110)

· 临床报道 ·

高龄非输卵管性不孕妇女不同助孕方案妊娠结局的比较

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【摘要】目的 为高龄非输卵管性不孕女性推荐更合理的助孕方案。方法 选择行宫腔内人工授精 (intrauterine insemination, IUI)和体外受精-胚胎移植(*in vitro* fertilization and embryo transfer, IVF-ET)的1312名高龄输卵管通畅不孕女性(年龄 ≥ 35 岁患者)共2094个周期进行回顾性分析,其中IUI组827个周期,IVF组启动周期1267个,移植周期798个。根据患者的年龄层次分为35~37岁,38~39岁和 ≥ 40 岁3组,回顾性分析各组的临床资料和助孕结局。结果 3个不同年龄层的IUI组临床妊娠率分别为10.78%、8.72%和4.14%,IVF-ET组的移植周期临床妊娠率分别为53.03%、47.51%和22.69%,IUI和IVF组内及组间各年龄层临床妊娠率比较,差异有统计学意义($P < 0.05$)。结论 随着患者年龄的增加,IUI和IVF两种助孕方案的临床妊娠率均明显降低,建议年龄 ≥ 40 岁输卵管通畅的不孕女性应积极行IVF治疗。

【关键词】 高龄妇女; 非输卵管性不孕; 宫腔内人工授精(IUI); 体外受精-胚胎移植(IVF-ET)

· 临床报道 ·

Comparison of pregnancy outcome of different assisted reproductive protocols for non-tubal infertility in women with advanced age

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【Abstract】 Objective To recommend a reasonable assisted reproductive protocol for non-tubal infertility women with advanced age. **Methods** A total of 2 094 cycles from 1 312 non-tubal infertility women who were 35 years old or older and performed intrauterine insemination/*in vitro* fertilization and embryo transfer (IUI/IVF) were included. The patients were divided into 2 groups: IUI group (827 cycles) and IVF group (1 267 initiating cycles and 798 embryo transfer cycles). They were further divided into three age subgroups according to their age: 35–37, 38–39, and ≥ 40 years old, then the clinical outcomes of each group were analyzed, retrospectively. **Results** The clinical pregnancy rates of three age levels in IUI group were 10.78%, 8.72%, 4.14%, respectively; and in IVF-ET group were 53.03%, 47.51%, 22.69%, respectively. There were statistical significances in the clinical pregnancy rates of the two groups in different age subgroups ($P < 0.05$). **Conclusion** With the increase of age, the clinical pregnancy rates of IUI and IVF were significantly decreased, which is more obvious in women over 40 years. So we suggest that when women who are older than 40 years old without tubal factor should be advised to try IVF treatment.

【Key words】 Advanced age women; Non-tubal infertility; Intrauterine insemination (IUI); *In vitro* fertilization and embryo transfer (IVF-ET)

新鲜胚胎与冻融胚胎移植后引起宫内外同时妊娠 69 例临床分析

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【摘要】目的 探讨辅助生殖技术(ART)引起宫内外同时妊娠(HP)的影响因素。**方法** 采用单因素及多因素 Logistic 回归分析的方法对经辅助生殖助孕治疗后发生 HP 的 69 例(新鲜胚胎移植 35 例, 冻融胚胎移植 34 例)患者的临床资料进行回顾性分析。**结果** 同期新鲜周期组临床妊娠 6 616 例, 其中 HP 患者 35 例(0.53%); 冻融周期组临床妊娠 3 516 例, 其中 HP 患者 34 例(0.97%), 冻融周期组中 HP 发生率与新鲜胚胎周期组比较, 差异有统计学意义($P=0.01$); HP 组与宫内双胎妊娠对照组和单纯异位妊娠对照组年龄、不孕年限、获卵数、Gn 用量、hCG 注射日的血清 E_2 值、孕酮值、内膜厚度、移植管距宫底距离、不孕类型之间比较, 差异均无统计学意义($P>0.05$)。HP 组中有宫腔操作史 46.37%(32/69), 高于宫内双胎妊娠的 26.25%(42/160), 差异有统计学意义($P<0.05$); HP 组中输卵管妊娠史有 39.13%(27/69), 高于宫内双胎妊娠的 23.12%(37/160), 差异有统计学意义($P<0.05$)。**结论** ART 中获卵数、Gn 用量、hCG 注射日的血清 E_2 值、孕酮值、内膜厚度、移植管距宫底距离、不孕类型对 HP 的发生影响不大, 既往有输卵管妊娠史、宫腔操作史及冻融周期中人工周期治疗方案与 HP 的发生有明显的相关性。

【关键词】 新鲜胚胎移植; 冻融胚胎移植(FET); 宫内外同时妊娠; 影响因素

· 临床报道 ·

Clinical analysis of 69 cases of heterotopic pregnancy induced by fresh embryo and frozen-thawed embryo transfer Li Yunjuan, Mo Yi, Liu Fengxia

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【Abstract】 Objective To explore the influence factors of the assisted reproductive technology (ART) on the heterotopic pregnancy (HP). **Methods** By using univariate and multivariate Logistic regression analysis, clinical data of 69 cases (35 cases of fresh embryo transfer, 34 cases of frozen-thawed embryo transfer) with HP after assisted reproductive treatment were retrospectively analyzed. **Results** In fresh embryo transfer group, there were 6 616 cases of clinical pregnancy, including 35 patients with HP (0.53%) and in frozen-thawed embryo transfer group, there were 3 516 cases of clinical pregnancy, including 34 patients with HP (0.97%). The incidence of HP was statistically different between the two groups ($P=0.01$). The age, duration of infertility, number of oocytes retrieved, Gn dosage, serum E₂ values and progesterone (P) level on hCG injection day, endometrial thickness, the distance of transplant tube from the bottom of the palace and types of infertility were not statistically significantly different between HP group and 2 control groups (intrauterine twin pregnancy group and pure ectopic pregnancy group)($P>0.05$). HP group has a history of uterine cavity operation in 46.37% (32/69), which was higher than that of intrauterine twin pregnancy (26.25%, 42/160), the difference was statistically significant ($P<0.05$). The patients with history of tubal pregnancy in HP group accounted for 39.13% (27/69), which was higher than that of intrauterine twin pregnancy (23.12%, 37/160), the difference was statistically significant ($P<0.05$). **Conclusion** In the ART, the number of oocytes retrieved, the dosage of Gn used, the E₂ and P values on the day of hCG injection, endometrial thickness, the distance of transplant tube from the bottom of the palace and the type of infertility had little effect on the occurrence of HP, there was a significant correlation between the history of tubal pregnancy, the history of uterine cavity operation and the treatment of artificial cycles during the freezing and thawing cycles and the occurrence of heterotopic pregnancy.

【Key words】 Fresh embryo transfer; Frozen-thawed embryo transfer (FET); Heterotopic pregnancy; Influence factors

体外受精 - 胚胎移植患者卵子捐赠知识和态度的调查分析

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【摘要】目的 调查分析体外受精 - 胚胎移植(IVF-ET)患者对卵子捐赠的知识和态度现状, 为赠、受孕工作提供理论依据。**方法** 采用便利抽样法, 抽取郑州市某三级甲等医院行 IVF-ET 治疗的不孕女性 500 例, 采用《体外受精 - 胚胎移植患者卵子捐赠知识和态度问卷》对其进行问卷调查。**结果** 卵子捐赠知识回答正确率不高, 只有 22.76%; 条目“并不是只要身体健康就可以进行卵子捐赠”回答正确率最高, 为 58.54%, 答对率最低的条目为“捐赠卵子会导致自身卵子数量不足而影响治疗”, 回答正确率仅为 4.47%; IVF-ET 患者对卵子捐赠态度得分为(24.4 ± 5.0)分, 处于较低水平, 其中, 卵子捐赠意愿部分得分最低, 为(7.9 ± 3.4)分。**结论** IVF-ET 患者缺乏对卵子捐赠知识的了解, 卵子捐赠态度也不积极, 应重视对 IVF-ET 患者卵子捐赠知识的宣传。

【关键词】 体外受精 - 胚胎移植(IVF-ET); 不孕症; 卵子捐赠; 知识; 态度

· 临床报道 ·

Investigation and analysis on knowledge and attitude of oocyte donation in patients of *in vitro* fertilization and embryo transfer Cai Libai, Liu Yanjin, Dong Yuezhi, Sun Yingpu

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【Abstract】 Objective To investigate the knowledge and attitude towards oocyte donation in patients of *in vitro* fertilization and embryo transfer (IVF-ET), and provide theoretical basis for oocyte donation.

Methods A convenience sample of 500 IVF-ET women in a tertiary hospital in Zhengzhou was investigated by the knowledge and attitude questionnaire of oocyte donation.

Results The accurate rate of oocyte donation knowledge was very low, only by 22.76%. And 58.54% of IVF-ET women got the right answer on the item of “physical health is not the only requirement of oocyte donation” with the highest accurate. The lowest accurate rate (4.47%) of the item was “The oocyte donation can reduce the quantity of the ova and affect the treatment of donors”.

Oocyte donation attitude score was 24.4 ± 5.0 which was relatively low. The lowest score of oocyte donation was the donation willingness only with 7.9 ± 3.4 . **Conclusion** The patients of IVF-ET were lack of the knowledge about understanding of oocyte donation, and the attitude towards oocyte donation was not positive either. It's necessary to provide information about the oocyte donation to patients of IVF-ET.

【Key words】 *In vitro* fertilization and embryo transfer (IVF-ET); Infertility; Oocyte donation-IVF; Knowledge; Attitude

依托孕烯单根皮下埋植剂(Implanon[®])的月经模式变化和 对痛经治疗的临床研究

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【摘要】目的 评估依托孕烯单根皮下埋植剂(Implanon[®])的避孕效果、月经模式的改变和对痛经的治疗效果。**方法** 以接受依托孕烯单根皮下埋植剂避孕的妇女 200 例为研究对象, 术后随访 24 个月, 分析其避孕效果, 痛经缓解程度, 不良反应和继用率。**结果** 术后 24 个月, 190 例受试者完成随访, 随访率 95%。随访期间, 无 1 例受试者意外怀孕, 避孕率 100%。另外, 61 例埋植前有痛经的受试者, 55 例埋植后痛经得到缓解, 缓解率为 90.2%。主要不良反应为月经模式改变 141 例(74.2%), 包括不规则阴道流血 60 例(31.6%)、闭经 6 例(3.2%), 经期延长 63 例(33.2%)、月经频发 41 例(21.6%); 月经稀发 20 例(10.5%)、经量减少 66 例(34.7%)、经量增加 10 例(5.3%)。其他不良反应还有体质量增加 32 例(16.8%), 痤疮 21 例(11.1%), 激素相关不良反应 63 例(33.2%)。随访期间, 16 例受试者, 包括阴道不规则流血(10 例)、闭经(6 例)提前取出植入剂, 继用率为 91.6%。**结论** 依托孕烯单根皮下埋植剂的避孕效果好, 有效缓解痛经程度, 安全可靠, 继用率高, 可在临床上推广应用。

【关键词】 依托孕烯; 避孕效果; 安全性; 继用率

Contraceptive and dysmenorrheal relief efficacy of single rod etonogestrel implant (Implanon®)

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【Abstract】 Objective To evaluate the contraceptive and dysmenorrheal relief efficacy, and safety of single rod Etonogestrel implant (Implanon®). **Methods** A total of 200 females who received single rod Etonogestrel implant for contraception were enrolled. The participants were followed up for 24 months to evaluate the contraceptive efficacy, relief rate of dysmenorrheal, side effects and continuation rate of Implanon®. **Results** A total of 190 participants finished the 24-month follow-up. During the period, the contraceptive efficacy was 100%, and the relief rate of dysmenorrheal was 90.2%(55/61). The major side effects were menstrual changes (141/190, 74.2%), including irregular bleeding (60/190, 31.6%), amenorrhea (6/190, 3.2%), prolonged bleeding (63/190, 33.2%), frequent bleeding (41/190, 21.6%), infrequent bleeding (20/190, 10.5%), decreased volume of bleeding (66/190, 34.7%), and increased volume of bleeding (10/190, 5.3%). Other side effects included gaining weight (32/190, 16.8%), acne (21/190, 11.1%), and hormone-associated side effects (63/190, 33.2%). During the follow-up, a total of 16 participants terminated implanon at an early stage, including 10 cases of irregular bleeding and 6 cases of amenorrhoea, yielding a continuation rate of 91.6%. **Conclusion** Single rod Etonogestrel implant (Implanon®) is effective and safe in contraception with relieved dysmenorrheal and a high continuation rate.

【Key words】 Etonogestrel; Contraception; Safety; Continuation rate

干细胞诱导分化为生殖细胞的研究进展

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【摘要】干细胞具有多系谱分化的可塑性,是再生医学的研究热点。通过各种调控、诱导手段从干细胞获得生殖细胞,为生殖细胞发生与发育障碍导致的不孕不育患者带来希望。本文将探讨从各种干细胞[胚胎干细胞(embryonic stem cells, ESCs)、诱导多能干细胞(induced pluripotent stem cells, iPSCs)、原始生殖细胞(primordial germ cells, PGCs)、精原干细胞(spermatogonial stem cells, SSCs)和卵巢干细胞(ovarian stem cells, OSCs)]获得生殖系细胞的研究进展并提出其临床应用前景与挑战。

【关键词】胚胎干细胞(ESCs); 诱导多能干细胞(iPSCs); 原始生殖细胞(PGCs); 精原干细胞(SSCs); 卵巢干细胞(OSCs)

· 综述 ·

Review on the differentiation of stem cells into germline cells Wang Xinxin, Wu Junwei, Guo Ruixia, Ma Shanshan, Meng Nan, Yang Bo, Guan Fangxia

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【Abstract】 Stem cells are a hotspot of regenerative medicine as they are plastic with multi-lineage differential potential. Regulating and inducing differentiation of stem cells into germline cells bring hope to infertile patients with dysfunction of generation and development of germ cells. Herein, we discuss the current researches on how to get germ cells from stem cells [embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), primordial germ cells (PGCs), spermatogonial stem cells (SSCs), and ovarian stem cells (OSCs)], as well as the prospects and challenges in clinical application.

【Key words】 Embryonic stem cells (ESCs); Induced pluripotent stem cells (iPSCs); Primordial germ cells (PGCs); Spermatogonial stem cells (SSCs); Ovarian stem cells (OSCs)

胞外囊泡在配子成熟中作用的研究进展

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【摘要】 细胞外囊泡(EVs)是细胞在激活或凋亡过程中释放的一种超微膜性囊泡, 可运载多种蛋白质、脂质、DNA 及 RNAs 等, 为细胞间通讯提供了一种新方式。越来越多的研究表明, EVs 通过不同机制在配子成熟过程中发挥重要作用。现就 EVs 在精子和卵子成熟过程中作用的研究进展做一综述。

【关键词】 细胞外囊泡(EVs); 精子成熟; 卵子成熟

· 综述 ·

Research progress on the role of extracellular vesicles in gamete maturation Liu Xiangbin, Liu Wei
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【Abstract】 Extracellular vesicles (EVs) are ultrastructural membraneous vesicles, released from activated or apoptic cells, that carry various proteins, lipids, DNAs and RNAs. EVs provide a bandy new way of cell-to-cell communication. More and more evidences have demonstrated that EVs may play important roles in various physiological and pathological processes including gamate maturation. This article reviews some of research progress and application prospect on function and mechanism of EVs in sperm and oocyte maturation.

【Key words】 Extracellular vesicle (EVs); Sperm maturation; Oocyte maturation

卵泡液代谢组学研究进展

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【摘要】探索并找到能够成功预测卵子质量的生物标志物是提高人类辅助生殖技术(ART)成功率的关键因素之一。继形态学、基因组学、蛋白质组学之后, 新近发展的代谢组学研究方法可能会成为寻找卵泡液中预测卵子质量标志物的较有前景的方法之一。代谢组学分析以其客观、准确、代谢物种类少和测量相对简单的优点成为最近的研究热点。本文就卵泡液代谢组学的研究进展做一综述。

【关键词】代谢组学; 卵子; 卵泡液; 生物标志物

· 综述 ·

Progress on follicular fluid metabolomics Zhang Yijing, Sun Xiaoxi

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【Abstract】 The exploration and discovery of biomarkers that can successfully predict oocyte quality is one of the key factors to improve the success rate of human assisted reproductive technology (ART). After the emergence of morphological, genomic and proteomic studies, metabolomics rise as one of the most promising methods to search for the prediction of oocyte quality in follicular fluid. Metabolomics has recently become an immediate areas of research focus with its objectivity, accuracy, less varieties of metabolites, and relatively simple measurement. This paper reviews the research progress of follicular fluid metabolomics which is a field worthy of research.

【Key words】 Metabolomics; Oocyte; Follicular fluid; Biomarkers

不明原因复发性流产免疫学发病机制的研究进展

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【摘要】 复发性流产发生率为 1%~5%, 其中 40%~60% 原因不明, 称为不明原因复发性流产(unexplained recurrent spontaneous abortion, URSA)。近年研究表明, URSA 的发生与免疫失衡关系密切, 又称为同种免疫型复发性流产。本文论述 URSA 免疫学的发病机制、诊断、治疗的最新研究进展, 重点论述了发病机制中免疫失衡方面的研究进展。

【关键词】 不明原因复发性流产(URSA); 机制; 细胞因子; 治疗

· 综述 ·

Research advances in the immunological pathogenesis of unexplained recurrent spontaneous abortion

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【Abstract】 Recurrent abortion occurs in 1%-5% couples, and among them 40%-60% cases have shown no clear etiology. Recent studies show URSA relates to imbalanced immune system closely, thus URSA is also regarded as alloimmune recurrent abortion. This review summarizes the research advances in immunological pathogenesis, diagnosis, and management of URSA and focuses on the insights into mechanism behind immune imbalance.

【Key words】 Unexplained recurrent spontaneous abortion; Mechanism; Cytokine; Management

人类子宫移植的研究进展

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【摘要】 子宫移植后第一例婴儿的安全出生证明了子宫移植技术的可行性, 这一成果不仅给研究人员极大的鼓舞, 而且给广大的子宫原因性不孕女性带来了希望; 但由于手术会对活体供者带来巨大手术风险, 且移植后的免疫抑制用药方案仍面临着诸多挑战, 由此引起社会的广泛关注。总之, 虽然子宫移植技术仍处于初步探索研究阶段, 但仍具有可能成为首先考虑的治疗子宫性不孕的方法。本文就近年来国外关于人类子宫移植的研究进展作一综述。

【关键词】 移植; 子宫; 人类; 不孕症; 免疫抑制

· 综述 ·

Progress of human uterus transplantation Zhang Shuai, Zhang Yunshan

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【Abstract】 The firstly successful birth of a healthy infant following the uterus transplantation certificated the feasibility of this technology, which not only encouraged the researchers, but also brings hope to women who suffered from absolute uterine factors infertility. But the surgery itself may carry huge risk to the live donors and the immunosuppression protocols after transplantation are still faced with many challenges, thus it caused wide attention to the society. In conclusion, although the uterus transplant technology is still at the initial stage of exploration research, it still has the potential to become the first correct method for the treatment of absolute uterine factors infertility. The recent progress in the foreign studies of human uterine transplantation is reviewed in this paper.

【Key words】 Transplantation; Uterus; Human; Infertility; Immunosuppression

小鼠早产模型的研究进展

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梁江红和李成功对本文有同等贡献, 均为第一作者

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【摘要】 早产是世界范围内导致 5 岁以下儿童死亡的首要原因, 同时早产会增加儿童神经功能发育障碍和成年后患慢性疾病的风险, 因此探讨早产发生机制对儿童健康具有重要意义。早产(PTB)是一个多因素导致的综合征, 具体发生机制尚不清楚。由于伦理学的限制, 基于人类的早产实验研究困难, 因此采用动物模型来验证临床观察假说十分重要。自上世纪九十年代起, 小鼠成为研究早产的主要动物, 本文综述了几种常用的建立小鼠早产模型的方法, 包括激素模型、感染模型、炎症模型等, 并对其效率和优缺点进行了比较分析, 为早产的基础和临床研究提供一定的参考依据。

【关键词】 早产(PTB); 小鼠模型; 脂多糖(LPS); 炎症因子; RU486; 前列腺素; 表面活性剂相关蛋白 A (SP-A)

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Advances in mouse model for preterm birth Liang Jianghong, Li Chenggong, Ye Xin, Li Zigang, Tang Huiyang

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【Abstract】 Preterm birth (PTB) is the leading cause of worldwide cause of death for children under 5-year old, at the same time increases the risk of preterm children's neurological development disorders and chronic diseases in adulthood, so explore the mechanisms of PTB is important for children's health. PTB is a multifactorial syndrome; the specific mechanism is unclear now. Due to limitations of ethics, experimental studies in humans PTB is difficult, so using animal models to validate clinical observation is very important. Since 1990s, the mice become the main animal model of PTB, several methods commonly used are reviewed here, including models of hormones, infection, inflammation, at the same time we compared their efficiency, advantages and disadvantages, to provide reference for the basic and clinical research on PTB.

【Key words】 Preterm birth; Mouse model; Lipopolysaccharides (LPS); Inflammatory factors; RU486; Prostaglandin; Surfactant-associated protein A (SP-A)

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