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孕激素维持妊娠与黄体支持临床实践指南

中国医师协会生殖医学专业委员会

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【摘要】 近年来国内外关于孕激素在维持妊娠以及黄体支持领域的临床及基础研究十分活跃,不断有新的循证医学证据涌现。基于当前的最佳证据,本指南针对辅助生殖技术(assisted reproductive technology, ART)黄体支持、先兆流产、复发性流产以及早产中孕激素的应用方面,按照循证临床实践指南制订的方法和步骤,引入推荐意见分级的评估、制订及评价(grading of recommendations assessment, development and evaluation, GRADE)方法,结合临床医师的经验,考虑我国患者的偏好与价值观,平衡干预措施的利与弊,形成了15条推荐意见,以期为临床实践提供参考。

【关键词】 孕激素; 黄体酮; 黄体功能不足; 妊娠; 黄体支持; 指南; 循证; GRADE

基金项目: 国家重点研发计划课题(2018YFC1002106、2018YFC1002104)

Clinical practice guidelines for progesterone in pregnancy maintenance and luteal phase support

Chinese Association of Reproductive Medicine

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【Abstract】 In recent years, the clinical and basic research on progesterone in pregnancy maintenance and luteal phase support at home and abroad is very active, and new evidence-based medicine is emerging. Based on the new evidences, the guideline covered luteal phase support strategy for assisted reproductive technology (ART), threatened miscarriage, recurrent miscarriage and preterm birth. The grading of recommendations assessment, development and evaluation (GRADE) system was used to rate the quality of evidence and the strength of recommendations. Recommendations were derived from evidence body, the balance of benefits and harms and patient's

values and preferences. Totally 15 recommendations were made. This guideline was intended to serve as a tool for clinicians and patients for best decisions-making in China.

【Key words】 Progesterone; Progestin; Luteal phase defect; Pregnancy; Luteal phase support; Guideline; Evidence-based; GRADE

Fund program: National Major Research Program of China (2018YFC1002106,2018YFC1002104)

·临床研究·

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口服避孕药预处理对改良长方案体外 受精/卵胞质内单精子显微注射活产 率影响的一项倾向评分匹配研究

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【摘要】 目的 探讨口服避孕药(oral contraceptive, OC)预处理对改良长方案体外受精-胚胎移植(*in vitro* fertilization and embryo transfer, IVF-ET)/卵胞质内单精子显微注射(intracytoplasmic sperm injection, ICSI)妊娠结局的影响。方法 回顾性分析了2012年1月至2017年12月期间于中国人民解放军陆军第七十三集团军医院生殖中心采用改良长方案13 542个周期,根据降调节前是否采用OC

预处理分为 OC 组 (591 例) 和非 OC 组 (12 951 例) 。通过倾向评分匹配方法均衡两组间的变量后, 比较两组的获卵数、成熟卵母细胞数、受精卵数、人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 扳机日雌二醇水平、hCG 扳机日内膜厚度、妊娠率、活产率等。结果 匹配前, OC 组 hCG 扳机日雌二醇水平 [3 118.00 (2 529.00) ng/L] 低于非 OC 组 [3 422.00 (2 733.00) ng/L] , 差异有统计学意义 ($P=0.001$) , 两组新鲜周期的获卵数、成熟卵母数、受精数、hCG 扳机日内膜厚度、临床妊娠率、活产率差异均无统计学意义 ($P>0.05$) 。但通过多因素 logistics 回归分析校正混杂因素后, OC 组相对非 OC 组是降低活产率的负面因素 (临床妊娠率 $OR=0.83$, 95% $CI=0.68\sim 1.02$; 活产率 $OR=0.82$, 95% $CI=0.68\sim 0.99$) 。匹配后, OC 组与非 OC 组的临床妊娠率及活产率 (临床妊娠率 $OR=0.94$, 95% $CI=0.75\sim 1.14$, $P=0.59$; 活产率 $OR=0.91$, 95% $CI=0.74\sim 1.13$, $P=0.38$) 差异均无统计学意义。Post-hoc 效能检验表明研究的样本量能够在效能 $\geq 80\%$ 的水平上检测到主要终点不小于 3.7% 的差异。结论 OC 预处理对改良长方案的助孕结局没有显著的影响。

【关键词】 避孕药, 口服; 妊娠率; 活产率; 改良长方案

基金项目: 厦门市医学优势亚专科建设项目 (厦卫科教【2018】296 号文)

A propensity score matching study of oral contraceptive pretreatment on the live birth rate of modified long down-regulation protocol in *in vitro* fertilization and embryo transfer and intracytoplasmic sperm injection cycles

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【 Abstract 】 **Objective** To investigate the effect of oral contraceptive pretreatment on pregnancy outcome of modified long down-regulation protocol in *in vitro* fertilization and embryo transfer and intracytoplasmic sperm injection cycles. **Methods** Totally 13 542 cycles were retrospectively analyzed in Reproductive Medicine Center of the 73th Group Military Hospital of PLA from January 2012 to December 2017. According to whether use oral contraceptives (OC) before down-regulation, they were divided into OC group (591 cases) and non-OC group (12 951 cases). After the variables between the two groups were balanced by the propensity score matching method, the number of oocytes obtained, number of mature oocytes, number of fertilized oocytes, number of high-quality embryos, estradiol level on human chorionic gonadotropin (hCG) trigger day, endometrial thickness on hCG trigger day, the clinical pregnancy rate and the live birth rate of the two groups were compared. **Results** Before matching, the estradiol level on hCG trigger day in OC group [3 118.00(2 529.00) ng/L] was lower than that in non-OC group [3 422.00(2 733.00) ng/L], with statistically significant difference ($P=0.001$), there was no significant difference between OC group and non-OC group in the number of harvested oocytes

and mature oocytes, fertilization number, number of viable embryos, endometrial thickness on hCG trigger day, the clinical pregnancy rate and the live birth rate. However, after adjusting for confounding factors through multi-factor logistics regression analysis, OC group was the negative factor to reduce the live birth rate compared with non-OC group (clinical pregnancy rate $OR=0.83$, 95% $CI=0.68-1.02$; live birth rate $OR=0.82$, with 95% $CI=0.88-0.99$). After matching, the clinical pregnancy rate and the live birth rate of OC group and non-OC group had no statistically significant differences (clinical pregnancy rate $OR=0.94$, 95% $CI=0.75-1.14$, $P=0.59$; live birth rate $OR=0.91$, 95% $CI=0.74-1.13$, $P=0.38$). A post-hoc power calculation demonstrated that the study sample size yielded $>80\%$ power to detect a no less than 3.7% difference between groups in the primary outcome. **Conclusion** The pretreatment of oral contraceptives has no significant effect on the outcome of modified long down-regulation protocol.

【Key words】 Contraceptive oral; Pregnancy rate; Live birth rate; Modified long down-regulation protocol

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· 临床研究 ·

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国产重组人促卵泡激素在辅助生殖技术控制性超促排卵的临床应用

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【摘要】 目的 评价国产重组人促卵泡激素 (recombinant human follicle-stimulating hormone , rhFSH) 用于辅助生殖技术 (assisted reproductive technology , ART) 控制性超促排卵 (controlled ovarian hyperstimulation , COH) 的有效性 & 安全性。方法 本试验采用多中心、随机、双盲、阳性平行对照、非劣效研究方法 , 于 2017 年 7 月至 2019 年 6 月间选取 6 家生殖医学中心纳入卵巢储备正常的不孕女性进行 ART 的 COH 治疗。受试者随机分为试验组 (国产 rhFSH , $n=134$) 和对照组 (进口 rhFSH , $n=133$) , 研究过程中因各种因素排除受试者共 8 例 , 试验组 7 例 , 对照组 1 例 , 最终依照研究方案完成试验的受试者试验组 127 例 , 对照组 132 例。比较两组受试者 COH 周期中获得的卵母细胞总数、rhFSH 用药情况、卵母细胞受精率、优质胚胎数、临床妊娠率、活产率、新生儿情况及不良反应发生率等指标。结果 试验组和对照组在 COH 周期中获得的卵母细胞总数分别为 (13.0 ± 5.8) 枚和 (12.9 ± 5.7) 枚 , 差异无统计学意义 ($P > 0.05$) ; 在 82 例卵胞质内单精子显微注射 (intracytoplasmic sperm injection , ICSI) 受试者中 , 试验组 (39 例) 获得 M_{II} 卵母细胞数 [(9.9 ± 3.9) 枚] 显著高于对照组 (43 例) [(7.5 ± 3.0) 枚 , $P=0.003$] ; 卵母细胞受精率试验组 [63.82% (1048/1642)] 显著高于对照组 [56.19% (958/1705) , $P < 0.001$] 。 rhFSH 用药时间和总量、优质胚胎数、临床妊娠率、早产率、活产率、新生儿异常发生率、新生儿体重、Apgar 评分等两组间差异无统计学意义 (P 均 > 0.05) ; 治疗期间卵巢过度刺激综合征 (ovarian hyperstimulation syndrome , OHSS) 和其他不良反应发生率差异无统计学意义 (P 均 > 0.05) , 且均为进口 rhFSH 已知的不良反应。结论 在卵巢储备正常的不孕女性中使用相同卵巢刺激治疗方案 , 国产 rhFSH 有效性 & 安全性与进口 rhFSH 相当。

【关键词】 国产重组人促卵泡激素 ; 控制性超促排卵 ; 有效性 ; 安全性

Clinical application of domestic recombinant human follicle-stimulating hormone in controlled ovarian hyperstimulation with assisted reproductive technology

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【 Abstract 】 Objective To evaluate the efficacy and safety of domestic recombinant human follicle-stimulating hormone (rhFSH) in assisted reproductive technology (ART) of controlled ovarian hyperstimulation (COH). **Methods** In a multicenter, randomized, double-blind, positive, parallel controlled non-inferiority clinical trial, the infertile women with normal ovarian reserve who received ART-COH in six reproductive medical centers from July 2017 to June 2019 were randomly divided into two groups: experimental group (domestic rhFSH, $n=134$) and control group (imported rhFSH, $n=133$). Eight subjects were excluded due to various reasons during the experimental process, 7 in experimental group and 1 in control group. At last, 127 subjects in experimental group and 132 subjects in control group complete the experiment following the research protocol. The total number of oocytes, usage of FSH, fertilization rate of oocytes, the number of high-quality embryos, clinical pregnancy rate, live birth rate, neonatal characteristics and the incidence of adverse reactions were compared between the two groups during the cycle of COH. **Results** During the initiation cycle of ovulation induction therapy, the total number of oocytes obtained in experimental group and control group were 13.0 ± 5.8 and 12.9 ± 5.7 , respectively, with no statistically significant difference ($P>0.05$). Among the 82 intracytoplasmic sperm injection (ICSI) patients, the number of M_{II} oocytes obtained in experimental group (39 cases) was markedly higher than that in control group (43 cases) (9.9 ± 3.9 vs. 7.5 ± 3.0 , $P=0.003$). The fertilization rate of oocytes in experimental group was obviously higher than that in control group [63.82% ($1048/1642$) vs. 56.19% ($958/1705$), $P<0.001$]. There were no significant differences of stimulated duration and dosage of rhFSH, number of high-quality embryos, clinical pregnancy rate, preterm rate, live birth rate, incidence of neonatal abnormalities, neonatal weight or Apgar score between the two groups (all $P>0.05$). The incidence of ovarian hyperstimulation syndrome and other adverse reactions in treatment period were not significantly different between the two groups (all $P>0.05$), which were known adverse reaction occurred in the imported rhFSH. **Conclusion** The efficacy and safety of domestic rhFSH were the same as that of imported rhFSH in infertile patients with normal ovarian reserve under the same ovarian stimulation regimen.

【 Key words 】 Domestic recombinant human follicle-stimulating hormone; Controlled ovarian hyperstimulation; Efficacy; Safety

·临床研究·

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经皮雌二醇贴片与口服戊酸雌二醇在激素替代冻融胚胎移植周期临床疗效的比较

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【摘要】 目的 比较激素替代冻融胚胎移植周期应用经皮雌二醇贴片与口服戊酸雌二醇的临床疗效。方法 回顾性队列研究分析 2018 年 6 月至 2019 年 12 月期间行激素替代冻融胚胎移植周期患者的临床资料共 363 例。A 组患者应用经皮雌二醇贴片，B 组患者口服戊酸雌二醇，比较两组患者的临床结局。结果 临床妊娠率 A 组为 55.7% (113/203)，B 组为 58.4% (87/149)，组间差异无统计学意义 ($P=0.663$)。人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 阳性率 [63.5% (129/203) 比 65.8% (98/149)]、早期流产率 [10.6% (12/113) 比 9.2% (8/87)]、异位妊娠率 [1.8% (2/113) 比 4.6% (4/87)] 组间差异均无统计学意义 (P 均 >0.05)。孕激素内膜转化日血清雌二醇水平 B 组 [(271.6 \pm 73.8) ng/L] 显著高于 A 组 [(209.5 \pm 65.9) ng/L, $P=0.008$]。结论 激素替代冻融胚胎移植周期，经皮雌二醇贴片临床效果与口服戊酸雌二醇相同，推荐用于有慢性肝肾功能疾病、血栓高危因素、血脂异常等情况的患者。

【关键词】 雌二醇； 激素替代； 胚胎移植

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Comparison of clinical efficacy of transdermal estradiol patch and oral estradiol valerate in hormone replacement frozen-thawed embryo transfer cycles

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【 Abstract 】 Objective To compare the clinical efficacy of transdermal estradiol patch and oral estradiol valerate in hormone replacement frozen-thawed embryo transfer cycle. **Methods** Clinical data of 363 patients undergoing hormone replacement frozen-thawed embryos transfer from June 2018 to December 2019 were retrospectively analyzed. Patients in group A received transdermal estradiol patch. Patients in group B received estradiol valerate orally. The clinical outcomes of the two groups were compared. **Results** The clinical pregnancy rate was 55.7% (113/203) in group A and 58.4% (87/149) in group B, with no significant difference between the two groups ($P=0.663$). There were no significant differences in human chorionic gonadotropin (hCG) positive rate [63.5%(129/203) vs. 65.8% (98/149)], early abortion rate [10.6% (12/113) vs. 9.2% (8/87)] and ectopic pregnancy rate [1.8% (2/113) vs. 4.6% (4/87)] between the two groups (all $P>0.05$). The serum estradiol level in group B [(271.6±73.8) ng/L] was significantly higher than that in group A [(209.5±65.9) ng/L] on the day of endometrial conversion of progesterone ($P=0.008$). **Conclusion** The clinical effect of the transdermal estradiol patch is the same as that of oral estradiol valerate in hormone replacement frozen-thawed embryo transfer cycle. It is recommended for patients with chronic liver and kidney disease, high risk factors for thrombosis, dyslipidemia.

【Key words】 Estradiol; Hormone replacement; Embryo transfer

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阿托西班在试管婴儿新鲜移植周期中的应用效果分析

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【摘要】 目的 探讨缩宫素受体拮抗剂阿托西班在体外受精/卵胞质内单精子显微注射 (*in vitro* fertilization/intracytoplasmic sperm injection, IVF/ICSI) 新鲜胚胎移植周期中的应用效果分析。方法 选取自 2016 年 1 月至 2019 年 12 月期间在郑州大学第二附属医院生殖医学部行 IVF/ICSI 治疗的 2349 个新鲜取卵移植周期,将符合纳入条件的患者随机分成阿托西班组 (1176 个周期) 和对照组 (1173 个周期),比较两组的相关指标和妊娠结局。结果 阿托西班组的胚胎种植率 [50.31% (1046/2079)]、临床妊娠率 [64.37% (757/1176)]、活产率 [53.17% (553/1040)] 明显高于对照组 [39.09% (817/2090), 51.32% (602/1173), 41.01% (431/1051)], 差异均有统计学意义 ($P < 0.001$)。两组的多胎妊娠率、多胎活产率、异位妊娠率及出生缺陷率比较,差异均无统计学意义 ($P > 0.05$)。阿托西班组的流产率 [13.47% (102/757)] 低于对照组 [16.45% (99/602)], 但差异无统计学意义 ($P > 0.05$)。结论 阿托西班可以抑制子宫收缩,减少子宫蠕动,提高胚胎种植率、临床妊娠率与活产率,并不增加子代出生缺陷的风险。因此,在 IVF/ICSI 新鲜移植周期中应用缩宫素受体拮抗剂阿托西班可以有效改善临床结局。

【关键词】 阿托西班; 子宫收缩; 受精, 体外; 胚胎移植; 卵胞质内单精子显微注射; 临床妊娠率; 活产率; 出生缺陷率

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Analysis of the application of atosiban in the fresh embryo transfer cycle in the test-tube baby program

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【 Abstract 】 Objective To explore the application of oxytocin receptor antagonist atosiban in the fresh embryo transfer cycle of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) program. **Methods** We selected 2349 fresh embryo transfer cycles, ranging from January 2016 to December 2019 in Reproductive Medicine Center, the Second Affiliated Hospital of Zhengzhou University. Patients were randomly categorized into atosiban group (1176 cycles) and control group (1173 cycles). The related indicators and clinical outcomes were compared between the two groups. **Results** The implantation rate [50.31% (1046/2079)], the clinical pregnancy rate [64.37% (757/1176)] and the live birth rate [53.17% (553/1040)] in atosiban group were remarkably higher than those of control

group [39.09% (817/2090), 51.32% (602/1173), 41.01% (431/1051)], and the differences were significant statistically (all $P < 0.001$). There were no differences in multiple pregnancy rate, multiple live birth rate, ectopic pregnancy rate and birth defect rate between the two groups (all $P > 0.05$). Miscarriage rate of atosiban group [13.47% (102/757)] was lower than that of control group [16.44% (99/602)], but there was no significant difference ($P > 0.05$). **Conclusion** Atosiban could inhibit uterus contraction and peristaltic to improve implantation rate, clinical pregnancy rate and live birth rate, and atosiban did not increase the risk of birth defect in offspring. Therefore, application of oxytocin receptor antagonist atosiban could improve the clinical outcome in the fresh embryo transfer cycle of IVF/ICSI.

【 Key words 】 Atosiban; Uterine contraction; Fertilization *in vitro*; Embryo transfer; Intracytoplasmic sperm injection; Clinical pregnancy rate; Live birth rate; Birth defect rate

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Ang1-7、A779、Ang II 对胰岛素抵抗的大鼠卵巢颗粒细胞胰岛素信号通路蛋白的影响

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【摘要】 目的 探讨 Ang1-7、Mas 受体拮抗剂 A779、Ang II 作用后,对胰岛素抵抗的大鼠卵巢颗粒细胞葡萄糖摄取及胰岛素信号通路蛋白的影响。方法 ①构建大鼠卵巢颗粒细胞胰岛素抵抗模型 将颗粒细胞分为空白组和模型组 模型组细胞用地塞米松、胰岛素进行处理,检测两组细胞培养基上清液 24 h 内葡萄糖浓度、乳酸浓度的差值。②进一步将模型组细胞分别加入不同药物处理 24 h :Ang II 组、Ang1-7 组、Ang1-7+Ang II 组、A779 组、Ang1-7+A779 组,并检测药物作用后细胞培养基上清液 24 h 内葡萄糖浓度差值。③采用 Western blotting 检测空白组、模型组、各药物处理组颗粒细胞 Akt、GSK-3 β 、AS160 及其磷酸化蛋白 (P-Akt、P-GSK-3 β 、P-AS160) 以及 Mas 受体蛋白的表达。结果 ①跟空白组相比,模型组的葡萄糖浓度差值小、乳酸浓度差值小,提示颗粒细胞胰岛素抵抗模型建立成功。②与模型组比较,Ang1-7 组葡萄糖浓度差值大 (5.55 ± 0.21 , $P=0.0021$), Ang II 组差值小, Ang1-7+Ang II 组、A779 组差异无统计学意义 ($P>0.05$), Ang1-7+A779 组葡萄糖浓度差值小 (4.89 ± 0.20 , $P=0.0108$)。③空白组、模型组、各药物处理组颗粒细胞的 Akt、GSK-3 β 、AS160 的表达无明显差异。与模型组比较,Ang1-7 组 P-Akt、P-GSK-3 β 、P-AS160 的表达增强,Ang II 组 P-Akt、P-GSK-3 β 、P-AS160 的表达减弱。与 Ang1-7 组比较,Ang1-7+A779 组 Mas 受体表达量降低。结论 ①Ang1-7 作用后,胰岛素抵抗的大鼠卵巢颗粒细胞葡萄糖浓度差值增加,Ang II 作用后与 Ang1-7 相反,二者相互拮抗,同时 Ang1-7、Ang II 作用后颗粒细胞胰岛素信号通路关键蛋白 P-Akt、P-GSK-3 β 及 P-AS160 也出现相反变化,表明通过细胞葡萄糖浓度差值体现的细胞葡萄糖代谢有可能是胰岛素信号通路蛋白 P-Akt、P-GSK-3 β 及 P-AS160 表达变化的结果。②Ang1-7 作用后受体 Mas 表达上调,加入 Mas 受体拮抗剂 A779,细胞葡萄糖代谢受抑制,P-Akt、P-GSK-3 β 及 P-AS160 表达降低,提示 Ang1-7 改善葡萄糖代谢过程中,有受体 Mas 参与。

【关键词】 多囊卵巢综合征; 胰岛素抵抗; 血管紧张素 II

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Effects of Ang1-7, A779 and Ang II on insulin signaling pathway proteins in ovarian granulosa cells of insulin resistant rat

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【 Abstract 】 Objective To determine the changes of glucose and insulin signaling pathway proteins in rat ovarian insulin resistant granulosa cells by detecting

Ang1-7, MAS receptor inhibitors A779 and Ang II. **Methods** First, rat ovarian granulosa cells were cultured with dexamethasone and insulin to establish the insulin resistance (IR) model, and the concentration differences of glucose and lactic acid in both blank and IR model groups were detected. According to the different drugs treated, the cells in the IR model group were divided into Ang II group, Ang1-7 group, Ang1-7+Ang II group, A779 group, Ang1-7+A779 group. After 24 h, the concentration differences of glucose of all groups were tested. At last, Western blotting was used to detect the expressions of P-Akt/Akt, P-Gsk-3 β /GSK-3 β , P-AS160/AS160 in the Mas receptor protein and key proteins in the insulin signaling pathway in the above groups. **Results** 1) Compared with the blank group, the concentration differences of glucose and lactic acid of the supernatant were reduced after applying dexamethasone and insulin to rat ovarian granulosa cells, suggesting that the IR model was successfully established. 2) Compared with the model group, the concentration difference of glucose in the Ang1-7 group was increased (5.55 ± 0.21 , $P=0.002$), while the Ang II subgroup was decreased. There was no significant difference of the concentration difference of glucose between the Ang1-7+Ang II group and the A779 group ($P>0.05$). However, the concentration difference of glucose in the Ang1-7+A779 group was decreased (4.89 ± 0.20 , $P=0.010$). 3) There was no difference in the expressions of Akt, GSK-3 β , AS160 among the blank group, model group and the different drugs treated groups. Compared with the model group, the expressions of P-Akt, P-GSK-3 β , and P-AS160 in the Ang1-7 group were enhanced, while the expressions of P-Akt, P-GSK-3 β , and P-AS160 in the Ang II group were decreased. And compared with Ang1-7 group, Mas receptor expression in Ang1-7+A779 group was decreased. **Conclusion** 1) The effect of Ang1-7 on improving the IR condition of rat ovarian granulosa cells in IR model was opposite to Ang II, which was achieved by improving the expression of the phosphorylation expression of Akt, GSK-3 β , AS160 proteins in insulin signaling pathway. 2) The addition of A779 can inhibit the improvement of Ang1-7 on Mas, glucose metabolism and insulin signaling pathway, which meant in the role of Ang1-7 on improvement of the glucose metabolism, its downstream Mas receptor was involved in the process.

【Key words】 Polycystic ovary syndrome; Insulin resistance; Angiotensin II

Fund program: The Second Hospital of Hebei Medical University (2h201822)

· 流行病学研究 ·

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上海市中心城区产后妇女避孕需求及 产后避孕服务利用调查

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【摘要】 目的 调查上海市中心城区产后妇女避孕节育现状及避孕相关生殖健康服务利用情况。方法 2019年8月至12月期间,采用横断面调查的方法对在上海市4个区(长宁区、静安区、普陀区、杨浦区)产后42d健康检查门诊就诊和前往儿童保健门诊的妇女进行问卷调查。数据分析采用频率和logistic回归分析等方法。结果 调查的1170名产后妇女中有420名已恢复性生活,恢复时间为分娩后(3.6±1.5)个月。按照产后时间不同进行分组,已恢复性生活的调查对象在产后1~3个月、4~6个月、7~9个月和10~12个月坚持采用避孕措施的比例分别为69.4%(43/62)、77.2%(186/241)、79.2%(57/72)和71.1%(32/45)。是否计划妊娠、再生育意愿以及产后避孕指导是影响避孕行为的主要因素。产后不同时期的妇女采用的避孕方法均以避孕套为主,长效可逆避孕方法使用率低。在产后访视和产后42d检查时分别有43.3%(395/913)和34.6%(369/1067)的调查对象获得了具体的避孕方法指导。37.6%(420/1117)的调查对象认为产后42d检查是避孕最佳健康宣教时机,而30.5%(341/1117)的妇女认为孕期健康教育时就应该给予指导。结论 约四分之一的上海市中心城区妇女在产后未坚持采用避孕措施;宫内节育器、皮下埋植剂等长效、可逆的避孕方法使用率低。应加强产后避孕指导,强化专业队伍培训,重视避孕药具的正确选择和使用,引导妇女正确认识长效避孕方法。同时,避孕指导服务可提前至孕期开展,做到关口前移。

【关键词】 产后妇女; 产后避孕; 卫生服务; 需求

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Demands and utilization of contraceptive services in women during the first 12 months after delivery: a cross sectional survey in urban areas of Shanghai

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【 Abstract 】 Objective To investigate the use of contraceptives among postpartum women in the urban areas of Shanghai and to understand women's demands and utilization of contraceptive service. **Methods** A cross-sectional survey was conducted using questionnaires in postpartum women in the clinics for 42-day postpartum follow-up and child health care in 4 districts in Shanghai (including Changning District, Jingan District, Putuo District and Yangpu District) from August 2019 to December 2019. Data were analyzed using frequency description and logistic regression. **Results** In total, 1170 postpartum women were enrolled. Among them, 420 women resumed sexual intercourse at an average length of (3.6±1.5) months postpartum and the proportions of consistent contraceptive use were 69.4%(43/62), 77.2% (186/241), 79.2% (57/72) and 71.1% (32/45), at periods of 1 to 3 months, 4 to 6 months, 7 to 9 months and 10 to 12 months after delivery respectively. Planned pregnancy, willingness to reproduce, and postpartum contraceptive guidance were associated with contraceptive behavior. Condom was the main approach used by postpartum women, while long-acting reversible contraceptive method was seldom used. The proportion of receiving guidance on contraception during postpartum home visits and 42-day postpartum follow-up were 43.3% (395/913) and 34.6% (369/1067) respectively. Totally, 37.6% (420/1117) of the total considered that the best time for contraceptive health education was at the 42-day postpartum follow-up, while 30.5% (341/1117) of them preferred health education during pregnancy. **Conclusion** About one-quarter of postpartum women do not adhere to contraception in the urban areas of Shanghai. The proportion of using long-acting reversible contraceptive methods, such as intrauterine devices and subcutaneous, remains low. It is necessary to strengthen postpartum contraceptive services, to provide professional training, and strengthen

guidance on the proper selection and use of contraceptive methods, especially for long-acting contraceptive methods. Meanwhile, the guidance for contraception should be advanced during pregnancy.

【Key words】 Postpartum women; Postpartum contraception; Health service; Demand

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双绒毛膜三羊膜囊三胎妊娠射频消融 减胎病例临床结局分析

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【摘要】 目的 探讨射频消融术 (radiofrequency ablation, RFA) 对双绒毛膜三羊膜囊 (dichorionic triamniotic, DCTA) 三胎选择性减胎的安全性以及影响妊娠结局的因素。方法 采用回顾性队列研究方法收集 2016 年 1 月 1 日至 2020 年 1 月 1 日期间在南方科技大学第一附属医院深圳市人民医院产科因 DCTA 三胎要求 RFA 选择性

减胎病例的患者资料,对手术经过、临床结局和并发症,以及其分娩胎盘进行分析。结果 共有 12 例 DCTA 病例纳入本回顾性分析, RFA 手术时孕周为 (15.6±1.3) 周, 分娩孕周为 (36.9±1.1) 周 (34⁺⁴~38⁺²周)。12 例中 8 例接受介入性产前诊断, 与未接受介入性产前诊断的病例相比, 两组从 RFA 手术到分娩的间隔差异以及分娩孕周差异均无统计学意义 (*P*>0.05)。共分娩新生儿 23 例, 6 例 (26%) 小于胎龄儿。无论是独立绒毛膜单胎还是单绒毛膜双羊膜囊 (monochorionic diamniotic , MCDA) 保留胎, 出生体质量的平均百分位数明显低于单胎妊娠胎儿体质量的第 50 百分位数 (*P*<0.001)。1 例 DCTA 中的 MCDA 保留胎 RFA 术后 4 h 死亡 (8.3%) , 死前保留胎一度出现胎儿心动过速伴胎动消失, 分娩后胎盘检查显示 MCDA 保留胎侧胎盘苍白而减灭胎侧胎盘瘀血。收集 10 例 DCTA 中 MCDA 保留胎存活的胎盘, 9 例可见保留胎胎盘循环通过双胎之间血管吻合支不同程度灌注了减灭胎部分胎盘小叶, 1 例无明显灌注减灭胎胎盘的病例 MCDA 保留胎体质量百分位数最低。结论 RFA 减胎对于 DCTA 三胎减胎安全有效, 减胎后进行介入性产前诊断手术不影响 RFA 术后继续妊娠时间, 术中监测 MCDA 保留胎心率和胎动异常与不良结局有关, 胎盘检查有助于了解不良结局原因, 保留胎生长潜能或许与双胎之间的血管吻合类型有关。

【关键词】 三胎; 射频消融术; 胎盘; 妊娠结局; 双绒毛膜三羊膜囊

Analysis of the clinical outcome of dichorionic triamniotic triplets after selective feticide by radiofrequency ablation

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【 Abstract 】 **Objective** To investigate the safety of selective feticide by radiofrequency ablation (RFA) in dichorionic triamniotic (DCTA) triplets and factors related to the clinical outcome. **Methods** A retrospective cohort study was designed to review the clinical records and pregnancy outcome of DCTA triplets patients who underwent RFA for selective feticide performed at the First Affiliated Hospital of Southern University of Science and Technology, Shenzhen People's Hospital from January 1,2016 to January 1,2020. Placentas were collected after delivery for gross examination and perfusion study with the mixture of vinylidene chloride and self-curing denture acrylic. **Results** A total of 12 DCTA cases were recruited. Selective feticide by RFA were performed at a mean gestational age of 15.6 weeks, and cases delivered at a mean gestational age of 36.9 weeks (34⁺⁴–38⁺² weeks). Eight of the cases undertook invasive prenatal diagnosis weeks after RFA. The interval between RFA to delivery and gestational ages at delivery were similar between women undertook prenatal diagnosis and those who did not (*P*>0.05). Six of the 23 newborns (26%) were small for gestational age. The average birth weight of either monochorionic singleton

fetus or the remained co-twin of the monochorionic diamniotic (MCDA) twin as lower than that of singleton pregnancy ($P<0.001$). One case of DCTA (8.3%) underwent intrauterine fetal death of the MCDA co-twin 4 h after RFA. Fetal tachycardia and cessation of fetal movement of the co-twin were observed before death. By the time of delivery, placental examination revealed the pale anemia look of the placental part of the co-twin and the reddish appearance of the part of the reduced fetus, which suggested a hypovolemic shock after an uncompleted RFA as the cause of co-twin death. A total of 10 MCDA placentas from cases with a living MCDA co-twins were collected. Various degree of placental perfusion on the reduced fetal side of placenta was noticed in nine cases. The co-twin with the placenta which did not have such kind of perfusion had a birth weight at the lowest percentile. **Conclusion** Selective feticide by RFA is a safe procedure for DCTA triplet, and prenatal diagnosis has no adverse impact on pregnancy outcome. Ultrasound monitoring of fetal heart rate and fetal movement of the MCDA co-twin after RFA is helpful for predicting clinical outcome. Postnatal placental examination provides clues for adverse outcome, and the growth potential of the MCDA co-twin might be related to the type of anastomosis between the two fetuses.

【Key words】 Triplets; Radiofrequency ablation; Placenta; Pregnancy outcome; Dichorionic triamniotic

· 临床报道 ·

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迈之灵预防卵巢过度刺激综合征的临床价值

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【摘要】 目的 评价口服迈之灵对预防和治疗体外受精-胚胎移植 (*in vitro* fertilization-embryo transfer, IVF-ET) 后卵巢过度刺激综合征 (ovarian hyperstimulation syndrome, OHSS) 发生及其严重程度的作用。方法 选择 2018 年 2 月至 2019 年 10 月期间在中山大学附属第六医院行 IVF-ET 助孕取卵术后因 OHSS 高风险取消移植的 100 例患者，前瞻性随机对照分组，试验组患者 (50 例) 取卵术后口服迈之灵 300 mg, bid×10 d, 对照组患者无迈之灵治疗，其他治疗一致，比较两组之间 OHSS 发生率以及严重程度。结果 女方年龄、体质质量指数 (body mass index, BMI)、抗苗勒管激素 (anti-Müllerian hormone, AMH)、促性腺激素 (gonadotropin, Gn) 使用总量、获卵数等基本条件组间比较差异均无统计学意义 ($P>0.05$)，试验组与对照组中重度 OHSS 发生率差异有统计学意义 [4.00% (2/50) 比 18.00% (9/50), $P=0.025$]，对照组腹水穿刺 3 例，试验组腹水穿刺 0 例，无重度 OHSS 发生。结论 口服迈之灵能有效预防 OHSS 高危患者的中重度 OHSS 发生率，并降低 OHSS 严重程度。

【关键词】 迈之灵； 受精，体外； 胚胎移植； 卵巢过度刺激综合征

Clinical value of Aescuven forte in preventing ovarian hyperstimulation syndrome

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【Abstract】 Objective To evaluate the effect of oral Aescuven forte on the incidence and severity of ovarian hyperstimulation syndrome (OHSS). **Methods** A total of 100 patients who cancelled transplantation after oocyte retrieval for *in vitro* fertilization-embryo transfer assisted reproduction due to high risk of OHSS between February 2018 and October 2019 in Reproductive Medicine Research Center, the Sixth Affiliated Hospital, Sun Yat-Sen University were randomized into two groups in this prospective randomized controlled trial. The patients in experimental group (50 cases) received 300 mg, bid of Aescuven forte orally for 10 d after oocyte retrieval, while control group (50 cases) did not receive Aescuven forte; otherwise, both groups underwent the same treatments. The incidence rate and severity of OHSS were compared between the two groups. **Results** No significant differences were found in variables such as age, body mass index (BMI), anti-Müllerian hormone (AMH) level, total dosage of gonadotropin (Gn) used, and the number of retrieved oocytes between the two groups ($P>0.05$). The incidence rate of moderate to severe OHSS in experimental group and control group was 4.00% (2/50) and 18.00% (9/50), respectively, with a statistically significant difference ($P=0.025$). Control group included 3 cases of paracentesis due to ascites, while experimental group did not include any

cases of paracentesis or severe OHSS. **Conclusion** Oral administration of Aescuven forte effectively prevent the incidence of moderate to severe OHSS in high-risk patients and reduced the severity of OHSS.

【Key words】 Aescuven forte; Fertilization *in vitro*; Embryo transfer; Ovarian hyperstimulation syndrome

· 个案报道 ·

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促性腺激素释放激素激动剂垂体降调节后多卵泡发育的病例分析及文献复习

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【摘要】 目的 结合既往临床病例及文献复习,总结促性腺激素释放激素激动剂 (gonadotropin-releasing hormone agonist, GnRH-a) 垂体降调节后多卵泡发育的诊疗特征。方法 报道 1 例于本院应用 GnRH-a 垂体降调节后多卵泡发育的患者情况,并结合中外文献报道的 16 例个案的病例特点进行回顾性分析。结果 应用 GnRH-a 后发生多卵泡发育的情况,目前无法预测亦无法避免。应用 GnRH-a 后的“flare-up”效应和卵泡刺激素受体基因的突变可能是发病原因。结论 GnRH-a 垂体降调节后多卵泡发育可行取卵手术,建议新鲜周期全部胚胎冷冻,择期行冻融胚胎移植。

【关键词】 受精,体外; 胚胎移植; 垂体降调节; 促性腺激素释放激素激动剂

Case analysis and literature review on multiple ovarian follicles grewed after pituitary down-regulation by gonadotropin-releasing hormone agonist

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【 Abstract 】 Objective To summarize the diagnosis and treatment characteristics of multiple ovarian follicles grew after pituitary downregulation by gonadotropin-releasing hormone agonist (GnRH-a). **Methods** This paper reported one patient with multiple ovarian follicles grew after pituitary downregulation using GnRH-a in our hospital, and the characteristics of 16 cases reported in Chinese and foreign literatures were retrospectively analyzed. **Results** It is difficult to predict and avoid the development of multiple ovarian follicles after application of GnRH-a, and the "flare-up" effect after application of GnRH-a and the mutation of follicle-stimulating hormone (FSH) receptor gene may be the cause of the disease. **Conclusion** The oocyte extraction operation is feasible for multiple ovarian follicles grew after pituitary downregulation. It is suggested to freeze the whole embryos in fresh cycle, and conducted embryo thawing transplantation at another time.

【 Key words 】 Fertilization *in vitro*; Embryo transfer; Pituitary downregulation; Gonadotrophin-releasing hormone agonist

· 个案报道 ·

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陈旧性子宫穿孔合并输卵管嵌顿 2 例并文献复习

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【摘要】 目的 探讨陈旧性子宫穿孔合并输卵管嵌顿发病原因及总结输卵管嵌顿患者临床表现、鉴别诊断及辅助检查征象。方法 回顾性分析 2 例陈旧性子宫穿孔合并输卵管嵌顿的病例并进行文献回顾。结果 术中见输卵管嵌顿, 术后病理检查证实嵌顿

组织为输卵管。结论 陈旧性子官穿孔合并输卵管异位临床表现无特异性,对于宫腔操作的患者要行全面检查,争取早发现、早治疗,改善预后。

【关键词】 陈旧性; 子宫穿孔; 输卵管嵌顿

Obsolete uterine perforation complicated with fallopian tube incarceration: two cases report and literature review

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【 Abstract 】 **Objective** To investigate the causes of obsolete uterine perforation with tubal incarceration and summarize the clinical manifestations, differential diagnosis and auxiliary examination signs of tubal incarceration. **Methods** Two cases of obsolete uterine perforation with tubal incarceration were retrospectively analyzed and the literatures were reviewed. **Results** Oviduct incarceration was observed during operation, and postoperative pathological examination confirmed that the incarcerated tissue was oviduct. **Conclusion** Obsolete uterine perforation complicated with fallopian tube incarceration was lack of specific manifestations, and the patients undergoing intrauterine manipulation should be given comprehensive examination for early diagnosis and treatment to improve prognosis of patients.

【Key words】 Obsolete; Uterine perforation; Fallopian tube incarceration

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46, Y, t (X;19) 伴生精阻滞型非梗阻性无精子症 个案报道及文献回顾

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【摘要】 目的 探究生精阻滞型非梗阻性无精子症的染色体遗传学因素。方法 回顾分析1例生精阻滞型非梗阻性无精子症患者X与常染色体平衡易位并进行文献回顾。结果 本例非梗阻性无精子症患者，染色体核型为46,Y,t(X;19)(p22.1;q13.3)，其父母核型正常，Y染色体微缺失检查未见明显异常，全外显子测序未见明显致病基因突变，染色体微阵列分析(chromosomal microarray analysis, CMA)未见明显致病拷贝数变异(copy number variation, CNV)，患者睾丸组织病理提示：精母细胞阻滞型非梗阻性无精子症。结论 46,Y,t(X;19)平衡异位可以导致生精阻滞型非梗阻性无精子症。

【关键词】 染色体平衡易位；生精阻滞；非梗阻性无精子症；遗传咨询
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46,Y,t(X;19) associated with non-obstructive azoospermia (maturation arrest type): case report and literature review

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【 Abstract 】 Objective To explore the chromosomal genetic factors of maturation arrest non-obstructive azoospermia (NOA). **Methods** A case of maturation arrest NOA patients with chromosome reciprocal translocation was retrospective analyzed with literature review. **Results** The karyotype of 46,Y,t(X;19)(p22.1;q13.3) was detected in a NOA patient, and the karyotypes of his parents were normal. There were no micro-deletions of Y chromosome. Also, no obvious pathogenic gene mutations were found in whole-exome sequencing (WES). Furthermore, there were no pathogenic copy number variations (CNVs) detected by chromosomal microarray analysis (CMA) in the patient. The histopathological analysis

revealed that the spermatogenesis arrested at spermatocyte stage. **Conclusion** 46,Y,t(X;19) chromosome reciprocal translocation could lead to maturation arrest NOA.

【 Key words 】 Chromosome reciprocal translocation; Maturation arrest; Non-obstructive azoospermia; Genetic counseling

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·综述·

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血液系统恶性肿瘤患者的生育力保存

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【摘要】 随着肿瘤诊断和治疗方案的不断改进, 癌症患者的生存率得到了显著提高。烷基化化疗和全身照射 (total body irradiation, TBI) 等性腺毒性抗癌方案经常用于治疗年轻的血液系统恶性肿瘤患者, 这可能导致女性卵巢功能不全 (premature ovarian insufficiency, POI) 或男性生殖细胞大量丢失。本文在针对生育力保存的背景、方法和适应证的基础上, 对血液系统恶性肿瘤患者在生育力保存方法中的选择及应用做一简要综述, 以期为血液系统肿瘤患者生育力保存的临床处理提供相关知识。

【关键词】 生育力保存; 血液系统恶性肿瘤; 淋巴瘤; 白血病; 肿瘤生殖学

Fertility preservation in patients with hematological malignancies

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【 Abstract 】 With the continuous improvement of cancer diagnosis and treatment methods, the survival rate of cancer patients has been significantly improved. Gonadotoxic anticancer regimens such as alkylating chemotherapy and total body irradiation (TBI) are often used to treat young patients with hematological malignancies, but may cause premature ovarian insufficiency (POI) in women or massive loss of germ cells in men. On the basis of the background, methods and indications of fertility preservation, this review briefly summarizes the selection and application of fertility preservation methods for patients with hematological malignancies in order to provide them clinical suggestions for fertility preservation.

【 Key words 】 Fertility preservation; Hematological malignancies; Lymphoma; Leukemia; Oncofertility

·综述·

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宫腔微生物对胚胎种植的影响及机制研究进展

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【摘要】 随着 16S rRNA 测序技术及宏基因组学的发展, 研究证实子宫腔内有微生物菌群的定植。以乳酸杆菌为子宫内膜主导微生物群的患者行辅助生殖技术助孕后的种植率、临床妊娠率较高, 妊娠结局较好。子宫内膜微生物在胚胎着床、妊娠维持中的作用机制尚不清楚。目前认为可能机制为其参与子宫内膜免疫调节、直接与子宫内膜相互作用调节炎症因子表达, 进而影响子宫内膜蜕膜化过程及胚胎种植; 子宫内膜共生微生物竞争抑制保持稳态。本文就宫腔微生物来源、组成成分、对辅助生殖技术妊娠结局

的影响及其影响机制等方面的研究进展进行综述,旨在为今后研究子宫内膜微生物对胚胎种植中的作用提供新的思路。

【关键词】 宫腔微生物; 生殖技术,辅助; 胚胎种植

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Effect of intrauterine microbial on embryo implantation and its mechanism

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【Abstract】 With the development of 16S rRNA sequencing technology and metagenomics, the colonization of microbial flora in uterine cavity has been confirmed. The implantation rate, the clinical pregnancy rate and pregnancy outcome of patients with *Lactobacillus* dominated endometrial microbiome after assisted reproductive technology were higher. The mechanism of endometrial microorganisms in embryo implantation and pregnancy maintenance is still unclear. At present, it is believed that the possible mechanism is involved in endometrial immune regulation and the direct interaction with endometrium to regulate the expression of inflammatory factors, thus affecting the process of endometrial decidualization, embryo implantation, and the maintenance of homeostasis by symbiotic microorganisms. This article reviews the recent studies on the sources and components of the endometrial microbiota, the influence and mechanism of endometrial microbiota on the pregnancy outcome of assisted reproductive technology, and aims to provide new ideas for future research on the role of endometrial microorganisms on embryo implantation.

【Key words】 Intrauterine microbiome; Reproductive technology, assisted; Embryo implantation

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Kisspeptin 对下丘脑-垂体-卵巢轴的调控作用

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【摘要】 Kisspeptin 是调节女性生殖功能重要的神经肽, 主要在下丘脑促性腺激素释放激素 (gonadotropin-releasing hormone, GnRH) 神经元的上游起作用, 与 GnRH 神经元上的相应受体 GPR54 结合后刺激 GnRH 的释放, 从而导致生殖轴后续一系列的活动。然而, 近年来研究显示, Kisspeptin 不仅在中枢下丘脑和垂体调控女性生殖功能, 而且在卵巢局部也发挥作用。卵巢局部的 Kisspeptin 不仅参与调控卵母细胞、颗粒细胞、黄体的功能, 同时又受促性腺激素、光周期、交感神经、代谢的影响。本文就 Kisspeptin 的中枢调控以及卵巢局部作用进行综述。

【关键词】 Kisspeptin; 下丘脑; 垂体; 卵巢

基金项目: 国家自然科学基金 (81573787); 上海市浦东新区卫生系统重点学科群建设资助 (PWZxq2017-13)

Regulatory effect of Kisspeptin on hypothalamic-pituitary-ovarian axis

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【 Abstract 】 Kisspeptin is an important neuropeptide regulating female reproductive function. It mainly acts on the upstream of hypothalamic gonadotropin-releasing hormone (GnRH) neurons. It binds to the corresponding receptor GPR54 on GnRH neurons to stimulate the release of GnRH, which leads to a series of subsequent activities of the reproductive axis. However, in recent years, it has been found that Kisspeptin exists not only in the central hypothalamus and pituitary,

but also in the peripheral ovary, indicating that Kisspeptin not only regulates the female reproductive function in the central, but also plays a local role in the ovary. Kisspeptin is not only involved in the regulation of oocyte, granulosa cell and luteal function, but also affected by gonadotropin, photoperiod, sympathetic nerve and metabolism. This article reviews the central regulation effect and the local ovarian role of kisspeptin.

【Key words】 Kisspeptin; Hypothalamus; Pituitary; Ovary

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·综述·

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外泌体 miRNA 在配子发育及不孕相关疾病中的研究进展

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【摘要】 外泌体是一种细胞外囊泡, 包含很多生物活性物质, 如核酸、蛋白质、脂质等, 在细胞间通讯、炎症反应、免疫监督、肿瘤发生等生理或病理过程中发挥作用。微小 RNA (microRNA, miRNA) 是内源性的非编码 RNA, 可以通过调节 mRNA 参与细胞增殖、分化、凋亡等过程。目前, 外泌体在生殖领域的研究处于起步阶段, 有研究表明外泌体 miRNA 可能与配子发育、胚胎形成及不孕相关疾病等有关, 本文总结最新发表文献, 主要对外泌体 miRNA 在配子发育及相关疾病的研究进展进行综述。

【关键词】 不孕症; 外泌体; 微小 RNA; 配子发育

Research progress of exosomal miRNA in gamete development and infertility-related diseases

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【Abstract】 Exosomes, a kind of extracellular vesicles, contain many biologically active substances, such as nucleic acids, proteins and lipids, and play an important role in intercellular communication, inflammatory response, immune surveillance, tumor occurrence and other physiological or pathological processes. MicroRNA (miRNA) is an endogenous non-coding RNA that can participate in cell proliferation, differentiation, apoptosis and other processes by regulating mRNA expression. At present, the research of exosomes in the field of reproduction is in its infancy. Some studies have shown that the expression of exosomal mircoRNA is related to gamete development, embryogenesis and diseases related to infertility. This article summarizes the latest published literature, mainly reviewing the research progress of exosomal miRNA in gamete development and related diseases.

【Key words】 Infertility; Exosomes; MicroRNA; Gamete development