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· 临床研究 ·

年龄 ≤ 35 岁女性供精人工授精不同助孕方案的妊娠结局及围产结局比较

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【摘要】 目的 探讨年龄 ≤ 35 岁女性供精人工授精 (artificial insemination by donor, AID) 周期中不同助孕方案的临床结局及围产结局是否存在差异。方法 本研究为回顾性队列研究, 分析 2016 年 1 月 1 日至 2021 年 1 月 31 日期间于郑州大学第三附属医院生殖医学中心行 AID 助孕患者的临床资料, 根据是否进行促排卵治疗分为自然周期 (natural cycle, NC) 组、来曲唑 (letrozole, LE)/克罗米芬 (clomiphene, CC) 组、促性腺激素 (gonadotropin, Gn) 组和 LE/CC+Gn 组。分别比较各组间患者的临床结局、并发症发生以及子代健康情况, 并利用 logistic 回归分析探究不同助孕方案对 AID 临床结局和围产结局的影响。结果 NC 组、LE/CC 组、Gn 组和 LE/CC+Gn 组间周期取消率 [0.5% (11/2 147)、1.1% (12/1 045)、1.6% (9/549)、3.2% (9/315), $P<0.001$]、临床妊娠率 [31.5% (673/2 136)、35.8% (370/1 033)、42.8% (231/540)、38.2% (117/306), $P<0.001$]、多胎妊娠率 [0.7% (5/673)、3.2% (12/370)、3.5% (8/231)、6.8% (8/117), $P<0.001$]、流产率 [12.8% (86/673)、9.2% (34/370)、5.2% (12/231)、8.5% (10/117), $P=0.008$]以及活产率 [27.2% (581/2 136)、31.4% (324/1 033)、40.0% (216/540)、34.3% (105/306), $P<0.001$] 差异均存在统计学意义, 而异位妊娠率、早产率以及过期产率组间差异均无统计学意义 (均 $P>0.05$) ; 对混杂因素进行调整后, 除 LE/CC+Gn 组流产率高于 NC 组 (aOR=2.141, 95% CI: 1.12~4.09; $P=0.021$) , 其余各指标与 NC 组差异均无统计学意义 (均 $P>0.05$) 。对于一直使用同一种方案的患者, 仅 NC 组和 LE/CC 组累积妊娠率和累积活产率随助孕周期的增加而提高, 差异均有统计学意义 (均 $P<0.001$) 。无论是否调整混杂因素, 各组间新生儿死亡率、低体重发生率、正常体重率、巨大儿发生率、男婴占比差异均无统计学意义 (均 $P>0.05$) 。结论 在女方年龄 ≤ 35 岁的 AID 患者群体中, 刺激周期临床妊

妊娠结局与自然周期相似，不会增加 AID 周期中多胎妊娠和新生儿不良结局的风险，选择 LE/CC 刺激方案能够提高卵泡发育或排卵功能异常患者的累积妊娠率。

【关键词】 授精，人工（非丈夫供体）； 妊娠结局； 围产结局

基金项目：国家自然科学基金（81904291）

Comparison of pregnancy outcomes and perinatal outcomes of different protocols for artificial insemination by donor cycles in female patients aged ≤ 35 years

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【Abstract】 Objective To investigate whether there are differences in clinical pregnancy and perinatal outcomes among different protocols for artificial insemination by donor (AID) in female patients aged ≤ 35 years. **Methods** This retrospective cohort study analyzed clinical data of patients who underwent AID at the Reproductive Medicine Center of the Third Affiliated Hospital of Zhengzhou University from January 1, 2016 to January 31, 2021. Based on ovulation induction therapy, patients were divided into 4 groups: natural cycle (NC) group, letrozole (LE)/clomiphene (CC) group, gonadotropin (Gn) group and LE/CC combined with Gn (LE/CC+Gn) group. The clinical outcomes, incidence of complications, and offspring health were compared among these groups, and logistic regression analysis was employed to investigate the effects of different protocols on the clinical and perinatal outcomes of AID cycles. **Results** In NC group, LE/CC group, Gn group and LE/CC+Gn group, the cycle cancellation rate [0.5% (11/2 147), 1.1% (12/1 045), 1.6% (9/549), 3.2% (9/315), $P<0.001$], the clinical pregnancy rate [31.5% (673/2 136), 35.8% (370/1 033), 42.8% (231/540), 38.2% (117/306), $P<0.001$], the multiple pregnancy rate [0.7% (5/673), 3.2% (12/370), 3.5% (8/231), 6.8% (8/117), $P<0.001$], the abortion rate [12.8% (86/673), 9.2% (34/370), 5.2% (12/231), 8.5% (10/117), $P=0.008$] and the live birth rate [27.2% (581/2 136), 31.4% (324/1 033), 40.0% (216/540), 34.3% (105/306), $P<0.001$] were statistically significant, while the differences among the four groups in the ectopic pregnancy rate, the preterm birth rate, and the overdue birth rate were not statistically significant (all $P>0.05$). After adjusting for confounding factors, the differences were not statistically significant in all indicators compared with the NC group (all $P>0.05$), except for the miscarriage rate in the LE/CC+Gn group, which was significantly higher than that in the NC group (aOR=2.141, 95% CI: 1.12-4.09; $P=0.021$). For patients who have been using the same treatment protocol, the cumulative pregnancy rate and the cumulative live birth rate in the NC group and the LE/CC group increased with the increase of assisted reproductive cycles, and the difference was statistically significant (all $P<0.001$). Regardless of whether confounding factors were adjusted, there were no statistically significant differences in neonatal mortality rate, low birth weight rate, normal birth weight rate, macrosomia rate, and

male-to-female ratio among the groups (all $P>0.05$). **Conclusion** In AID cycles with female patients aged ≤ 35 years, stimulated cycles had similar pregnancy outcomes to natural cycles and did not increase the risk of adverse neonatal outcomes or multiple pregnancies. Choosing the LE/CC stimulation protocol can improve the cumulative pregnancy rate of patients with abnormal ovarian follicle development or ovulation function.

【Key words】 Insemination, artificial, heterologous; Pregnancy outcome; Perinatal outcome

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· 临床研究 ·

不孕症患者子宫内膜息肉危险因素 分析及其对 FET 结局的影响

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【摘要】 目的 探讨子宫内膜息肉(endometrial polyps, EPs)治疗后对冻融胚胎移植妊娠结局的影响。方法 采用回顾性病例对照研究, 收集 2021 年 6 月至 2022 年 12 月期间因不孕症就诊于山西省儿童医院/山西省妇幼保健院生殖医学中心接受体外受精(*in vitro* fertilization, IVF)助孕的患者资料, 将行宫腔镜检查的患者作为研究对象。宫腔镜和病理诊断 EPs 患者作为 EPs 组, 非 EPs 患者作为非 EPs 组, 对两组患者一般临床资料进行危险因素分析。对治疗后接受冻融胚胎移

植的患者和非 EPs 组移植的患者间进行妊娠结局的比较。结果 行宫腔镜检查的患者共 3 413 例, 纳入 EPs 组 444 例, 非 EPs 组 1 501 例。EPs 发生率为 13.01% (444/3 413)。EPs 组与非 EPs 组的孕次、产次、自然流产次数、人工流产次数、基础卵泡刺激素、基础黄体生成素、不孕年限、不孕类型、慢性子宫内膜炎、息肉摘除史、子宫内膜异位症组间比较差异均有统计学意义 (均 $P < 0.05$)。EPs 危险因素的多因素 logistic 回归分析显示, 不孕年限 ($OR=1.068$, 95% CI : 1.029~1.109, $P < 0.001$)、慢性子宫内膜炎 ($OR=1.925$, 95% CI : 1.481~2.502, $P < 0.001$)、原发不孕 ($OR=1.803$, 95% CI : 1.408~2.308, $P < 0.001$)、息肉摘除史 ($OR=9.424$, 95% CI : 5.586~15.897, $P < 0.001$)、子宫内膜异位症 ($OR=2.432$, 95% CI : 1.344~4.401, $P=0.003$) 是 EPs 发病的独立危险因素, 基础黄体生成素 ($OR=0.954$, 95% CI : 0.916~0.993, $P=0.022$) 为 EPs 发病的保护因素。与非 EPs 移植组相比, EPs 治疗移植组临床妊娠率、持续妊娠率、未着床率差异均无统计学意义 (均 $P > 0.05$)。结论 不孕年限、慢性子宫内膜炎、原发不孕、息肉摘除史、子宫内膜异位症是 EPs 发病的独立危险因素, 基础黄体生成素为 EPs 发病的独立保护因素。EPs 治疗后进行冻融胚胎移植患者, 可以取得与非 EPs 移植患者相似的妊娠结局。

【关键词】 不孕症; 危险因素; 妊娠结局; 冻融胚胎移植; 子宫内膜息肉; 慢性子宫内膜炎

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Risk factors analysis of endometrial polyps in infertile patients and its influence on FET outcome

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【Abstract】 **Objective** To analyse the influence of endometrial polyps (EPs) treatment on the frozen-thawed embryo transfer (FET) pregnancy outcome. **Methods** Using a retrospective case-control study, the data of patients were collected who received *in vitro* fertilization (IVF) and hysteroscopy in the Reproductive Medicine Center of Children's Hospital of Shanxi and Women Health Center of Shanxi from June 2021 to December 2022. Patients undergoing hysteroscopy were studied. According to the diagnosis results of hysteroscopy and pathology, they were selected as the EPs group or the non-endometrial polyps (NEPs) group. Then analysis of EPs risk factors was made, and the pregnancy outcome of FET after the EPs treatment was compared. **Results** A total of 3 413 patients underwent hysteroscopy in this study. The EPs group included 444 patients and the NEPs group included 1 501 patients respectively. The prevalence of EPs was 13.01% (444/3 413). There were significant differences between EPs group and NEPs group

in gravidity, parity, spontaneous abortion times, induced abortions times, basal follicle-stimulating hormone (bFSH), basal luteinizing hormone (bLH), infertility duration, infertility types, the prevalence of chronic endometritis, the history of polyps removal and endometriosis (all $P<0.05$). Multivariate logistic regression analysis of risk factors associated with EPs showed that infertility duration ($OR=1.068$, 95% CI : 1.029–1.109, $P<0.001$), chronic endometritis ($OR=1.925$, 95% CI : 1.481–2.502, $P<0.001$), primary infertility ($OR=1.803$, 95% CI : 1.408–2.308, $P<0.001$), history of polyps removal ($OR=9.424$, 95% CI : 5.586–15.897, $P<0.001$), endometriosis ($OR=2.432$, 95% CI : 1.344–4.401, $P=0.003$) were independent risk factors for EPs, and bLH ($OR=0.954$, 95% CI : 0.916–0.993, $P=0.022$) was an independent protective factor for EPs. Compared with NEPs transplantation group, there were no significant differences in clinical pregnancy rate, on-going pregnancy rate and none implantation rate in the EPs treatment transplantation group (all $P>0.05$). **Conclusion** Infertility duration, chronic endometritis, primary infertility, history of polyps removal, endometriosis were independent risk factors, and bLH was an independent protective factor. Patients in EPs treatment transplantation group could achieve the similar pregnancy outcome as NEPs transplantation group.

【Key words】 Infertility; Risk factors; Pregnancy outcome; Frozen-thawed embryo transfer; Endometrial polyps; Chronic endometritis

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· 临床研究 ·

囊胚的发育天数及质量对冻融周期单囊胚移植的临床结局影响

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【摘要】 目的 探讨囊胚的发育天数及质量对冻融周期单囊胚移植的临床结局影响，为冻融周期单囊胚移植的选择策略提供依据。**方法** 回顾性队列研究分析2013年1月至2021年6月期间在清远市人民医院生殖医学中心进行单囊胚解冻移植治疗的患者资料，共893个周期。根据囊胚发育天数分为第5天(day 5, D5)组和第6天(day 6, D6)组，再根据囊胚质量分为四个亚组，分别为D5 优质胚胎亚组($n=423$)、D5 非优质胚胎亚组($n=129$)、D6 优质胚胎亚组($n=196$)、D6 非优质胚胎亚组($n=145$)，比较各组的一般资料、临床结局和新生儿结局。**结果** ①D5组的临床妊娠率[60.14% (332/552)]、着床率[60.14% (332/552)]和活产率[47.64% (263/552)]均显著高于D6组[45.75% (156/341)、45.75% (156/341)、36.36% (124/341)]，均 $P<0.001$ ，但两组的女方体质量指数、不孕年限、移植日内膜厚度和流产率差异均无统计学意义(均 $P>0.05$)，此外，两组的新生儿出生体质量、低出生体质量发生率、巨大儿发生率和男女性别比等新生儿出生结局差异均无统计学意义(均 $P>0.05$)。②D5 优质胚胎亚组、D5 非优质胚胎亚组、D6 优质胚胎亚组、D6 非优质胚胎亚组的临床妊娠率分别为61.00% (294/482)、54.29% (38/70)、51.00% (127/249)、31.52% (29/92)，活产率分别为48.96% (236/482)、38.57% (27/70)、41.37% (103/249)、22.83% (21/92)，组间差异均有统计学意义(均 $P<0.001$)，D5 优质胚胎亚组的临床妊娠率和活产率最高，D6 非优质胚胎组的临床妊娠率和活产率最低。四个亚组的新生儿出生体质量、巨大儿发生率和男女性别比等新生儿出生结局差异均无统计学意义(均 $P>0.05$)，而低出生体质量发生率分别为5.08% (12/236)、0 (0/27)、4.85% (5/103)、23.81% (5/21)，差异有统计学意义($P=0.014$)。③D5 非优质胚胎亚组的临床妊娠率和活产率与D6 优质胚胎亚组比较差异均无统计学意义(均 $P>0.05$)，进一步比较两亚组中不同级别的囊胚，D5 非优质胚胎亚组的4BC临床妊娠率和活产率均略低于D6 优质胚胎亚组的4AA、4AB、4BA，流产率均略高于D6 优质胚胎亚组的4AA、4AB、4BA，但差异均无统计学意义(均 $P>0.05$)；D5 非优质胚胎亚组的4BC临床妊娠率和活产率均比D6 优质胚胎亚组的4BB略高，但差异均无统计学意义(均 $P>0.05$)。**结论** 冻融周期单囊胚移植时，建议优先选择D5 优质囊胚，当面临D5 非优质囊胚和D6 优质囊胚时，最优的囊胚移植顺序可能是D6 4AA>D6 4BA>D6 4AB>D5 4BC>D6 4BB。

【关键词】 单囊胚移植； 冻融周期； 囊胚质量； 临床妊娠率； 活产率

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Effect of blastocyst at different developmental stages and quality on the clinical outcomes of single blastocyst transfer in frozen-thawed cycles

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【Abstract】 Objective To explore the effect of the developmental stages and quality on pregnancy outcome and birth outcome, and provide evidence for single blastocyst selection in frozen-thawed cycles. **Methods** A retrospective cohort study analysis was performed on the data of patients with a total of 893 cycles who underwent single blastocyst transfer in frozen-thawed cycles in the Center for Reproductive Medicine, Qingyuan People's Hospital from January 2013 to June 2021. The cycles were divided into day 5 (D5) and day 6 (D6) groups according to the time of blastocyst formation. Then the two groups were divided into four subgroups according to the quality of blastocyst, namely, D5 good-quality embryo subgroup, D5 non-good-quality embryo subgroup, D6 good-quality embryo subgroup and D6 non-good-quality embryo subgroup. The general data, clinical outcomes and neonatal outcomes of each group were compared. **Results** 1) The clinical pregnancy rate [60.14% (332/552)], the implantation rate [60.14% (332/552)] and the live birth rate [47.64% (263/552)] in D5 group were significantly higher than those in D6 group [45.75% (156/341), 45.75% (156/341), 36.36% (124/341), all $P<0.001$], but there were no significant differences in body mass index, duration of infertility, intimal thickness of transplanted day and miscarriage rate between the two groups (all $P>0.05$). In addition, there were also no significant differences in birth weight, low birth weight rate, fetal macrosomia rate and male/female ratio (all $P>0.05$). 2) There were significant differences in clinical pregnancy rate [61.00% (294/482), 54.29% (38/70), 51.00% (127/249), 31.52% (29/92)] and live birth rate [48.96% (236/482), 38.57% (27/70), 41.37% (103/249), 22.83% (21/92)] among D5 good-quality embryo subgroup, D5 non-good-quality embryo subgroup, D6 good-quality embryo subgroup and D6 non-good-quality embryo subgroup (all $P<0.001$). D5 good-quality embryo subgroup had the highest clinical pregnancy rate and live birth rate, while D6 non-good-quality embryo subgroup had the lowest clinical pregnancy rate and live birth rate. There were also no significant differences in birth weight, fetal macrosomia rate and male/female ratio among the four subgroups (all $P>0.05$), while there was a significant difference in low birth weight rate [5.08% (12/236), 0 (0/27), 4.85% (5/103), 23.81% (5/21)] among the four subgroups ($P=0.014$). 3) There were no significant differences in clinical pregnancy rate and live birth rate between D5 non-good-quality embryo subgroup and D6 good-quality embryo subgroup (all $P>0.05$). The clinical pregnancy rate and the live birth rate of 4BC in D5 were lower than those of 4AA, 4AB and 4BA in D6, while the miscarriage rate of 4BC in D5 was higher than that of 4AA, 4AB and 4BA in D6, but there were no significant differences (all $P>0.05$). The clinical pregnancy rate and the live birth rate of 4BC in D5 were higher than those of 4BB in D6, but there were no significant differences (all $P>0.05$). **Conclusion** In the frozen-thawed cycle of single blastocyst transplantation, D5 good-quality blastocysts are preferred. When faced with D5 non-

good-quality embryos and D6 good-quality embryos, the optimal choice was D6 4AA>D6 4BA>D6 4AB>D5 4BC>D6 4BB.

【Key words】 Single blastocyst transfer; Frozen-thawed cycle; Blastocyst quality; Clinical pregnancy rate; Live birth rate

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· 临床研究 ·

季节对新鲜周期胚胎移植临床结局的影响

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【摘要】 目的 探讨取卵日的季节、温度和累积日照是否影响体外受精 (*in vitro* fertilization, IVF) 新鲜周期移植结局。方法 本研究为回顾性队列研究, 分析 2015 年 8 月至 2019 年 10 月期间在郑州大学第三附属医院生殖医学科行 IVF 助孕患者, 根据取卵日期分为四组, 春季组: 取卵日期在 3~5 月; 夏季组: 取卵日期在 6~8 月; 秋季组: 取卵日期在 9~11 月; 冬季组: 取卵日期在 12 月~次年 2 月, 分析四组间促排卵及移植的临床结局, 主要观察指标是临床妊娠率和活产率, 并通过二元逻辑回归分析影响临床妊娠率及活产率的因素。结果 四组间的流产率和活产率差异均无统计学意义 (均 $P>0.05$)。通过组间两两比较提示冬季组的临床妊娠率 [56.9% (816/1435)] 低于夏季组 [61.5% (1359/2210)], $P=0.005$, 以冬季组为参照, 夏季组的临床妊娠率较高 (aOR=1.25, 95% CI: 1.09~1.44, $P=0.002$), 春季组 (aOR=1.14, 95% CI: 0.99~1.32, $P=0.073$) 和秋季组 (aOR=1.09, 95% CI:

0.94~1.26, $P=0.254$) 的临床妊娠率与冬季组差异无统计学意义。二元逻辑回归分析显示平均温度越高, 临床妊娠率越高 ($aOR=1.01$, 95% CI : 1.00~1.01, $P=0.005$)。取卵日的季节、温度以及累积日照对活产率无显著影响。结论 夏季和高温是临床妊娠率的独立且有利的影响因素。而不同季节、温度以及累积日照对活产率无显著影响。

【关键词】 受精, 体外; 季节; 温度; 活产率; 临床妊娠率

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Effects of season on clinical outcomes of fresh embryo transfer

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【Abstract】 Objective To investigate whether there is an association between season, temperature, as well as cumulative sunlight exposure on the day of oocyte retrieval and clinical outcomes of *in vitro* fertilization (IVF) and fresh embryo transfer. **Methods** It was a retrospective cohort study, including patients who underwent IVF in the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University from August 2015 to October 2019. They were divided into four groups according to the oocyte retrieval date. Spring group: the oocyte retrieval date was from March to May. Summer group: the date of oocyte retrieval was from June to August. Autumn group: the date of oocyte retrieval was from September to November. Winter group: the date of oocyte retrieval was from December to February of the next year. The main outcome measures were clinical pregnancy rate and live birth rate. Binary logistic regression was used to explore the factors affecting clinical pregnancy rate and live birth rate. **Results** There were no significant differences in the miscarriage rate and the live birth rate among the four groups (all $P>0.05$). The pairwise comparison between the groups indicated that the clinical pregnancy rate in the winter group [56.9% (816/1 435)] was lower than that in the summer group [61.5% (1 359/2 210), $P=0.005$]. Taking winter as the reference, the clinical pregnancy rate in summer was higher ($aOR=1.25$, 95% CI : 1.09-1.44, $P=0.002$). The clinical pregnancy rate in spring ($aOR=1.14$, 95% CI : 0.99-1.32, $P=0.073$) and autumn ($aOR=1.09$, 95% CI : 0.94-1.26, $P=0.254$) was not significantly different from winter. Binary logistic regression analysis showed that higher mean temperature was associated with higher clinical pregnancy rate ($aOR=1.01$, 95% CI : 1.00-1.01, $P=0.005$). Season, temperature and cumulative sunshine on the day of egg retrieval had no significant effect on the live birth rate. **Conclusion** Summer and high temperature are independent and favorable influencing factors of clinical pregnancy rate. However, different seasons, temperatures and cumulative sunshine had no significant effect on live birth rate.

【Key words】 Fertilization *in vitro*; Season; Temperature; Live birth rate; Clinical pregnancy rate

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· 临床研究 ·

比较 SNP-array 和高通量测序在胚胎植入前遗传学检测中的效能

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【摘要】 目的 评估单核苷酸多态性微阵列 (single nucleotide polymorphisms array, SNP-array) 技术和第二代高通量测序 (next generation sequencing, NGS) 技术在胚胎植入前遗传学检测 (preimplantation genetic testing, PGT) 中的检测能力和效率。方法 回顾性描述分析 2020 年 1 月至 2022 年 8 月期间于广西壮族自治区妇幼保健院生殖中心就诊、夫妇双方均携带有明确致病性基因突变并要求进行第三代试管婴儿助孕的 188 例患者资料。经卵胞质内单精子注射受精和体外培养后, 共收获 995 枚囊胚并进行活检。患者胚胎细胞遗传物质经全基因组扩增之后, 分别采用 SNP-array 或 NGS 分析其携带致病基因突变和染色体拷贝数变异 (copy number variation, CNV) 的情况, 同时采用 Sanger 测序或间隙聚合酶链反应 (polymerase chain reaction, PCR) 对突变进行直接检测。分析女方年龄和获囊胚数的关系、胚胎携带突变和致病性 CNVs 的比例, 比较不同分子诊断技术在 PGT 中的检测成功率和准确性。经遗传学检测后, 选择合适的胚胎进行子宫腔内移植, 并于中孕期进行羊水穿刺产前诊断。结果 ①成功对 924 个胚胎进行遗传学检测, 总的检测成功率为 92.9%。根据遗传学检测结果, 共有 389 个 (42.1%) 胚胎可用于移植。②对胚胎进行缺失型 α -地中海贫血突变检测, 间隙 PCR 的成功率 [84.9% (465/548)] 低于 SNP-array [98.7% (81/82)] 和 NGS [92.5% (431/466)]。对点突变进行检测, Sanger 测序的成功率 [98.5% (440/447)] 与 SNP-array [95.6% (110/115)] 和 NGS [96.1% (319/332)] 的差异无统计学意义。有 38 个胚胎因等位基因脱扣导致直接位点检测法的结果与 SNP 单体型分析的结果不一致。另外,

有 4 个胚胎因染色体重组导致 SNP 单体型分析失败。③与 NGS 相比, SNP-array 检测 CNV 的成功率 [83.7% (165/197)] 较低, 但是可检出更多种类的染色体拷贝数异常。④共进行了 152 例胚胎移植, 其中有 107 例成功临床妊娠, 有 69 例完成了羊水穿刺产前诊断, 有 42 个健康儿顺利分娩。结论 从检测效率考虑, SNP-array 适用于分析胚胎携带多个基因突变、罕见单基因突变或者缺失型突变, 而 NGS 适用于检测常见的单基因突变类型。同时辅以 Sanger 测序和间隙 PCR 等技术对突变位点直接进行检测, 可进一步提高 PGT 的检测成功率和准确性。本研究成果可为 PGT 从业者根据突变类型和患者的需求选择合适的检测平台提供依据。

【关键词】 胚胎植入前遗传学检测; SNP 单体型分析; 第二代高通量测序技术

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Comparison of SNP-array and next generation sequencing in preimplantation genetic testing

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【Abstract】 **Objective** To evaluate the detection ability and efficiency of single nucleotide polymorphisms array (SNP-array) and next generation sequencing (NGS) in preimplantation genetic testing (PGT). **Methods** Totally 188 couples who carried pathogenic gene mutation and requested preimplantation genetic testing for monogenic (PGT-M) treatment were retrospectively analyzed in the Reproductive Center of Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region during January 2020 and August 2022. After ovulation induction, insemination was conducted by intracytoplasmic sperm injection (ICSI) and cultured *in vitro*, 995 blastocysts were harvested and biopsied. After whole genome amplification (WGA) of the genetic material from embryonic cell samples, their carrying status of mutations and chromosome copy number variations (CNVs) were analyzed by SNP-array or NGS, respectively, and along with mutation direct detection by Sanger sequencing or Gap-PCR. The relationship between female age and the number of blastocysts was analyzed, as well as the proportion of embryos carrying mutations and pathogenic CNVs. The detection success rate and accuracy of different molecular diagnostic techniques used in PGT were compared. Amniocentesis prenatal diagnosis was performed in the second trimester after successful intrauterine transfer of embryos. **Results** 1) A total of 924 embryo samples were successfully performed genetic testing, with a total success rate of 92.9%, and 389 embryos (42.1%) can be transferred according to these results. 2) In detecting deletional α -thalassemia, the success rate of Gap-PCR [84.9% (465/548)] was lower than that of SNP-array [98.7% (81/82)] and NGS [92.5% (431/466)]. However, the success rate of direct mutation detection by Sanger sequencing [98.5% (440/447)] was not significantly different from that by SNP-array [95.6% (110/115)] and NGS [96.1% (319/332)]. There were 38 embryo samples with direct mutation detection results

inconsistent with those based on SNP haplotyping. In addition, 4 embryo samples failed SNP haplotyping due to chromosomal recombination. 3) Compared with NGS, SNP-array had a lower success rate [83.7% (165/197)] in detecting CNVs, but it could find out more types of chromosomal abnormalities. 4) A total of 152 embryo transfers were performed, 107 patients got clinical pregnancies, 69 patients completed amniocentesis prenatal diagnosis, and 42 healthy infants were delivered.

Conclusion In considering the detection efficiency, SNP-array is suitable for analyzing embryos which carry multiple pathogenic genes, rare monogenic or deletion mutations, whereas NGS is suitable for detecting common types of mutations. Meanwhile, using Sanger sequencing and Gap-PCR to directly detect the mutations can improve the success rate and accuracy of PGT. Our findings would provide a basis for PGT technicians to select appropriate detection platforms based on the type of mutations and the situation of patients.

【Key words】 Preimplantation genetic testing; SNP haplotyping; Next generation sequencing

Fund program: Guangxi Medical and Health Appropriate Technology Research and Development Project (S201541)

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· 实验研究 ·

ESR1 和 *PRKN* 基因甲基化在多囊卵巢综合征发病中的作用及机制研究

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【摘要】 目的 探讨 *ESR1* 和 *PRKN* 基因甲基化水平与多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 发生的关系及其机制。方法 采用病例对照研究, 选取 2021 年 1 月至 2021 年 6 月期间在山西医科大学第一医院生殖医学科就诊的 60 例 PCOS 患者 (PCOS 组) 及 40 例正常育龄妇女 (对照组) 为研究对

象,提取全血 DNA 及总 RNA,采用甲基化特异性聚合酶链反应(methylation specific polymerase chain reaction, MS-PCR)技术检测研究对象外周血 *ESR1* 和 *PRKN* 基因启动子区的甲基化状态,并采用实时荧光定量 PCR 检测 *ESR1* 和 *PRKN* 基因 mRNA 表达水平,分析 *ESR1* 和 *PRKN* 基因启动子区甲基化状态和 mRNA 表达水平与 PCOS 发生的关系。结果 PCOS 组患者外周血 *ESR1* 基因启动子区甲基化水平 [56.7% (34/60)] 显著低于对照组 [77.5% (31/40), $P=0.035$]; *PRKN* 基因启动子区甲基化水平 [76.7% (46/60)] 显著高于对照组 [52.5% (21/40), $P=0.012$]。PCOS 组患者外周血 *ESR1* mRNA 表达水平 (1.30 ± 0.93) 显著高于对照组 (0.97 ± 0.50 , $P=0.034$); PCOS 组患者的 *PRKN* mRNA 表达水平 (1.06 ± 0.83) 与对照组相比差异无统计学意义 (1.15 ± 1.01 , $P>0.05$)。结论 PCOS 患者 *ESR1* 和 *PRKN* 基因甲基化水平改变导致其表达水平改变,进而在 PCOS 的发生中发挥了重要作用。

【关键词】 甲基化; 多囊卵巢综合征; *ESR1*; *PRKN*

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Role and mechanism of *ESR1* and *PRKN* gene methylation in the pathogenesis of polycystic ovary syndrome

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【 Abstract 】 **Objective** To investigate the relationship between methylation levels of *ESR1*, *PRKN* genes and the occurrence of polycystic ovary syndrome (PCOS). **Methods** In a case-control study, 60 patients with PCOS (PCOS group) and 40 women of normal reproductive age (control group) attending the Department of Reproductive Medicine, the First Hospital of Shanxi Medical University from January 2021 to June 2021 were enrolled. The peripheral blood DNA and total RNA were extracted, and the methylation specific polymerase chain reaction (MS-PCR) technique was used to detect the methylation status of *ESR1* and *PRKN* genes promoter regions. The mRNA expression levels of *ESR1* and *PRKN* genes were measured by real-time quantitative PCR. The relationship between the methylation status, mRNA expression levels of these two genes and the occurrence of PCOS were analyzed. **Results** The methylation level of *ESR1* gene in PCOS patients [56.7% (34/60)] was significantly lower than that in control group [77.5% (31/40), $P=0.035$]; while the methylation level of *PRKN* gene in PCOS patients [76.7% (46/60)] was significantly higher than that in control group [52.5% (21/40), $P=0.012$]. The expression level of *ESR1* mRNA in PCOS patients (1.30 ± 0.93) was significantly higher than that in control group (0.97 ± 0.50 , $P=0.034$); while there was no difference of *PRKN* expression level between PCOS (1.06 ± 0.83) and control groups (1.15 ± 1.01 , $P>0.05$). **Conclusion** The methylation levels in the promoter regions of *ESR1* and *PRKN* genes lead to the changes of the mRNA expression levels, which in turn play an important role in the occurrence of PCOS.

【Key words】 Methylation; Polycystic ovary syndrome; *ESR1*; *PRKN*

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· 实验研究 ·

miR-29a-3p 靶向 *SGMS2* 调控 PCOS 卵巢颗粒细胞慢性炎症的机制研究

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【摘要】 目的 探究 miR-29a-3p/*SGMS2* 轴对人类卵巢颗粒样肿瘤细胞系 (human ovarian granulosa-like tumor cell line, KGN) 炎症反应的调控机制。方法 通过构建并验证过表达和敲低 miR-29a-3p 及 *SGMS2* 转染 KGN 细胞模型, 双荧光素酶报告基因实验检测 miR-29a-3p 与 *SGMS2* 的结合; MTT 法检测各组细胞的增殖; 免疫荧光法观察增殖细胞核抗原 (proliferating cell nuclear antigen, PCNA) 和 Ki67 蛋白荧光强度; 流式细胞术检测细胞凋亡; 酶联免疫吸附法检测细胞上清液中肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白介素 (interleukin, IL)-6、IL-1 β 和鞘磷脂的表达; Western blotting 检测细胞中 Caspase-3、cleaved-Caspase-3、*SGMS2* 和 p-p65 蛋白表达。结果 miR-29a-3p 与 *SGMS2* 之间存在位点结合, 且能够负向调控 *SGMS2* 的表达水平。KGN 细胞中过表达 *SGMS2* 能够增高其吸光度值 ($P=0.007$), 并增强其 PCNA 和 Ki67 蛋白的免疫荧光强度 (均 $P<0.001$); 过表达 *SGMS2* 能够降低 KGN 细胞的凋亡率 ($P=0.001$), 升高炎症因

子 TNF- α 、IL-6、IL-1 β 和鞘磷脂的表达水平 (均 $P<0.001$)。过表达 *SGMS2* 时 KGN 细胞中 cleaved-Caspase-3、p-p65 和 *SGMS2* 蛋白表达量升高 ($P=0.001$, $P<0.001$, $P<0.001$)。而敲低 *SGMS2* 时, 以上结果具有与过表达 *SGMS2* 相反的变化趋势。结论 miR-29a-3p 与 *SGMS2* 之间存在靶向负向调节关系, *SGMS2* 能够促进 KGN 细胞的炎症反应, 可为多囊卵巢综合征等妇科内分泌疾病的治疗提供靶点。

【关键词】 多囊卵巢综合征; miR-29a-3p; 神经鞘磷脂合成酶 2; 卵巢颗粒细胞; 炎症

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Mechanism study of miR-29a-3p targeting *SGMS2* to regulate chronic inflammation in PCOS ovarian granulosa cells

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【Abstract】 Objective To investigate the regulatory mechanism of miR-29a-3p/*SGMS2* axis on the inflammatory response of ovarian granulosa cells (KGN). **Methods** By constructing and validating overexpression and knockdown of miR-29a-3p and *SGMS2* transfected KGN cell models, dual luciferase reporter gene assay was used to detect the binding of miR-29a-3p to *SGMS2*. MTT assay was used for detecting the cell proliferation. Fluorescence intensity of proliferating cell nuclear antigen (PCNA) and Ki67 protein were detected by immunofluorescence. Apoptosis was detected by flow cytometry. The expression levels of tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-1 β and sphingomyelin in cell supernatant were detected by enzyme-linked immunosorbent assay. The protein expression levels of Caspase-3, cleaved-Caspase-3, *SGMS2* and p-p65 in KGN were detected by Western blotting. **Results** miR-29a-3p had site-specific binding to *SGMS2* and can negatively regulated *SGMS2* expression level. Overexpression of *SGMS2* in KGN cells was able to increase their levels of absorbance ($P=0.007$) and enhanced the immunofluorescence intensity of the protein of PCNA and Ki67 (all $P<0.001$). Overexpression of *SGMS2* could reduce the apoptosis rate of KGN cells ($P=0.001$). Overexpression of *SGMS2* increased the expression levels of TNF- α , IL-6, IL-1 β and sphingomyelin (all $P<0.001$). The expressions of cleaved-Caspase-3, p-p65 and *SGMS2* proteins were elevated in KGN cells when *SGMS2* was overexpressed ($P=0.001$, $P<0.001$, $P<0.001$), while knock down *SGMS2*, the above results had a trend of change opposite to overexpression of *SGMS2*. **Conclusion** There is a targeted negative regulatory relationship between miR-29a-3p and *SGMS2*, which

can promote the inflammatory response of KGN and may provide a target for the treatment of polycystic ovary syndrome.

【Key words】 Polycystic ovary syndrome; miR-29a-3p; Sphingomyelin synthase 2; Ovarian granulosa cells; Inflammation

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• 临床报道 •

小剂量阿托西班对选择性单胚胎移植患者妊娠结局的影响

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【摘要】 目的 探讨小剂量缩宫素受体拮抗剂阿托西班对选择性单胚胎移植 (elective single embryo transfer, eSET) 妊娠结局的影响。方法 回顾性队列研究分析 2015 年 1 月至 2021 年 8 月期间于天津市第一中心医院生殖医学科接受 eSET 且为第 1~2 次接受胚胎移植患者的临床资料, 根据胚胎发育时间和治疗方案不同分为新鲜卵裂期胚胎周期、冻融卵裂期胚胎周期及冻融囊胚周期。根据移植前 30 min 是否静脉推注小剂量阿托西班分为阿托西班组和对照组, 利用倾向性评分匹配 (propensity score matching, PSM) 进行 1:2 匹配, 分析比较各组患者的生化妊娠率、临床妊娠率、流产率、异位妊娠率、活产率及出生缺陷率的差异。结果 通过 PSM 新鲜卵裂期胚胎周期共纳入 243 例患者 (阿托西班组 81 例, 对照组 162 例), 冻融卵裂期胚胎周期共纳入 210 例患者 (阿托西班组 70 例, 对照组 140 例), 冻融囊胚周期共纳入 216 例患者 (阿托西班组 72 例, 对照组 144 例)。新鲜卵裂期胚胎、冻融卵裂期胚胎或冻融囊胚 eSET 时, 阿托西班组的生化妊娠率、临床妊娠率、流产率、异位妊娠率、活产率及出生缺陷率与对照组比较差异均无统计学意义 (均 $P>0.05$)。结论 胚胎移植前静脉推注小剂量阿托西班未能显著改善 eSET 患者的妊娠结局。

【关键词】 单胚胎移植; 妊娠结局; 活产; 阿托西班; 流产

Effect of low-dose atosiban on pregnancy outcome in patients with elective single embryo transfer

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【Abstract】 Objective To investigate the effect of low-dose oxytocin receptor antagonist atosiban on the pregnancy outcome of the elective single embryo transfer (eSET). **Methods** A retrospective cohort study was performed on the clinical data of patients who got eSET at Department of Reproductive Medicine, Tianjin First Central Hospital from January 2015 to August 2021 and had a first- or second-time embryo transfer. They were divided into fresh cleavage stage embryo cycles, frozen-thawed cleavage stage embryo cycles, and frozen-thawed blastocyst cycles, depending on the days of embryological development and the treatment strategy. Patients were divided into atosiban group and control group according to whether or not they received an intravenous injection of 6.75 mg of atosiban 30 min before implantation. Propensity score matching (PSM) with a ratio of 1 : 2 was utilized to match the patients in each group. The differences in the rates of biochemical pregnancy, clinical pregnancy, abortion, ectopic pregnancy, live birth, and birth defects were evaluated. **Results** PSM included 243 patients in fresh cleavage stage embryo cycles (81 patients in the atosiban group and 162 patients in control group), 210 patients in frozen-thawed cleavage stage embryo cycles (70 patients in the atosiban group and 140 patients in control group), and 216 patients in frozen-thawed blastocyst cycles (72 patients in the atosiban group and 144 patients in control group). At eSET of fresh cleavage stage embryos, frozen-thawed cleavage stage embryos, or frozen-thawed blastocysts, the biochemical pregnancy rate, the clinical pregnancy rate, the miscarriage rate, the ectopic pregnancy rate, the live birth rate, and the birth defect rate in atosiban group were not statistically different from those in control group (all $P>0.05$). **Conclusion** Intravenous injection of low dosage of atosiban before eSET failed to significantly improve the pregnancy outcome of infertile patients.

【Key words】 Single embryo transfer; Pregnancy outcome; Live birth; Atosiban; Abortion

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• 临床报道 •

比较卵巢储备功能正常患者拮抗剂方案超促排卵中 hCG 扳机与双扳机的应用效果

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【摘要】 目的 研究卵巢储备功能正常人群拮抗剂方案超促排卵中，人绒毛膜促性腺激素（human chorionic gonadotropin, hCG）扳机与双扳机对体外受精-胚胎移植（*in vitro* fertilization and embryo transfer, IVF-ET）结局的影响。方法 采用回顾性队列研究，分析 2019 年 1 月至 2022 年 12 月期间在四川省妇幼保健院生殖医学中心 IVF-ET 助孕的 239 例患者资料，患者卵巢储备功能正常，采用拮抗剂方案超促排卵。根据扳机方式不同分为两组，A 组：重组 hCG（recombinant hCG, rhCG）250 μg（*n*=143）；B 组：促性腺激素释放激素激动剂 0.2 mg 联合 hCG 2 000 U 进行双扳机（*n*=96）。比较两组患者卵母细胞及胚胎发育情况、妊娠结局等。结果 两组成熟卵率、正常受精率、第 3 天胚胎形成率、第 3 天优质胚胎率、囊胚形成率、优质囊胚率差异均无统计学意义（均 *P*>0.05）。A 组的中度卵巢过度刺激综合征（ovarian hyperstimulation syndrome, OHSS）发生率为 1.40%（2/143），高于 B 组 [0（0/96）]，但差异无统计学意义（*P*>0.05）。新鲜及解冻胚胎移植周期胚胎着床率和临床妊娠率差异均无统计学意义（均 *P*>0.05）。结论 卵巢储备功能正常患者，双扳机与 hCG 扳机比较，卵母细胞、胚胎质量、妊娠结局无明显差异，双扳机似乎有减少 OHSS 发生的趋势。

【关键词】 受精，体外； 胚胎移植； 拮抗剂方案； 人绒毛膜促性腺激素扳机； 双扳机

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Comparison of the application effects between hCG trigger and dual trigger in patients with normal ovarian reserve undergoing controlled ovarian hyperstimulation with antagonist protocol

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【Abstract】 Objective To investigate the effects of human chorionic gonadotropin (hCG) trigger and dual trigger on the outcome of *in vitro* fertilization and embryo transfer (IVF-ET) during superovulation with an antagonist regimen in individuals with normal ovarian reserve function. **Methods** A retrospective cohort study was carried out. A total of 239 patients with normal ovarian reserve undergoing IVF-ET from January 2019 to November 2022 at the Reproductive Medicine Center of Sichuan Provincial Women's and Children's Hospital were enrolled. The patients were divided into two groups based on the types of the trigger, group A ($n=143$) was given 250 μg recombinant hCG (rhCG), group B ($n=96$) was given a dual trigger comprising 0.2 mg gonadotropin releasing-hormone agonist and 2 000 U hCG. The quality of oocytes and embryos, outcomes of pregnancy between the two groups were compared. **Results** There were no statistically significant differences in mature oocyte rate, normal fertilization rate, embryo formation rate on day 3 (D3), high-quality embryo rate, blastocyst formation rate, or high-quality blastocyst rate between the two groups (all $P>0.05$). The incidence of moderate ovarian hyperstimulation syndrome (OHSS) in group A was 1.40% (2/143), which was higher than that of group B [0 (0/96)], but the difference was not statistically significant ($P>0.05$). There were no statistically significant differences in embryo implantation rate and clinical pregnancy rate between the two groups during the fresh and frozen-thawed embryo transfer cycles (all $P>0.05$). **Conclusion** In patients with normal ovarian reserve function, there are no significant differences in oocyte and embryo quality, and pregnancy outcome between the dual trigger and hCG trigger. The dual trigger has a tendency to reduce the incidence of OHSS.

【Key words】 Fertilization *in vitro*; Embryo transfer; Gonadotropin-releasing hormone antagonist protocol; Human chorionic gonadotropin trigger; Dual trigger

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• 临床报道 •

反复着床失败患者慢性子宫内膜炎的诊治价值

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【摘要】 目的 探索反复着床失败 (recurrent implantation failure, RIF) 患者合并慢性子宫内膜炎 (chronic endometritis, CE) 经过抗生素治疗后行冻融胚胎移植 (frozen-thawed embryo transfer, FET) 的妊娠结局。方法 采用回顾性队列研究分析 2018 年 1 月至 2021 年 12 月期间于华中科技大学同济医学院附属同济医院生殖医学中心就诊的 496 例 RIF 患者, 在下次冻融胚胎助孕前行宫腔镜检查及子宫内膜组织活检。依据内膜组织病理学检查结果和后续的治疗方案, 共纳入患者 494 例, 分为 CE 治愈组 (CD138 强阳性经抗生素治疗后转阴, $n=103$)、可疑 CE 组 (CD138 弱阳性, $n=76$)、非 CE 组 (CD138 阴性, $n=230$)、对照组 (宫腔镜检查+诊断性刮宫, 未进行 CE 组织病理学筛查, $n=85$), 分析比较各组患者宫腔镜术后首次 FET 的妊娠结局。结果 RIF 人群中 CE 的发病率为 25.5% (105/411), 宫腔镜诊断 CE 的灵敏度为 55.2%, 特异度为 83.0%。CE 患者在经过 1 个周期抗生素治疗后转阴率为 86.7% (91/105), 2 个周期治疗后转阴率为 98.1% (103/105)。通过多因素 logistic 回归分析去除年龄、卵巢储备功能、既往移植周期数、FET 周期移植胚胎数、胚胎类型以及优质胚胎数等混淆因素后, 与对照组相比, CE 治愈组 FET 周期临床妊娠率得到明显改善 ($OR=2.625$, 95% CI : 1.104~6.239, $P=0.029$)。结论 RIF 患者应重视 CE 的筛查, 如果确诊为 CE, 建议在胚胎移植前给予药物治疗, 有利于改善 FET 周期的妊娠结局。

【关键词】 宫腔镜; CD138; 慢性子宫内膜炎; 反复着床失败; 冻融胚胎移植

基金项目: 国家重点研发计划专项 (2021YFC2700603)

Value of diagnosis and treatment of chronic endometritis in patients with recurrent implantation failure

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【Abstract】 Objective To explore the pregnancy outcomes of frozen-thawed embryo transfer (FET) after antibiotic treatment in patients with recurrent implantation failure (RIF) and chronic endometritis (CE). **Methods** A retrospective cohort study was conducted to analyze 496 women with RIF undergoing hysteroscopy and endometrial biopsy before the next FET in Reproductive Medicine Center of Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology from January 2018 to December 2021. According to the pathological results of endometrial biopsy and subsequent treatment, the patients were divided into cured CE group (strong positive CD138 was converted to negative after antibiotic treatment, $n=103$), suspected CE group (weak positive CD138, $n=76$), non-CE group (negative CD138, $n=230$) and control group (hysteroscopy and diagnostic

only, no CE-related histopathological screening, $n=85$). The pregnancy outcomes after FET were compared among the four groups. **Results** The prevalence of CE in the patients with RIF was 25.5% (105/411), and the sensitivity of hysteroscopy for the diagnosis of CE was 55.2% and the specificity was 83.0%. The conversion rate of patients with CE was 86.7% (91/105) after 1 cycle of antibiotic treatment and 98.1% (103/105) after 2 cycles of treatment. After removing the confounding factors of age, ovarian reserve function, number of previous transfer cycles, number and type of embryos transferred in FET cycle, and number of high-quality embryos, multivariate regression analysis showed that the clinical pregnancy rate of the cured CE group improved significantly after antibiotic treatment ($OR=1.841$, 95% CI : 1.123–3.020, $P=0.029$). **Conclusion** Patients with RIF should be screened for CE, and if CE is diagnosed, pharmacological treatment is recommended prior to embryo transfer, which is beneficial to improve pregnancy outcomes in FET cycles.

【Key words】 Hysteroscopy; CD138; Chronic endometritis; Recurrent implantation failure; Frozen-thawed embryo transfer

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• 临床报道 •

经阴囊联合经直肠超声对梗阻性无精子症定位诊断的价值

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【摘要】 目的 评估经阴囊联合经直肠超声检查诊断梗阻性无精子症的临床准确性。方法 回顾性分析 2015 年 6 月至 2020 年 5 月期间在上海交通大学医学院附属第一人民医院男科就诊的 58 例无精子不育症患者资料。超声检查提示梗阻性无精子症并进行手术证实,将其声像图上的定性与定位参数与手术结果进行对照分析。结果 58 例声像图提示输精管道梗阻中,3 例睾丸内梗阻行睾丸显微取精术;21 例附睾梗阻中 18 例行附睾输精管吻合术;6 例输精管梗阻行输精管吻合术;3 例射精管梗阻,其中有 2 例低位梗阻行经尿道射精管切开术,1 例高位梗阻行睾丸显微取精术;25 例先天性输精管道缺如者行阴囊探查术并留取精子以备辅助生殖。57 例术中附睾液或睾丸组织镜检到精子,超声定性诊断正确率为 98.3%(57/58)。54 例术中所见与术前超声定位一致,定位诊断的符合率为 93.1%(54/58)。结论 阴囊联合经直肠超声检查能较准确地定性和定位诊断梗阻性无精子症,对该病的正确诊断及治疗方案选择具有十分重要的临床意义。

【关键词】 显微外科手术; 阴囊超声; 经直肠超声; 梗阻性无精子症
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Value of scrotal combined with transrectal ultrasound in the emplacement diagnosis of obstructive azoospermia

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【Abstract】 **Objective** To evaluate the accuracy of imaging findings on scrotal and transrectal ultrasonography in diagnosing the disease of obstructive azoospermia. **Methods** Retrospective analysis of the data of 58 patients with azoospermia and infertility were performed who visited the Department of Andrology in the Shanghai General Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from June 2015 to May 2020. Obstructive azoospermia was revealed by ultrasonography and confirmed by surgery. The qualitative and positional parameters on the sonogram were compared with the surgical results. **Results** Among 58 patients with obstructive azoospermia diagnosed by ultrasonography, 3 patients with intratesticular obstruction performed microsurgical sperm extraction. In 21 patients with epididymal obstruction, 18 cases were treated by vasoepididymostomy. Six patients with vas deferens obstruction were treated by vasovasostomy. Two cases with low-level ejaculatory duct obstruction were treated by transurethral resection of the ejaculatory duct, and 1 case with high-level ejaculatory duct obstruction was treated by microsurgical sperm extraction. A total of 25 patients with congenital absence of bilateral vas

deferens performed scrotal exploration and sperm collection for assisted reproduction. Sperm was detected in epididymal fluid or testicular tissue in 57 cases. The accuracy of the diagnosis of obstructive azoospermia by ultrasound scan was 98.3% (57/58) with reference to the existence of sperm identified in the surgery. The intraoperative findings of 54 cases were consistent with the preoperative ultrasound localization, and the coincidence rate of emplaced diagnosis was 93.1% (54/58). **Conclusion** Scrotal and transrectal ultrasound can accurately diagnose obstructive azoospermia qualitatively and regionally, which is of great clinical significance for the correct diagnosis and treatment of the disease.

【 Key words 】 Microsurgery; Scrotal ultrasonography; Transrectal ultrasonography; Obstructive azoospermia

Fund program: Clinical Research Plan of SHDC (SHDC2020CR3088B)

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· 现场调查 ·

2010—2019 年云南省农村育龄人群孕前健康风险分析

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【摘要】 目的 了解云南省农村育龄人群的疾病与健康状况, 获得孕前人群健康风险的时间、空间及人群分布数据。方法 对 2010—2019 年 10 年间云南省参加免费孕前优生健康检查的 1 445 656 对农村夫妇健康风险因素的三间分布进行统计分析。结果 2010—2019 年间, 云南省农村育龄人群中, 妻子生育年龄风险逐年增高 (线性检测值 5 175.82, $P<0.001$), 偏瘦率逐年降低 (线性检测值 503.43, $P<0.001$); 丈夫和妻子超重率逐年上升 (丈夫线性检测值 6 358.09, $P<0.001$; 妻子为 4 947.09, $P<0.001$); 生育间隔期避孕率逐年下降 (线性检测值 40 389.67, $P<0.001$)。云南省 16 个州市的地区分布方面, 超重率、吸烟率、饮酒率、高血压患病率、乙肝表面抗原阳性率、梅毒阳性率、糖尿病风险、地中海贫血风险、环境暴露、不孕症风险差异均具有统计学意义 (州市卡方检验均 $P<0.05$)。人群分布方面, 备孕胎次越高, 孕前健康风险越高; 经济越落后, 生育年龄风险越高, 乙肝梅毒阳性率越高, 地中海贫血、不孕症风险越高; 经济越发达, 超重率越高, 环境暴

露风险越高，男性吸烟饮酒率越高（线性检测均 $P<0.05$ ）。结论 需高度重视超重、肥胖发展趋势，加强避孕节育宣传指导。乡村振兴应关注落后地区的乙肝、梅毒传播；地中海贫血综合防控资源的分配需要向滇南高风险地区倾斜；需精准防控孕前生殖健康风险，推进项目向及时、连续、完整、系统的服务转型，阻断疾病代际传递。

【关键词】 孕前优生； 健康风险； 三间分布； 健康云南

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Pre-pregnancy health risk analysis of rural population of childbearing age in Yunnan Province from 2010 to 2019

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【Abstract】 Objective To understand the disease and health status of rural population of childbearing age in Yunnan, and to obtain the temporal, spatial and population distribution data of health risks of pre-pregnancy population.

Methods The temporal, spatial and population distribution of health risk factors of 1 445 656 rural couples who participated in free pre-pregnancy health examination in Yunnan Province from 2010 to 2019 was analyzed statistically.

Results From 2010 to 2019, among the rural population of childbearing age in Yunnan Province, the risk of wife's childbearing age increased year by year (linear by linear association value 5 175.82, $P<0.001$). The emaciation rate was the opposite (linear by linear association value 503.43, $P<0.001$). The rate of overweight in husbands and wives increased gradually (husbands linear by linear association value 6 358.09, $P<0.001$; wives linear by linear association value 4 947.09, $P<0.001$). The rate of contraceptive use between births declined year by year (linear by linear association value 40 389.67, $P<0.001$). There were significant differences in the rates of overweight, smoking, drinking, prevalence of hypertension, anti-hepatitis B positive, syphilis positive and the risk of diabetes, thalassaemia, environmental exposure and infertility risk in 16 cities of Yunnan Province (all Chi-square test $P<0.05$). In terms of population distribution, the higher the number of pregnancy, the higher the health risk before pregnancy. The poorer the economy was, the higher of the risks of childbearing age, the positive rate of hepatitis B and syphilis, the risk of thalassemia and infertility. The richer the economy was, the higher of the rates of overweight, environmental exposure, and smoking and drinking in men (all linear by linear association $P<0.05$). **Conclusion** We need to attach great importance to the development trend of overweight, obesity, and strengthen the promotion and guidance of contraception and birth control. Rural revitalization should pay attention to the spread of hepatitis B and syphilis in backward areas. The allocation of comprehensive prevention and control resources for thalassemia need to be tilted towards high-risk areas in southern Yunnan. It is necessary to accurately prevent and control reproductive health risks before pregnancy, promote the transformation

of projects to timely, continuous, complete, and systematic services, and block the intergenerational transmission of diseases.

【Key words】 Healthy birth before pregnancy; Health risks; Temporal, spatial and population distribution; Healthy Yunnan

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· 综述 ·

肉苁蓉对生殖功能调节作用的研究进展

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【摘要】 中医临床实践证明, 肉苁蓉具有补肾阳、益精血、润肠道的作用, 属滋补中药中的珍品。近年来, 侧重肉苁蓉的补肾阳作用, 对其生殖药理和毒理作用进行了深入研究, 有关的研究成果引起了中医药科研工作者的广泛关注。本文结合药用成分分析, 针对肉苁蓉提取物在调节生殖功能方面的作用进行综述。综合分析认为肉苁蓉提取物对雌、雄性生殖内分泌均有调节作用, 可以改善生殖功能, 为“肉苁蓉补肾阳”的中医经典理论观点提供了现代生命科学依据。

【关键词】 肉苁蓉; 药理作用; 补肾阳; 内分泌; 生殖

基金项目: 国家重点研发计划 (2016YFC0501007)

Progresses in pharmacological researches on the reproductive effects of *Cistanche deserticola*

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【Abstract】 The clinical practice of Traditional Chinese Medicine (TCM) has proved that *Cistanche deserticola* has the function of tonifying the kidney and strengthening Yang, replenishing essence and blood, moistening intestinal tracts, and so is a treasure of nourishing herbs in Chinese Medicine. In recent years, focusing on the tonifying kidney Yang, its reproductive effects of *Cistanche deserticola* in pharmacology and toxicology have been deeply studied, and the relevant research results have attracted wide attention from TCM researchers. In this review, the role of *Cistanche deserticola* extracts in regulating reproductive function was reviewed. The comprehensive analysis shows that the *Cistanche deserticola* extract regulates the reproductive endocrine of both female and male, which can improve the reproductive function, and provides a modern biological basis for the classical viewpoint of "*Cistanche deserticola* tonifying kidney and Yang".

【Key words】 *Cistanche deserticola*; Pharmacological action; Tonifying kidney Yang; Endocrine; Reproductive

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· 综述 ·

生殖过程中能量代谢调控与疾病的研究进展

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【摘要】 代谢是贯穿细胞生命周期的重要生理活动, 能量底物在生殖过程中具有调节卵泡发育、维持精子运动、影响胚胎植入前发育及诱导母-胎界面免疫耐受等重要功能。正常代谢可促进细胞生长发育, 而异常代谢可导致其功能失调, 且与女性生殖相关疾病的发生、发展密切相关。本研究对生殖过程中糖代谢、脂代谢和蛋白质(氨基酸)代谢及其与生殖疾病的关系作一概述, 有望通过调节能量代谢方式优化卵母细胞体外成熟方案, 为胚胎植入母-胎界面能量代谢的研究及不孕不育的诊断和治疗提供新的思路。

【关键词】 生殖; 能量代谢; 糖酵解; 脂代谢; 蛋白质代谢

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Research progress in energy metabolism and diseases during reproduction

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【Abstract】 Metabolism is an important physiological activity throughout the cell life cycle, and energy substrates play an important role in regulating follicle development, maintaining sperm motility, influencing preimplantation embryo development and inducing immune tolerance at the maternal-fetal interface. Normal metabolism can promote cell growth and development, while abnormal metabolism can lead to dysfunction, and is closely related to the occurrence and development of diseases related to female reproduction. This study provides an overview of glucose metabolism, lipid metabolism and protein (amino acid) metabolism in the reproductive process and their relationship with several reproductive diseases. It is expected to optimize *in vitro* maturation of oocytes by regulating the energy metabolism, and provide new approaches for the study of energy metabolism at the maternal-fetal interface of embryo implantation and the diagnosis and treatment of infertility.

【Key words】 Reproduction; Energy metabolism; Glycolysis; Lipid metabolism; Protein metabolism

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· 综述 ·

PLC ζ 的生殖生物学作用及其在辅助生殖中的潜在价值

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【摘要】 磷脂酶 C ζ (phospholipase C ζ , PLC ζ) 由 XY 催化结构域、EF-手型结构域和 C2 结构域组成, 通过经典磷脂酰肌醇 4,5-二磷酸[phosphatidylinositol (4,5)-bisphosphate, PIP₂] \rightarrow 1,4,5-三磷酸肌醇[(1,4,5)-inositol trisphosphate, IP₃] + 二酰基甘油信号转导通路, 特异性水解卵母细胞胞质内而非质膜上 PIP₂, 引起卵母细胞内 Ca²⁺振荡, 在激活卵母细胞、启动配子发育中起到不可替代的作用。PLC ζ 表达异常导致精子无法激活卵母细胞、与各类精子异常密切相关, 最终引起男性生育力低下甚至不育。综上, 本文针对 PLC ζ 的结构、生物学作用以及 PLC ζ 异常导致的临床疾病及治疗进展相关的文献研究进行综述。

【关键词】 生殖技术, 辅助; 不育, 男性; 磷脂酶 C ζ ; 卵母细胞激活

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Reproductive biology of PLC ζ and its potential value in assisted reproductive technology

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【Abstract】 Phospholipase C ζ (PLC ζ) is composed of XY domain, EF-hand domains and a C2 domain, which specifically hydrolyzes phosphatidylinositol (4,5)-bisphosphate (PIP₂) in the oocyte cytoplasm but not on the plasma membrane through the classical PIP₂ \rightarrow (1,4,5)-inositol trisphosphate (IP₃)+diacylglycerol (DAG) signal transduction pathway, which causes oscillation of calcium ion in oocytes, and plays an irreplaceable role in activating oocytes and initiating gamete development. Clinical data have shown that the reduced or absent expression level of PLC ζ can lead to the inability of sperm activating oocytes and are closely related to various sperm abnormalities, ultimately leading to male subfertility and even infertility. In summary, this article reviews the structure and biological functions of PLC ζ , the

clinical diseases caused by abnormal PLC ζ and their following therapeutic progresses.

【Key words】 Reproductive techniques, assisted; Infertility, male; PLC ζ ; Oocyte activation

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· 综述 ·

卵泡液中淋巴细胞亚群及其细胞因子对卵子质量的影响

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【摘要】 卵子质量是胚胎发育潜能的决定因素, 是影响人类辅助生殖技术结局的主要因素。优质卵子有助于提高受精率、妊娠率和活产率。卵子存在于卵泡液中, 卵泡液中的免疫组分参与卵母细胞的生长和排卵, 影响卵子质量。CD4⁺T 细胞中的 Th1、Th2、Th17 细胞和调节性 T 细胞以及自然杀伤细胞亚群的含量可影响卵子质量, CD8⁺T 细胞可能在卵巢中发挥主动免疫调节的作用, 保障卵子的生长。卵泡液中 B 细胞及其分泌的细胞因子对卵子质量的影响有待进一步研究。本综述主要对卵泡液中 T、B 淋巴细胞和自然杀伤细胞亚群以及其分泌的白细胞介素 (interleukin, IL) -4、IL-10、IL-15、IL-17、肿瘤坏死因子 α 、 γ -干扰素和转化生长因子- β 的表达情况进行汇总和分析, 探讨卵泡液中淋巴细胞和细胞因子对卵子质量的影响。

【关键词】 卵泡液; 淋巴细胞; 白细胞介素; 肿瘤坏死因子 α ; γ -干扰素; 转化生长因子- β

Effects of lymphocyte subsets and cytokine expression in follicular fluid on oocyte's quality

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【Abstract】 The quality of oocytes is a key factor in determining the developmental potential of embryo, and is a major factor affecting the outcome of assisted reproductive technology in human. High-quality oocytes contribute to increase fertilization rate, pregnancy rate and live birth rates. Oocytes are present in follicular fluid, the immune components in follicular fluid are involved in the growth and ovulation of oocytes and affect oocyte's growth. The content of Th1, Th2, Th17 cells and regulatory T cells in CD4⁺T cells and the subsets of natural killer (NK) cells can affect the quality of oocytes. Apart from this, CD8⁺T cells may play an active immunomodulatory role in the ovary to ensure oocyte's growth. The effects of B cells in follicular fluid and the cytokines they secreted on oocyte's quality need to be further studied. In this review, the expression of T, B lymphocytes and NK cells in follicle fluid and their secretion of interleukin (IL)-4, IL-10, IL-15, IL-17, tumour necrosis factor- α , interferon-gamma and transforming growth factor- β cytokines were summarized and analyzed, and the effects of lymphocytes and cytokines in follicular fluid on oocyte's quality were discussed.

【Key words】 Follicular fluid; Lymphocyte; Interleukin; Tumour necrosis factor- α ; Interferon- γ ; Transforming growth factor- β

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· 综述 ·

胰岛素样生长因子 1 在母-胎界面生物学功能和调节机制进展

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【摘要】 在母-胎界面，胰岛素样生长因子1（insulin-like growth factor 1, IGF-1）不仅可通过调控滋养细胞对氨基酸、葡萄糖、脂肪酸等的吸收转运，促进胎儿的生长发育，还可以通过调控蜕膜代谢、免疫应答、炎症等过程，进而调控蜕膜细胞的增殖分化，血管新生及蜕膜化过程，但目前母体蜕膜方面的研究还非常有限。IGF-1 受到上游激素、细胞因子、小分子营养物质、氧气、环境污染物等的调控。生长激素、米非司酮、泼尼松龙、褪黑素等药物调控 IGF-1 的表达，进而改善妊娠结局。对 IGF-1 在母-胎界面的作用机制及上游调控机制进行解析，有望发现更多改善妊娠结局的潜在靶点，为临床妊娠相关疾病带来新的诊疗策略。

【关键词】 胰岛素生长因子1； 代谢； 环境污染物； 激素； 蜕膜化
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Biological functions and regulatory mechanisms of insulin-like growth factor 1 at the maternal-fetal interface

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【Abstract】 At the maternal-fetal interface, insulin-like growth factor 1 (IGF-1) promotes fetal growth by regulating transport and absorption of amino acid, glucose, and fatty acid in trophoblast cells. Additionally, IGF-1 facilitates proliferation and differentiation of decidual cells, angiogenesis, and decidualization via regulating metabolism, immune responses, and anti- or pro-inflammatory responses of decidual cells. However, more studies are needed to verify the underlying mechanisms of IGF-1 in maternal decidual cells. IGF-1 is regulated by upstream hormones, cytokines, small molecule nutrients, oxygen, and environmental pollutants. Drugs, such as growth hormone, mifepristone, prednisolone and melatonin, can regulate the expression of IGF-1 and further improve pregnancy outcomes. Verifying the upstream and downstream mechanisms of IGF-1 at the maternal-fetal interface helps to find out more potential targets for the diagnosis and treatment of pregnancy-related diseases, and provide new ideas for the field.

【Key words】 Insulin-like growth factor 1; Metabolism; Environmental pollutant; Hormone; Decidualization

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