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人类卵母细胞与胚胎玻璃化冷冻中国专家共识 (2023 年)

中国医师协会生殖医学专业委员会

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【摘要】 人类卵母细胞和胚胎玻璃化冷冻是辅助生殖技术的重要组成部分。由中国医师协会生殖医学专业委员会发起, 参考最新国际指南和共识, 结合中国临床实践现状, 经充分讨论后形成该共识, 旨在加强玻璃化冷冻技术质量控制, 进一步改善卵母细胞及胚胎冷冻结局, 提升辅助生殖服务质量。

【关键词】 生殖技术, 辅助; 卵母细胞; 卵裂胚; 囊胚; 玻璃化冷冻; 共识

Chinese expert consensus on vitrification of human oocytes and embryos (2023)

Chinese Association of Reproductive Medicine

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【Abstract】 Vitrification of human oocytes and embryos is an important component of assisted reproductive technology. This consensus is initiated by the Chinese Association of Reproductive Medicine, with reference to the latest international guidelines and consensus, combined with the current situation of

clinical practice in China. The expert group formed this consensus after fully discussion, aiming at strengthening the quality control of vitrification technology, further improving the outcome of vitrification of oocytes and embryos, and improving the quality of assisted reproduction services.

【Key words】 Reproductive techniques, assisted; Oocytes; Cleavage-stage embryo; Blastocyst; Vitrification; Consensus

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· 临床研究 ·

早卵泡期长方案新鲜周期单胚胎移植活产的多因素分析及预测模型构建

任炳楠 张晓柯 郑威 张俊韦 于晓娜 管一春

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【摘要】 目的 分析影响早卵泡期长方案新鲜周期单胚胎移植活产的影响因素, 构建列线图预测模型, 为临床决策和个体化治疗提供参考。方法 本研究是一项基于辅助受孕人群的回顾性队列研究, 分析 2017 年 1 月至 2020 年 12 月期间于郑州大学第三附属医院生殖医学科接受体外受精/卵胞质内单精子注射-胚胎移植 (*in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer, IVF/ICSI-ET) 治疗、行早卵泡期长方案促排卵并进行新鲜周期单胚胎移植的 2 795 例患者的临床资料。使用随机抽样法, 按 3 : 1 的比例将患者分为建模组 (2 100 例) 和验证组 (695 例), 使用单因素和多因素 logistic 回归筛选与移植后新生儿活产相关的独立危险因素, 构建列线图预测模型。使用受试者工作特征 (receiver operator characteristic, ROC) 曲线、校准曲线和决策曲线对列线图预测模型的区分度和校准度进行评价。结果 多因素 logistic 回归分析显示, 年龄、孕前多囊卵巢综合征 (polycystic ovarian syndrome, PCOS)、人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 注射日孕酮水平、优质胚胎率、移植胚胎类型是影响活产的独立相关因素。经过分层分析显示, 年龄 ≥ 36 岁且 hCG 注射日孕酮水平 ≥ 5.20 nmol/L, 显著降低新生儿活产率, 存在两因素的交互作用 ($P=0.043$)。hCG 注射日孕酮水平 ≥ 5.20 nmol/L 且优质胚胎率 $< 59.60\%$, 显著降低新生儿活产率, 交互作用有统计学意义 ($P=0.010$)。通过列线图预测模型的构建, 建模组和验

证组的 ROC 曲线下面积 (area under the curve, AUC) 分别为 0.637 (95% CI: 0.615~0.658) 和 0.617 (95% CI: 0.579~0.654), 校准曲线显示列线图模型预测活产率与实际发生率具有较为良好的一致性。决策曲线显示预测活产率在 24.05%~68.75%, 本研究构建的列线图模型有着更好的净收益, 表明对于临床决策有着良好的应用价值。结论 年龄、孕前 PCOS、hCG 注射日孕酮水平、优质胚胎率、移植胚胎类型是影响早卵泡期长方案新鲜周期单胚胎移植活产的主要因素。当患者年龄 ≥ 36 岁和优质胚胎率 $< 59.60\%$ 分别合并 hCG 注射日孕酮水平 ≥ 5.20 nmol/L 时, 移植后活产率下降。基于上述因素构建的列线图可有助于预测早卵泡期长方案新鲜周期单胚胎移植的活产率。

【关键词】 单胚胎移植; 列线图; 活产率; 早卵泡期长效方案; 预测模型

Multivariate analysis and prediction model construction for live birth in patients with long-acting follicular phase in fresh single embryo transfer cycle

Ren Bingnan, Zhang Xiaoke, Zheng Wei, Zhang Junwei, Yu Xiaona, Guan Yichuan

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【Abstract】 **Objective** To explore risk factors associated with the live birth in patients with long-acting follicular phase in fresh single embryo transfer cycle and to construct nomogram prediction model for providing a reference for clinical decision-making and individualized treatment. **Methods** An assisted reproduction population-based retrospective cohort analysis of the clinical data of 2 795 patients with long-acting follicular phase in fresh single embryo transfer cycle who underwent *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) was performed in the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University from January 2017 to December 2020. These patients were randomly divided into modeling group and validation group according to 3 : 1. Univariate and multivariate logistic regression were used to screen potential risk factors for newborn live birth after fresh single embryo transfer. The nomogram model was established according to the regression coefficients. Besides, area under the receiver operator characteristic (ROC) curve, calibration curve and decision curve analysis were used to evaluate the discrimination and calibration of the model. **Results** Through multiple logistic regression analysis, female age, progestational polycystic ovary syndrome (PCOS), the level of progesterone on the day of human chorionic gonadotropin (hCG) injection, high-quality embryo rate, type of embryos transferred were independent risk factors associated with live birth. Stratified analysis found age ≥ 36 years together with the level of progesterone ≥ 5.20 nmol/L on the day of hCG injection could reduce the probability of live birth signally, and statistically significant interaction was found ($P=0.043$). The level of progesterone ≥ 5.20 nmol/L on the day of hCG injection together with high-quality embryo rate $< 59.60\%$ could reduce the probability of live

birth signally, and statistically significant interaction was found ($P=0.010$). The area under the curve (AUC) of modeling group and validation group was 0.637 (95% CI: 0.615–0.658) and 0.617 (95% CI: 0.579–0.654), respectively. The calibration curve showed that the predicted value of the model was in good agreement with the actual value. The decision curve analysis indicated the most beneficial clinical effect with the nomogram for live birth under threshold probabilities of 24.05%–68.75%, it had a good diagnostic value for clinical decision. **Conclusion** Female age, progestational PCOS, the level of progesterone on the day of hCG injection, high-quality embryo rate, type of embryos transferred were independent risk factors associated with live birth in patients with long-acting follicular phase in fresh single embryo transfer cycle. Female age ≥ 36 years and high-quality embryo rate $<59.60\%$ together with the level of progesterone ≥ 5.26 nmol/L on the day of hCG injection respectively could reduce the probability of live birth. The nomogram predictive model based on the above factors contribute to predict the probability of live birth.

【Key words】 Single embryo transfer; Nomogram; Live birth rate; Early follicular phase prolonged protocol; Prediction model

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• 临床研究 •

整倍体胚胎形态动力学参数对单囊胚移植妊娠结局的影响

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【摘要】 目的 探究胚胎发育过程中的形态动力学参数对整倍体单囊胚移植后妊娠结局的影响。方法 回顾性队列研究分析 2019 年 1 月至 2021 年 6 月期间于重庆医科大学附属妇女儿童医院生殖医学中心接受胚胎植入前遗传学检测-整倍体囊胚解冻复苏移植治疗的 394 例患者临床资料。根据妊娠结局分为未着床组 ($n=153$)、临床流产组 ($n=16$) 和活产组 ($n=225$)。比较各组患者的一般资料、胚胎质量及形态动力学参数的差异。结果 未着床组女性的年龄 [32.51 ± 4.08] 岁大于活产组患者 [31.34 ± 4.23] 岁, $P=0.025$], 优质胚胎率 [26.80% ($41/153$)] 低于活产组 [42.22% ($95/225$)], $P=0.007$]。与临床流产组相比, 未着床组的体

质量指数、优质胚胎率差异均无统计学意义(均 $P>0.05$)。三组间的形态动力学参数原核出现时间(time to pronuclei appearance, tPNa)、原核消失时间(time to PN fading, tPNf)、2-细胞时间(time to 2-cell, t2)、t3、t4 及 t8 差异均无统计学意义(均 $P>0.05$)。未着床组胚胎的桑椹胚融合时间(timing of compacted morula, tM) [(86.96±7.59) h]、开始形成囊胚腔的时间 [(96.73±7.20) h] 均显著高于活产组 [(85.00±7.00) h, $P=0.010$; (95.14±7.30) h, $P=0.037$] 和临床流产组 [(82.89±6.33) h, $P=0.040$; (93.02±6.10) h, $P=0.048$]。校正年龄和胚胎质量因素后,二元 logistic 回归结果显示形态动力学参数对着床和活产结局差异均无统计学意义(均 $P>0.05$)。结论 胚胎发育过程中的形态动力学参数不影响整倍体单囊胚移植的妊娠结局,不能用于预测整倍体囊胚移植的妊娠结局。

【关键词】 妊娠结局; 形态动力学参数; 整倍体囊胚; 胚胎质量

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Effect of euploid embryo morphokinetic parameters on pregnancy outcome of single blastocyst transfer

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【Abstract】 Objective To explore the effect of morphokinetic parameters during embryo development on pregnancy outcome of euploid single blastocyst transfer cycles, and to evaluate the predictive value of morphokinetic parameters for selective euploid single blastocyst transfer strategy. **Methods** A retrospective cohort study was conducted to analyze the clinical data of 394 patients who received preimplantation genetic testing-frozen-thawed embryo transfer (PGT-FET) in Center for Reproductive Medicine of Women and Children's Hospital of Chongqing Medical University from January 2019 to June 2021. According to the pregnancy outcomes, the patients were divided into non-implantation group ($n=153$), clinical miscarriage group ($n=16$) and live birth group ($n=225$). The patients' baseline characteristics, embryo quality and morphokinetic parameters were compared among the three groups. **Results** The maternal age in the non-implantation group [(32.51±4.08) years] was significantly higher than that in the live birth group [(31.34±4.23) years, $P=0.025$], and the proportion of high-quality embryos in the non-implantation group [26.80% (41/153)] was significantly lower than that in the live birth group [42.22% (95/225), $P=0.007$]. There were no significant differences in the body mass index and the proportion of high-quality embryos between the clinical miscarriage group and the non-implantation group ($P>0.05$). There was no significant difference in the proportion of high-quality embryos between the clinical miscarriage group and the non-implantation group ($P>0.05$). There were no significant differences in the morphokinetic parameters of time to pronuclei appearance (tPNa), time to PN fading (tPNf), time to 2-cell (t2), t3, t4 and t8 among the three groups (all $P>0.05$). The average timing of compacted morula (tM)

[[86.96±7.59) h] and timing of starting blastulation (tSB) [[96.73±7.20) h] of embryos in the non-implantation group were significantly higher than those in the live birth group [(85.00±7.00) h, $P=0.010$; (95.14±7.30) h, $P=0.037$, respectively] and the clinical miscarriage group [(82.89±6.33) h, $P=0.040$; (93.02±6.10) h, $P=0.048$]. After adjusting for age and embryo quality, the regression analysis showed that the morphokinetic parameters had no significant effect on implantation results (all $P>0.05$). **Conclusion** The morphokinetic parameters during embryonic development do not affect the pregnancy outcome of euploid single blastocyst transfer and cannot be used to predict the pregnancy outcome of euploid blastocyst transfer.

【Key words】 Pregnancy outcome; Morphokinetics; Euploid blastocyst; Embryo quality

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• 临床研究 •

不同原核来源囊胚冻融移植对临床妊娠结局及新生儿的影响

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【摘要】 目的 探讨零原核(nonpronuclear, 0PN)、单原核(monopronuclear, 1PN)、双原核(two pronuclei, 2PN)废弃胚胎来源冻融单囊胚的临床应用价值。方法 回顾性队列研究分析 2014 年 3 月至 2020 年 11 月期间于郑州大学第三附属医院生殖医学中心行冻融单囊胚移植的患者资料。根据移植囊胚的不同来源分为 4 组: A 组为 2PN 可利用胚胎来源(形态学评级为 I~Ⅲ级的 2PN 胚胎), B 组为 0PN 胚胎来源, C 组为 1PN 胚胎来源, D 组为 2PN 废弃胚胎来源(形态学评级为 IV 级的 2PN 胚胎), 分析 4 组患者基本资料, 并以 A 组为参照组, 分别比较 B、C、D 组的临床妊娠结局, 在单胎活产的周期比较新生儿情况, 采用 logistic 回归校正混杂因素, 计算校正后比值比(adjusted odds ratio, aOR)及 95%置信区间

(confidence interval, *CI*)。结果 经 logistic 回归校正混杂因素后,与 A 组相比, B 组的活产率明显低于 A 组 ($aOR=0.701$, 95% *CI*: 0.534~0.920, $P=0.011$); D 组的临床妊娠率、活产率均明显低于 A 组 ($aOR=0.595$, 95% *CI*: 0.456~0.777, $P<0.001$; $aOR=0.600$, 95% *CI*: 0.449~0.800, $P=0.001$), 余流产率、妊娠期并发症、多胎妊娠率与 A 组相比差异均无统计学意义 (均 $P>0.05$), C 组上述各项指标与 A 组相比差异均无统计学意义 (均 $P>0.05$); B 组、D 组巨大儿、大于胎龄儿 (large for gestational age, LGA) 的发生风险均明显高于 A 组 (巨大儿, B 组: $aOR=2.367$, 95% *CI*: 1.299~4.315, $P=0.005$; D 组: $aOR=2.711$, 95% *CI*: 1.463~5.026, $P=0.002$; LGA, B 组: $aOR=1.930$, 95% *CI*: 1.158~3.217, $P=0.012$; D 组: $aOR=2.039$, 95% *CI*: 1.174~3.543, $P=0.011$), 低出生体质量、小于胎龄儿、早产的发生风险 B 组、D 组与 A 组相比差异均无统计学意义 (均 $P>0.05$), C 组上述指标发生的风险与 A 组相比差异均无统计学意义 (均 $P>0.05$)。结论 在无可利用 2PN 胚胎时, 可将 0PN、1PN、2PN 废弃胚胎行囊胚培养后进行移植, 但要关注 0PN、2PN 废弃胚胎增加子代巨大儿、LGA 发生的风险。

【关键词】 妊娠率; 零原核; 单原核; 单囊胚移植; 活产率; 新生儿

Effect of frozen-thawed blastocyst transfer of different pronuclear zygotes origins on clinical pregnancy outcome and neonatal outcome

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【Abstract】 **Objective** To explore the clinical application value of frozen-thawed single blastocyst derived from nonpronuclear (0PN) zygotes, monopronuclear (1PN) zygotes and two-pronuclei (2PN) discarded embryos.

Methods A retrospective cohort analysis of the data of patients who underwent frozen-thawed single blastocyst transfer at the Reproduction Center of the Third Affiliated Hospital of Zhengzhou University from March 2014 to November 2020. According to the different sources of transplanted blastocysts, they were divided into 4 groups including group A derived from 2PN available embryos (2PN embryos with morphological rating I-III), group B derived from 0PN embryos, group C derived from 1PN embryos, group D derived from 2PN discarded embryos (2PN embryos with morphological rating IV). The basic data of the four groups were analyzed, and group A was used as the reference group to compare the clinical pregnancy outcomes of groups B, C and D, respectively. The neonatal situation was compared at the cycle of singleton live birth. Logistic regression was used to correct for confounding factors and calculate the adjusted odds ratio (aOR) and 95% confidence interval (*CI*).

Results After correcting for confounding factors by logistic regression, the live birth rate in group B was significantly lower than that in group A ($aOR=0.701$, 95% *CI*: 0.534-0.920, $P=0.011$). The clinical pregnancy rate and the live birth rate in group D were significantly lower than those in group A ($aOR=0.595$, 95% *CI*: 0.456-0.777, $P<0.001$; $aOR=0.600$, 95% *CI*: 0.449-0.800, $P=0.001$). The differences in miscarriage

rate, pregnancy complications and multiple pregnancy rate were not statistically significant compared with group A (all $P>0.05$). The differences in all the above indicators in group C were not statistically significant compared with group A ($P>0.05$). The risk of occurrence of macrosomia (group B: $aOR=2.367$, 95% CI : 1.299–4.315, $P=0.005$; group D: $aOR=2.711$, 95% CI : 1.463–5.026, $P=0.002$), large for gestational age (group B: $aOR=1.930$, 95% CI : 1.158–3.217, $P=0.012$; group D: $aOR=2.039$, 95% CI : 1.174–3.543, $P=0.011$) were significantly higher in groups B and D than in group A. The differences in the risk of occurrence of low birth weight, small for gestational age and preterm birth were not statistically significant in groups B and D compared with group A ($P>0.05$), and the difference in the risk of occurrence of the above indicators was not statistically significant in group C compared with group A ($P>0.05$). **Conclusion** When 2PN embryos are not available, abandoned 0PN, 1PN, and 2PN embryos can be transferred after blastocyst culture, but attention should be paid to the increased risk of macrosomia and large for gestational age in offspring.

【Key words】 Pregnancy rate; Nonpronuclear zygotes; Monopronuclear zygotes; Single blastocyst transfer; Live birth rate; Neonate

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• 临床研究 •

序贯胚胎移植法应用于反复种植失败者的临床结局分析

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【摘要】 目的 评估序贯胚胎移植法对改善反复胚胎种植失败 (recurrent implantation failure, RIF) 患者冻融胚胎移植周期临床妊娠结局的作用。方法 回顾性队列研究分析 2019 年 1 月至 2021 年 9 月期间在浙江大学医学院附属邵逸夫医院生殖医学中心行冻融胚胎移植的患者, 其中符合 RIF 诊断标准的患者共 842 例, 按胚胎移植方案分为卵裂期胚胎移植组 ($n=316$)、双囊胚移植组 ($n=212$)、序贯胚胎移植组 ($n=236$) 和单囊胚移植组 ($n=78$), 比较四组的临床基础信息以及妊娠结局。结果 卵裂期胚胎移植组临床妊娠率 [39.6% (125/316)] 显著低于双囊

胚移植组 [61.8% (131/212), $P<0.001$] 和序贯胚胎移植组 [53.0% (125/236), $P<0.001$], 与单囊胚移植组的临床妊娠率 [37.2% (29/78)] 相近, 双囊胚移植组和序贯胚胎移植组临床妊娠率差异无统计学意义 ($P>0.05$); 卵裂期胚胎移植组种植率 [23.9% (151/632)] 显著低于双囊胚移植组 [43.4% (184/424), $P<0.001$]、序贯胚胎移植组 [33.7% (159/472), $P<0.001$] 和单囊胚移植组 [35.9% (28/78), $P<0.001$]; 双囊胚移植组多胎率 [39.7% (52/131)] 显著高于卵裂期胚胎移植组 [23.2% (29/125), $P<0.001$]、序贯胚胎移植组 [26.4% (33/125), $P<0.001$] 和单囊胚移植组 [0% (0/33), $P<0.001$]。结论 对于 RIF 患者, 序贯胚胎移植较卵裂期胚胎移植及单囊胚移植可以提高临床妊娠率, 较双囊胚移植可以降低多胎率。

【关键词】 反复种植失败; 序贯胚胎移植; 囊胚; 妊娠率

Analysis of clinical outcomes of sequential embryo transfer in patients with recurrent implantation failure

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【Abstract】 **Objective** To evaluate the effect of sequential embryo transfer on improving clinical pregnancy outcomes during the frozen-thawed embryo transfer cycle in patients with recurrent implantation failure (RIF). **Methods** A retrospective cohort study was performed in patients who underwent frozen-thawed embryo transfer from January 2019 to September 2021 in the Center of Reproductive Medicine, Sir Run Run Shaw Hospital, Zhejiang University, including 842 patients with RIF. According to the embryo transfer plan, the patients were divided into four groups, including the cleavage embryo transfer group ($n=316$), two blastocysts transfer group ($n=212$), sequential embryo transfer group ($n=236$) and single blastocyst transfer group ($n=78$). The pregnancy outcome was compared among the four groups. **Results** The clinical pregnancy rate of cleavage embryo transfer group [39.6% (125/316)] was significantly lower than that of two blastocysts group [61.8% (131/212), $P<0.001$] and sequential embryo transfer group [53.0% (125/236), $P<0.001$], and there was no significant difference between two blastocysts group and sequential embryo transfer group ($P>0.05$). The clinical pregnancy rate was similar in cleavage embryo transfer group and single blastocyst transfer group [37.2% (29/78)]. The implantation rate of cleavage embryo transfer group [23.9% (151/632)] was significantly lower than that of two blastocysts transfer group [43.4% (184/424)], sequential embryo transfer group [33.7% (159/472)] and single blastocyst transfer group [35.9% (28/78)], and there were significant differences among the four groups (all $P<0.001$). The multiple births rate in two blastocysts transfer group [39.7% (52/131)] was significantly higher than that in cleavage embryo transfer group [23.2% (29/125), $P<0.001$], sequential embryo transfer group [26.4% (33/125), $P<0.001$] and single blastocyst transfer group [0% (0/33), $P<0.001$], and there was a significant difference between cleavage

embryo transfer group and two blastocysts transfer group ($P<0.001$). **Conclusion** For patients with RIF, sequential embryo transfer can improve the clinical pregnancy rate compared with cleavage embryo transfer and single blastocyst transfer, and reduce the multiple pregnancy rate compared with double blastocysts transfer.

【Key words】 Recurrent implantation failure; Sequential embryo transfer; Blastocyst; Pregnancy rate

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· 临床研究 ·

人工周期孕酮添加后子宫内膜厚度紧缩对冻融卵裂期胚胎移植后妊娠结局的影响

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【摘要】 目的 研究人工周期孕酮给药后子宫内膜厚度紧缩对冻融卵裂期胚胎移植患者妊娠结局的影响。方法 回顾性队列研究分析 2015 年 7 月 1 日至 2021 年 3 月 1 日期间于郑州大学第一附属医院生殖医学中心行首周期冻融卵裂期胚胎移植的 1 173 例患者临床资料。将移植日子宫内膜厚度较孕酮添加日内膜厚度减少 $\geq 5\%$ 患者定为紧缩组 (181 例), 余患者为未紧缩组 (992 例)。比较组间的临床妊娠率、持续妊娠率及活产率。结果 紧缩组患者临床妊娠率 [36.46% (66/181)]、持续妊娠率 [34.25% (62/181)] 均低于未紧缩组 [48.99% (486/992), $P=0.002$; 42.34% (420/992), $P=0.043$]。紧缩组活产率 [32.66% (59/181)] 略低于非紧缩组 [39.62% (393/992)], 但组间差异无统计学意义 ($P=0.075$)。运用多因素回归模型校正混杂因素, 最终模型结果显示: 孕酮添加后内膜厚度紧缩不利于患者获得临床妊娠 (aOR=0.578, 95% CI: 0.412~0.811, $P=0.002$) 以及持续妊娠 (aOR=0.685, 95% CI: 0.485~0.967, $P=0.031$)。结论 人工周期冻融卵裂期胚胎移植时, 孕酮添加后子宫内膜厚度紧缩不利于患者获得以及维持妊娠。建议解冻周期卵裂期胚胎移植的患者在孕酮添加后, 适时监测子宫内膜厚度变化情况。

【关键词】 胚胎移植; 妊娠结局; 卵裂期胚胎; 内膜紧缩

Effects of endometrial thickness compaction after progesterone addition on pregnancy outcomes after frozen-thawed cleavage embryo transfer cycles

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【Abstract】 Objective To investigate the effect of endometrial thickness compaction after administration of progesterone on pregnancy outcomes of frozen-thawed cleavage embryo transfer patients. **Methods** In this retrospective cohort study, the clinical data of 1 173 patients who received the first frozen-thawed cycle with cleavage embryo transfer in Center for Reproductive Medicine of the First Affiliated Hospital of Zhengzhou University from July 1, 2015 to March 1, 2021 were retrospectively analyzed. The patients with endometrial thickness decreased by $\geq 5\%$ on the day of transplantation compared with the day progesterone added was designated as the compaction group (181 cases), and the remaining patients were in the non-compacted group (992 cases). Clinical pregnancy rate, ongoing pregnancy rate, and live birth rate were compared between the two groups. **Results** The clinical pregnancy rate [36.46% (66/181)] and the ongoing pregnancy rate [34.25% (62/181)] of the patients in the compaction group were lower than those in the non-compacted group [48.99% (486/992), $P=0.002$; 42.34% (420/992), $P=0.043$]. In addition, the live birth rate in the compaction group [32.66% (59/181)] was lower than that in the non-compacted group [39.62% (393/992)], although not statistically significant ($P=0.075$). We used the multivariate regression model to correct confounding factors. The final model showed that endometrial compaction was inversely associated with clinical pregnancy (aOR=0.578, 95% CI: 0.412–0.811, $P=0.002$) and ongoing pregnancy (aOR=0.685, 95% CI: 0.485–0.967, $P=0.031$). **Conclusion** The compaction of endometrial thickness after the addition of progesterone is not conducive to the acquisition and maintenance of pregnancy in patients with cleavage embryo transfer. Based on the research's conclusions, we suggest that patients should timely detect the endometrial thickness after progesterone addition during the thaw cycle with cleavage embryo transferred.

【Key words】 Embryo transfer; Pregnancy outcome; Cleavage embryo; Endometrial compaction

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• 实验研究 •

lncRNA H19 调控 TGF- β 1 的表达及 对人卵巢颗粒细胞功能的影响

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【摘要】 目的 探讨多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 颗粒细胞 lncRNA H19 基因和转化生长因子 (transforming growth factor, TGF)- β 1 之间的关系及对颗粒细胞增殖和凋亡的影响。方法 分别以浓度 2 μ g/L、4 μ g/L、10 μ g/L TGF- β 1 处理人类卵巢颗粒细胞株 KGN, 采用 Q-PCR 方法检测 H19 的表达水平, 分别构建 H19 过表达质粒 pcDNA3.0-H19 和 siH19-1617 并转染 KGN, 采用 Western blotting 方法检测 TGF- β 1 的表达情况, 采用 CCK8 法检测颗粒细胞增殖情况, 采用流式细胞仪检测颗粒细胞凋亡情况。结果 加入 TGF- β 1 后, H19 的表达量较未处理的 KGN 细胞的表达量增加, 当 TGF- β 1 浓度 \geq 4 μ g/L 时 H19 的表达量显著增多, 差异具有统计学意义 ($P=0.023$); H19 过表达后, TGF- β 1 表达量显著高于转染空质粒的对照组 KGN+pcDNA3.0-NC ($P=0.017$), H19 沉默后 TGF- β 1 表达量显著低于对照组 KGN+NC ($P<0.001$)。H19 过表达后 KGN 细胞在 48 h 和 72 h 增殖能力增强, 凋亡能力减弱; H19 沉默后 KGN 细胞在 48 h 和 72 h 增殖能力减弱, 凋亡能力增强。结论 H19 可调控下游蛋白 TGF- β 1 的表达, 并可促进 PCOS 卵巢颗粒细胞增殖, 抑制细胞凋亡。

【关键词】 多囊卵巢综合征; 转化生长因子- β 1; 长链非编码 RNA H19; 颗粒细胞

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TGF- β 1 expression regulated by lncRNA H19 and its effect on the function of human ovarian granulosa cells

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【Abstract】 Objective To investigate the relationship between lncRNA H19 gene and transforming growth factor (TGF)- β 1 in polycystic ovary syndrome (PCOS) granulosa cells and their effects on the proliferation and apoptosis of granulosa cells. **Methods** Human ovarian granulosa cell line KGN was treated with

TGF- β 1 of 2 μ g/L, 4 μ g/L, and 10 μ g/L, and the expression level of H19 was detected by Q-PCR method, and the H19 overexpression plasmid pcDNA3.0-H19 and siH19-1617 were transfected into KGN, the expression of TGF- β 1 was detected by Western blotting, the proliferation of granulosa cells was detected by CCK8 method, and the apoptosis of granulosa cells was detected by flow cytometry. **Results** After adding TGF- β 1, the expression of H19 increased compared with untreated cells. When the concentration of TGF- β 1 \geq 4 μ g/L, the expression of H19 increased significantly, and the difference was statistically significant ($P=0.023$). After H19 was overexpressed, the expression of TGF- β 1 was significantly higher than that of control group KGN+pcDNA3.0-NC transfected with empty plasmid ($P=0.017$), and the expression of TGF- β 1 after H19 silencing was significantly lower than that of control group KGN+NC ($P<0.001$). After H19 overexpression, the proliferation ability of KGN cells was enhanced at 48 h and 72 h, but the apoptosis ability was weakened. After H19 was silenced, the proliferation ability of KGN cells was weakened at 48 h and 72 h, but the apoptosis ability was enhanced. **Conclusion** H19 can regulate the expression of downstream protein TGF- β 1, promote the proliferation of PCOS ovarian granulosa cells, and inhibit cell apoptosis.

【Key words】 Polycystic ovary syndrome; Transforming growth factor- β 1; Long noncoding RNA H19; Granulosa cell

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• 实验研究 •

非编码小 RNA 在不同 DNA 碎片化指数的精子细胞中的表达差异

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王玺博和徐健对本文有同等贡献

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【摘要】 目的 探究不同精子 DNA 碎片化指数(DNA fragmentation index, DFI) 精液精子细胞中的非编码小 RNA (small non-coding RNA, sncRNAs) 表达量差异。方法 筛选 2021 年 10 月至 2022 年 8 月期间于海军军医大学附属长海医院生殖医学中心门诊就诊的不育男性患者纳入研究。按 DFI 分为 DFI 正常组 (DFI<15%) 48 例、DFI 临界状态组 (DFI 为 15%~30%) 40 例和 DFI 升高组 (DFI>30%) 48 例, 比较 3 组患者的精子细胞中 sncRNAs 相对表达量的差异, 并分析差异 sncRNAs 与精子活力的相关性。结果 3 组样本的年龄、精子浓度差异均无统计学意义 (均 $P>0.05$)。3 组间精子活力差异有统计学意义 ($P<0.001$), 其中 DFI 升高组的精子活力 [$(30.36\pm4.75)\%$] 较 DFI 正常组 [$(63.38\pm9.56)\%$, $P<0.001$] 和 DFI 临界状态组 [$(56.50\pm5.87)\%$, $P=0.034$] 下降。3 组样本的 sncRNAs 靶点存在差异性表达, 与其余两组相比, DFI 升高组中 Glu-CTC-40-10 和 SeC-TCA-37-4 相对表达量降低, Gly-GCC、iMet-CAT-18-18 和 hsa-miR-151a-5p 相对表达量增加, 差异均有统计学意义 (均 $P<0.001$)。Spearman 相关性分析显示, Glu-CTC-40-10、SeC-TCA-37-4 与精子活力之间呈正相关 ($r=0.384$, $P<0.001$; $r=0.441$, $P<0.001$), Gly-GCC、iMet-CAT-18-18 和 hsa-miR-151a-5p 与精子活力之间呈负相关 ($r=-0.437$, $P<0.001$; $r=-0.423$, $P<0.001$; $r=-0.515$, $P<0.001$)。结论 与 DFI 正常的精子细胞相比, sncRNAs 在 DFI 临界状态及升高的精子细胞中存在差异性表达, 可能与 DFI 形成的分子机制有关, 具有作为男性不育生物学标志物的潜力。

【关键词】 不育, 男性; 非编码小 RNA; 精子 DNA 碎片化指数; 精液参数

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Differential expression of non-coding small RNA in spermatozoa with different DNA fragmentation index

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【Abstract】 Objective To investigate the expression differences of small non-coding RNAs (sncRNAs) in sperm cells with different DNA fragmentation index (DFI). **Methods** Male patients who visited the Center of Reproductive Medicine of the Changhai Hospital Affiliated to Naval Medical University from October 2021 to August 2022 were included in the study. According to the DFI value, they were divided into <15%, 15%–30% and >30%, which were denoted as normal DFI group ($n=48$), critical DFI group ($n=40$) and increased DFI group ($n=48$). The relative

expression levels of sncRNAs in sperm cells of 3 groups were compared. The correlation between differential sncRNAs and sperm motility was analyzed. **Results** There were no significant differences in age and sperm concentration among the three groups (all $P>0.05$). The sperm motility in the increased DFI group $[(30.36\pm4.75)\%]$ was lower than that in the normal DFI group $[(63.38\pm9.56)\%, P<0.001]$ and the critical DFI group $[(56.50\pm5.87)\%, P=0.034]$. Compared with the other two groups, the relative expression levels of Glu-CTC-40-10 and SeC-TCA-37-4 in the increased DFI group decreased, while the relative expression levels of Gly-GCC, iMet-CAT-18-18, and hsa-miR-151a-5p increased, with statistical significances (all $P<0.001$). Spearman correlation analysis showed that Glu-CTC-40-10, SeC-TCA-37-4 were positively correlated with sperm motility ($r=0.384, P<0.001; r=0.441, P<0.001$), and Gly-GCC, iMet-CAT-18-18 and hsa-miR-151a-5p were negatively correlated with sperm motility ($r=-0.437, P<0.001; r=-0.423, P<0.001; r=-0.515, P<0.001$). **Conclusion** Compared with semen with normal DFI, sncRNAs are differentially expressed in semen with critical and elevated DFI, which may be related to the molecular mechanism of DFI formation. SncRNAs have the potential to be used as biological markers of male infertility.

【 Key words 】 Infertility, male; Non-coding small RNA; Sperm DNA fragmentation index; Semen parameters

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• 临床报道 •

宫腔异常治疗对反复种植失败患者助孕结局的影响

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【摘要】 目的 探讨反复种植失败患者宫腔异常治疗后再次胚胎移植的生殖结局。方法 采用回顾性病例对照研究分析 2017 年 1 月 1 日至 2021 年 3 月 31 日

期间于天津医科大学总医院妇产科生殖医学中心接受宫腔镜检查的 89 例反复种植失败患者的临床资料, 根据宫腔镜镜下诊断及内膜病理, 将患者分为正常宫腔组 ($n=38$) 以及异常宫腔组 ($n=51$)。异常宫腔组患者接受相应的治疗后, 所有患者再次接受胚胎移植, 比较两组患者再次胚胎移植的生殖结局。结果 89 例反复种植失败患者中, 宫腔异常的发生率为 57.30% (51/89), 其中慢性子宫内膜炎的发生率为 39.33% (35/89), 是宫腔异常最常见的类型。38 例正常宫腔组患者, 再次胚胎移植有 16 例患者获得临床妊娠, 51 例异常宫腔组中 24 例患者获得临床妊娠。两组之间胚胎种植率、临床妊娠率和异位妊娠率差异均无统计学意义 (均 $P>0.05$)。正常宫腔组再次胚胎移植的早期自然流产率 [37.50% (6/16)] 显著高于异常宫腔组 [8.33% (2/24), $P=0.042$]。结论 反复种植失败患者宫腔异常以原发不孕患者为主。异常宫腔患者经治疗后可获得与正常宫腔相同的临床妊娠率。因此, 建议反复种植失败患者常规行宫腔镜检查评估宫腔环境。

【关键词】 宫腔镜; 反复种植失败; 生殖结局; 宫腔异常; 慢性子宫内膜炎

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Management of the uterine abnormalities on the reproductive outcomes in women with repeated implantation failure

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【Abstract】 **Objective** To analyze the reproductive outcomes of the subsequent embryo transfer (ET) cycles in women with repeated implantation failure (RIF) after the management of uterine cavity abnormalities. **Methods** This was a retrospective case-control study. The clinical data of 89 patients with repeated implantation failure who underwent hysteroscopy at Reproductive Medicine Center of the Department of Obstetrics and Gynecology, Tianjin Medical University General Hospital from January 1, 2017 to March 31, 2021 were analyzed. The patients were assigned to a normal uterine cavity (UC) group ($n=38$) and an abnormal UC group ($n=51$) according to hysteroscopic examination and endometrial biopsy results. Women in the abnormal UC group received relevant treatments, and all patients received the embryo transfer again. The reproductive outcomes were compared between the two groups in the subsequent ET cycles. **Results** The prevalence of uterine abnormalities was 57.30% (51/89) in women with RIF. Chronic endometritis accounted for the highest incidence 39.33% (35/89). Among 38 women in normal UC group, 16 women got clinical pregnancy in the subsequent ET cycles, and 24 women in 51 got clinical pregnancy in the abnormal UC group. There were no differences in the implantation rate, the clinical pregnancy rate, and the ectopic pregnancy rate between the two groups (all $P>0.05$). The early abortion rate was significantly higher in the normal UC group [37.50% (6/16)] than in the abnormal UC group [8.33% (2/24), $P=0.042$]. **Conclusion** The uterine

abnormalities mainly occurred in women with primary infertility. The clinical pregnancy rate of women after correction of uterine abnormalities was similar to those women with normal UC. Hysteroscopy was advised to performed routinely to evaluate the uterine environment in women with RIF.

【Key words】 Hysteroscopy; Repeated implantation failure; Reproductive outcome; Uterine abnormalities; Chronic endometritis

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· 临床报道 ·

AZFc 缺失非梗阻性无精子症患者非同步 micro-TESE 后 ICSI 临床结局分析

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【摘要】 目的 评价显微镜下睾丸切开取精术 (micro-dissection testicular sperm extraction, micro-TESE) 结合卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI) 技术的治疗效果, 指导无精子症因子 (azoospermia factor, AZF) c 区缺失导致的非梗阻性无精子症 (non-obstructive azoospermia, NOA) 的临床诊治。方法 通过回顾性研究分析了自 2015 年 1 月至 2019 年 12 月期间于北京大学第三医院生殖医学中心因 AZFc 缺失所致 NOA 行非同步 micro-TESE 患者的临床资料, 随访了手术成功获取精子的患者行 ICSI 助孕的临床结局, 包括受精率、优质胚胎率、临床妊娠率、流产率和活产率等。结果 共 47 例 AZFc 缺失 NOA 患者行非同步 micro-TESE, 28 例术中成功发现精子, 获精率 (sperm retrieval rate, SRR) 为 59.6% (28/47), 术后 25 例冷冻保存精子。15 例后期行解冻精子-ICSI 助孕, 14 例找到足够精子行 ICSI 助孕。14 个解冻精子-ICSI 周期后进行了 11 个周期移植, 1 例成功活产 1 子; 后 11 例患者进行第二次同步手术且均成功发现精子, 行 11 个新

鲜精子-ICSI 周期和 11 个周期移植, 3 例成功活产, 生育 1 子 2 女。结论 AZFc 缺失 NOA 患者有较大的概率通过 micro-TESE 在睾丸中成功获取精子, 并结合 ICSI 孕育具有自己生物学特征的后代, 对首次非同步方案使用冷冻精子 ICSI 助孕失败的患者, 可考虑第二次同步手术、使用新鲜精子进行 ICSI, 以提高精子的利用率和最终的活产率。

【关键词】 精子注射, 细胞质内; AZFc 缺失; 非梗阻性无精子症; 显微取精; 临床结局

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Analysis of clinical outcome of asynchronous micro-TESE and ICSI in patients with non-obstructive azoospermia caused by AZFc deletion

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【Abstract】 Objective To evaluate the therapeutic effect of micro-dissection testicular extraction (micro-TESE) combined with intracytoplasmic sperm injection (ICSI) technology, and guide the clinical treatment of non-obstructive azoospermia (NOA) with azoospermia factor (AZF) c-region deletion. **Methods** Through retrospective study, the clinical data of NOA patients with AZFc deletion were analyzed who underwent asynchronous micro-TESE in Reproductive Medicine Centre of Peking University Third Hospital from January 2015 to December 2019. The clinical outcomes of ICSI in patients who successfully obtained sperm were followed up, including fertilization rate, good-quality embryo rate, clinical pregnancy rate, abortion rate and live birth rate. **Results** A total of 47 patients with NOA caused by AZFc deletion underwent asynchronous micro-TESE and 28 cases successfully found spermatozoa during the operation. The sperm retrieval rate (SRR) was 59.6% (28/47). Totally 25 cases cryopreserved testicular spermatozoa and 15 cases underwent thawed-sperm ICSI and 14 of them found enough spermatozoa for ICSI. Among the 28 patients who successfully found sperm during the first micro-TESE operation, 14 gave up the use of sperm and another 14 later used the thawed sperm for ICSI. A total of 14 cryopreserved sperm ICSI cycles were carried out, followed by 11 embryo transfer cycles. Only one patient successfully gave birth to one health boy. After that 11 patients underwent the second synchronous micro-TESE and spermatozoa were all successfully found during the operation. Eleven cycles used fresh sperm for ICSI followed by 11 embryo transfer cycles. Finally, 3 patients successfully gave birth to 1 boy and 2 girls. **Conclusion** Patients of NOA caused by AZFc deletion have a high probability of successfully obtaining spermatozoa in testis through micro-TESE for ICSI to breed offspring with their own biological characteristics. For patients failed in the first asynchronous procedure, the second synchronous micro-TESE with fresh spermatozoa for ICSI can be considered to improve the utilization rate of sperm and the final live birth rate.

【Key words】 Sperm injection, intracytoplasmic; AZFc deletion; Non-obstructive azoospermia; Micro-dissection testicular sperm extraction; Clinical outcome

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· 个案报道 ·

细胞色素 P450 氧化还原酶缺陷症患者经体外受精-胚胎移植成功妊娠分娩 1 例报道及文献复习

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【摘要】 目的 探讨细胞色素 P450 氧化还原酶缺陷症 (cytochrome P450 oxidoreductase deficiency, PORD) 合并不孕症的早期发现、鉴别诊断及有效治疗。方法 回顾性分析 1 例 PORD 患者的临床诊治资料。结果 该患者疾病特点包括原发性闭经、不孕、生殖系统轻度畸形、双侧卵巢多发黄素化囊肿、高孕酮血症, 经内分泌科检验指标和基因筛查确诊 PORD, 给予口服地塞米松, 进行体外受精-胚胎移植后成功妊娠, 顺利分娩一健康儿。结论 PORD 属于罕见的常染色体隐性遗传病, 存在类固醇激素代谢障碍, 疾病特征多样, 合并不孕时易被误诊, 需要及时鉴别诊断, 给予恰当的地塞米松治疗后, 可以经过辅助生殖技术获得成功妊娠。

【关键词】 受精, 体外; 胚胎移植; 先天性肾上腺增生; 细胞色素 P450 氧化还原酶

基金项目: 国家重点研发项目 (2021YFC27006001)

Successful pregnancy and delivery of one patient with cytochrom P450 oxidoreductase deficiency after *in vitro* fertilization and embryo transfer: a case report and literature review

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【Abstract】 Objective To explore the timely detection, differential diagnosis and effective treatment of cytochrome P450 oxidoreductase deficiency (PORD) with infertility. **Methods** A retrospective analysis was conducted on the clinical diagnosis and treatment data of one PORD patient. **Results** The disease characteristics of this patient included primary amenorrhea, infertility, mild malformation of the reproductive system, multiple luteinized cysts in the bilateral ovaries, and hyperprogesteronemia. PORD was diagnosed by endocrine testing indicators and gene screening. Oral dexamethasone was given, and *in vitro* fertilization and embryo transfer (IVF-ET) was carried out. After successful pregnancy, a healthy infant was successfully delivered. **Conclusion** PORD is a rare autosome recessive genetic disease, which has steroid hormone metabolism disorder and various disease characteristics. It is easy to be misdiagnosed when combined with infertility. It needs timely differential diagnosis. After appropriate dexamethasone treatment, pregnancy can be successfully achieved through assisted reproductive technology.

【Key words】 Fertilization *in vitro*; Embryo transfer; Adrenal hyperplasia, congenital; Cytochrome P450 oxidoreductase

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· 个案报道 ·

左炔诺孕酮宫内节育系统在 IVF 中的应用: 3 例报道及文献复习

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【摘要】 目的 探讨左炔诺孕酮宫内节育系统在子宫内膜不典型增生和子宫腺肌病合并不孕患者行体外受精 (*in vitro* fertilization, IVF) 助孕中的疗效和使用特点。方法 回顾性分析了 2019 年至 2021 年期间就诊于山西医科大学第五临床医学院生殖医学科的 3 例子宫内膜不典型增生及子宫腺肌病合并不孕患者的病例资料, 所有患者均经过左炔诺孕酮宫内节育系统保守治疗成功后尽快采取了 IVF 助孕, 采用了高孕激素状态下促排卵方案及促性腺激素释放激素拮抗剂促排卵方案, 于冻融周期移植前取环。结果 2 例子宫内膜不典型增生均完全缓解, 其中 1 例获得健康单活胎, 1 例生化妊娠; 1 例子宫腺肌病完全缓解, 获得健康单活胎。结论 左炔诺孕酮宫内节育系统治疗由子宫内膜不典型增生和子宫腺肌病引起的不孕症, 可以达到更好的效果, 可有效改善子宫内膜容受性。

【关键词】 受精, 体外; 子宫腺肌病; 左炔诺孕酮宫内节育系统; 子宫内膜不典型增生; 子宫内膜容受性

基金项目: 国家自然科学基金青年科学基金项目 (82101689)

Application of levonorgestrel intrauterine system in IVF: three cases report and literature review

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【Abstract】 Objective To investigate the efficacy and characteristics of levonorgestrel intrauterine system in *in vitro* fertilization (IVF) assisted pregnancy for infertility patients with atypical endometrial hyperplasia and adenomyosis. **Methods** The clinical characteristics of 3 infertility patients with atypical endometrial hyperplasia and adenomyosis admitted to the Reproductive Medicine Center, the Fifth Clinical Medical College of Shanxi Medical University from 2019 to 2021 were retrospectively analyzed. All patients underwent IVF as soon as possible after the successful treatment of levonorgestrel intrauterine system. Using progestin-primed ovarian stimulation protocol and gonadotropin-releasing hormone antagonist protocol, the ring was removed before frozen-thawed transfer. **Results** Two cases of atypical endometrial hyperplasia were completely relieved, one case received healthy singleton fetus, and one case received biochemical pregnancy. One case had complete remission of adenomyosis and received healthy singleton fetus. **Conclusion** Levonorgestrel intrauterine system in the treatment of infertility caused by atypical endometrial hyperplasia and adenomyosis can not only achieve better therapeutic effect but also effectively improve endometrial receptivity.

【 Key words 】 Fertilization *in vitro*; Adenomyosis; Levonorgestrel intrauterine system; Atypical endometrial hyperplasia; Endometrial receptivity

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· 综述 ·

辅助生殖技术子代心血管健康及影响因素

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【摘要】 辅助生殖技术(assisted reproductive technology, ART)帮助众多不孕夫妇孕育了新生命。随着 ART 出生人口占比逐渐增高, ART 出生子代的健康问题引起越来越多的关注。生命早期具有的发育可塑性将环境因素与个体生长发育及疾病易感性联系起来, 表观遗传学可能是其中的作用机制。心血管疾病(cardiovascular disease, CVD)是人类健康的首要威胁, ART 治疗对子代心血管健康的影响非常值得重视。本文对 ART 子代心血管健康指标, 以及 ART 各项技术和操作、亲代因素、宫内环境和生长模式对子代心血管健康产生的影响和潜在机制进行了综述。这将有助于临床医师及胚胎学家加深对 ART 安全性的理解和重视, 促进技术和治疗过程的优化, 进一步保障和改善子代健康。

【关键词】 生殖技术, 辅助; 心血管疾病; 表观基因组学; 受精, 体外; 胚胎移植; 精子注射, 细胞质内; 植入前诊断; 妊娠, 多胎
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Cardiovascular health status and influencing factors of offspring in assisted reproductive technology

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【Abstract】 With the help of assisted reproductive technologies (ART), many infertile couples fulfil their wish to have a child. The health of these offspring attracts growing attention as the proportion of ART births rises. Early-life developmental plasticity connects environmental influences to individual growth and disease susceptibility, epigenetics may be the mechanism. Since cardiovascular disease (CVD) is the primary threat to human health, the impact of ART on the cardiovascular health of offspring is of great importance. This paper reviews the cardiovascular health indicators of ART offspring, the effects and potential mechanisms arising from several techniques and procedures of ART, parental factors, intrauterine environment and growth patterns. This review will aid clinicians and embryologists in better understanding and focusing on the safety of ART technology, promoting the optimization of technology and treatment processes, and further securing and improving the health of patients.

【Key words】 Reproductive techniques, assisted; Cardiovascular diseases; Epigenomics; Fertilization *in vitro*; Embryo transfer; Sperm injections, intracytoplasmic; Preimplantation diagnosis; Pregnancy, multiple

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• 综述 •

慢性炎症与卵巢功能不全发病机制及其治疗的研究进展

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【摘要】 早发性卵巢功能不全 (premature ovarian insufficiency, POI) 是常见的女性生殖内分泌疾病之一, 以卵巢储备减少、卵母细胞质量下降为主要特点, 是女性不孕症的主要原因之一。近来研究表明 POI 的发生发展与体内慢性炎症状态密不可分, 慢性炎症通过多种机制损伤颗粒细胞和卵母细胞。目前多种治疗手段通过降低患者体内炎症水平达到治疗效果。本文综述慢性炎症与 POI 的相关研究进展。

【关键词】 炎症; 早发性卵巢功能不全; 治疗

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Recent advances in the pathogenesis and treatment of chronic inflammation related to premature ovarian insufficiency

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【Abstract】 Premature ovarian insufficiency (POI) is one of endocrine diseases that is common in women. POI is closely tied to the decline in ovarian reserve and one of the leading causes of female infertility. Recent studies suggest that chronic inflammation contributes to the onset and development of POI. Chronic inflammation can cause injury or death of oocytes and granulosa cells, moreover, many recent treatments towards POI achieve the therapeutic efficacy through down-regulating inflammation. In this review, the recent research between chronic inflammation and the pathogenesis of POI is reviewed.

【Key words】 Inflammation; Premature ovarian insufficiency; Therapeutics

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• 综述 •

卵巢低反应的发病机制与治疗进展

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【摘要】 随着高龄产妇构成比不断增加，卵巢低反应（poor ovarian response, POR）事件发生日益增多，其所导致的体外受精周期取消率的增加和活产率的降低仍然是生殖临床医生面临的巨大挑战之一。既往 POR 的标准混乱且异质性强，造成了临床试验和实践的不便，2016 年提出的波塞冬（Patient-Oriented Strategies Encompassing Individualized Oocyte Number, POSEIDON）分类细化了患者亚群，并将概念更新为“低预后”，为规范 POR 标准带来了希望。随着基于 POSEIDON 标准的临床试验不断增加，有效治疗 POR 的循证医学证据不断丰富。本综述总结了当前临床试验进展，旨在为未来的 POR 临床诊疗提供依据。

【关键词】 卵巢低反应； POSEIDON； 控制性卵巢刺激； 促性腺激素； 双重刺激方案

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Research progress of pathogenesis and treatment of poor ovarian response

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【Abstract】 As the proportion of women with advanced maternal age increases, the incidence of poor ovarian response (POR) has been higher. Meanwhile, POR has become one of the biggest challenges for reproductive experts on account of its association with a higher cancellation rate and a lower live birth rate. Different definitions of POR population were previously used, and patient heterogeneity caused inconvenience to clinical trials and practices. In 2016, a new classification by the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) group was introduced, providing a more detailed stratification of the POR, and bringing forward the concept of "low prognosis" to promote more standardized strategies in these patients. Evidence-based medicine has confirmed the effectiveness of several strategies, with more and more clinical trials including POR population stratified by POSEIDON. This article reviewed newly published researches, trying to provide decision support for POR management.

【Key words】 Poor ovarian response; POSEIDON; Controlled ovarian stimulation; Gonadotrophin; Double ovarian stimulation

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· 综述 ·

母-胎界面 miRNA 对蜕膜巨噬细胞极化的调控作用

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【摘要】 妊娠的维持需要母-胎界面稳定的免疫环境, 既要维持免疫耐受保证胎儿发育, 又需要适度的免疫反应抵抗感染等。巨噬细胞在蜕膜组织中的分布和变化特征提示该细胞有重要的免疫调控作用, 如影响血管重塑、调控滋养细胞功能、调节免疫细胞活性等。微小 RNA (microRNA, miRNA) 是参与疾病发生发展的一类小非编码 RNA, 在肿瘤等病理机制中的功能已得到广泛研究, 但 miRNA 在妊娠过程中的调控作用, 特别是对蜕膜巨噬细胞功能的影响复杂多样。本文系统分析了母-胎界面中蜕膜巨噬细胞表型分布的特点, 并发现 M2 表型抑制或 M1 异常激活与妊娠并发症有关, 进一步讨论了 miRNA 对巨噬细胞免疫功能的调节及参与细胞极化调控的代谢相关途径, 证实 miRNA 表达的异常会导致不良妊娠的发生。充分了解母-胎界面 miRNA 调控蜕膜巨噬细胞极化的分子机制, 可以为不良妊娠的临床诊疗提供新的见解。

【关键词】 巨噬细胞; 微小 RNA; 极化; 母-胎界面

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Immune-metabolic characteristics and the role of miRNA in decidual macrophage polarization at maternal-fetal interface

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【Abstract】 Successful pregnancy requires a balanced immune environment at the maternal-fetal interface, which not only maintains immune tolerance to ensure fetal development, but also requires a moderate immune response to resist infection. The distribution and dynamic changes of macrophages in decidual tissue suggested that it plays an important role in immune regulation, such as influencing vascular remodeling, regulating trophoblast cell function and immune cell activity. MicroRNA (miRNA) is a class of small non-coding RNA involved in the occurrence and development of diseases, and its functions and mechanisms in tumor have been extensively studied. The regulatory role of miRNA in pregnancy, especially in decidual macrophage polarization, is complex. In this paper, we systematically analyzed the phenotypic distribution of decidual macrophages at the maternal-fetal interface, and suggested that the inhibition of M2 phenotype polarization or abnormal activation of M1 was associated with pregnancy complications. We further discussed the regulation of miRNA transcription in immune responses of macrophages and metabolic regulation of macrophage polarization. It was confirmed that abnormal miRNA expression led to adverse pregnancy. A full understanding of the molecular mechanisms of miRNA in inflammatory response and metabolism of decidual macrophages can provide a new insight to the clinical diagnosis and treatment of adverse pregnancy.

【Key words】 Macrophage; MicroRNA; Polarization; Maternal-fetal interface

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· 综述 ·

外泌体在卵母细胞发育及相关疾病中的研究进展

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【摘要】 外泌体是源自细胞膜系统的囊泡, 起源于内体多囊泡体, 释放到组织液中。外泌体作为细胞间通信的载体, 含有蛋白质、脂质、源自其供体细胞质的编码或非编码 RNA。卵泡是卵母细胞发育的重要微环境, 在卵母细胞发育过程中, 物质通过细胞外囊泡进行卵母细胞与卵泡周围卵丘和颗粒细胞之间的物质传递, 从而调节卵母细胞的基因表达。在正常和病理条件下, 外泌体由多种细胞释放, 参与多种疾病的发生发展, 可作为疾病的候选生物标志物及治疗干预的潜在目标。本文阐述了外泌体中的微小 RNA、长链非编码 RNA 及环状 RNA 等成分在卵母细胞发育状态中的作用机制及其在卵巢、子宫相关生殖系统疾病如多囊卵巢综合征、卵巢癌、子宫内膜异位症中的变化。针对外泌体的检测可以深入了解卵母细胞发育状态, 有助于疾病的预防、诊断和治疗。

【关键词】 外泌体; 微小 RNA; 长链非编码 RNA; 环状 RNA; 卵泡发育

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Research progress of exosomes in oocyte development and related diseases

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【Abstract】 Exosomes are vesicles derived from the cell membrane system that originate from endosomal multivesicular bodies and are released into the tissue fluid. Exosomes serve as carriers for intercellular communication and contain proteins, lipids, coding or non-coding RNAs derived from their donor cytoplasm. The follicle is an important microenvironment for oocyte development. In the process of oocyte development, substances are transferred between the oocyte and the cumulus and granulosa cells around the follicle through the extracellular follicle, thereby regulating the gene expression in oocytes. Under normal and pathological conditions, exosomes are released by a variety of cells and participate in the occurrence and development of various diseases, and can be used as candidate biomarkers for diseases and potential targets for therapeutic intervention. The aim of this review is to present the mechanism of microRNA, long non-coding RNA and circular RNA in exosomes in the developmental state of oocytes and their role in

ovarian and uterine related reproductive system diseases such as polycystic ovary syndrome, ovarian cancer and endometriosis. The detection of exosomes can provide an in-depth understanding of the developmental status of oocytes, which is helpful for the prevention, diagnosis and treatment of diseases.

【Key words】 Exosomes; MicroRNAs; Long-noncoding RNA; Circular RNA; Follicle development

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