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• 临床研究 •

# 添加不同 LH 活性药物对卵巢慢反应患者妊娠结局的影响: 一项回顾性队列研究

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**【摘要】** 目标 比较早卵泡期长方案促排卵发生慢反应时, 补充重组黄体生成素 (recombinant luteinizing hormone, rLH) 和人绝经期促性腺激素 (human menopausal gonadotropins, hMG) 对妊娠结局的影响。方法 回顾性队列研究分析 2017 年 1 月至 2020 年 1 月期间南京医科大学第一附属医院生殖医学科首次接受体外受精/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) 助孕并采用卵泡期长方案促排卵患者的临床资料。纳入卵巢功能正常、促排卵发生慢反应的患者 2 336 例, 根据添加不同的 LH 活性药物, 分为 hMG 组 (1 558 例) 和 rLH 组 (778 例)。比较两组患者的基本特征、促排卵的临床和实验室指标、新鲜胚胎移植及冻融胚胎移植周期的妊娠结局。通过 logistic 回归分析添加两种 LH 活性药物对卵巢慢反应患者累积活产率的影响。结果 两组患者的年龄、不孕类型和病因、体质量指数和卵巢功能指标差异均无统计学意义 (均  $P>0.05$ )。hMG 组卵泡刺激素 (follicle-stimulating hormone, FSH) 的使用时间 [ $(12.22\pm2.29)$  d] 和总剂量 [ $(2\,088.98\pm628.24)$  U] 较 rLH 组 [ $(11.89\pm2.37)$  d,  $P=0.001$ ;  $(1\,866.90\pm602.65)$  U,  $P<0.001$ ] 显著升高。hMG 组 LH 的使用时间 [ $(7.40\pm3.52)$  d] 和总剂量 [ $(537.30\pm484.49)$  U] 较 rLH 组 [ $(5.67\pm3.78)$  d、 $(498.10\pm472.04)$  U, 均  $P<0.001$ ] 显著升高。hMG 组的 LH 水平在促性腺激素 (gonadotropin, Gn) 启动日 [ $(0.78\pm0.77)$  U/L] 和刺激第 6 天 [ $(0.81\pm0.49)$  U/L] 均高于 rLH 组 [ $(0.67\pm0.32)$  U/L,  $P<0.001$ ;  $(0.71\pm0.33)$  U/L,  $P=0.002$ ], 但人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG) 注射日两组之间的 LH 水平差异无统计学意义 ( $P=0.303$ )。hCG 注射日 hMG 组的雌二醇水平 [ $(8\,377.14\pm7\,000.63)$  pmol/L] 和孕酮水平 [ $(3.84\pm2.18)$  nmol/L] 显著高于 rLH 组 [ $(7\,644.91\pm5\,145.64)$  pmol/L,  $P=0.009$ ;  $(3.14\pm1.80)$  ng/L,  $P<0.001$ ]。两组新鲜胚胎移植和冻融胚胎移植的临床妊娠率、

流产率和活产率差异均无统计学意义 (均  $P>0.05$ )。rLH 组的累积妊娠率 [89.46% (696/778)] 和累积活产率 [78.02% (607/778)] 高于 hMG 组 [84.60% (1318/1558),  $P=0.001$ ; 72.98% (1137/1558),  $P=0.008$ ]。多因素 logistic 回归分析显示, 影响慢反应患者累积活产率的因素包括年龄 ( $OR=0.930$ , 95%  $CI$ : 0.906~0.955,  $P<0.001$ )、窦卵泡计数 ( $OR=1.029$ , 95%  $CI$ : 1.005~1.054,  $P=0.018$ )、获卵总数 ( $OR=1.064$ , 95%  $CI$ : 1.029~1.100,  $P<0.001$ )、移植胚胎数 ( $OR=1.714$ , 95%  $CI$ : 1.293~2.272,  $P<0.001$ )、移植胚胎的发育时期 ( $OR=1.567$ , 95%  $CI$ : 1.243~1.975,  $P<0.001$ )、移植日子宫内膜厚度 ( $OR=1.122$ , 95%  $CI$ : 1.077~1.170,  $P<0.001$ )以及添加不同的 LH 活性药物 ( $OR=1.348$ , 95%  $CI$ : 1.101~1.651,  $P=0.004$ )。结论 卵巢功能正常的患者行早卵泡期长方案促排卵, 发生慢反应时添加 rLH 较添加 hMG 可以获得更高的累积活产率。

【关键词】 卵巢慢反应; 重组黄体生成素; 人绝经期促性腺激素; 卵泡期长方案; 累积活产率

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## Effects of different exogenous LH activity drugs on pregnancy outcomes in patients with suboptimal ovarian response: a retrospective cohort study

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【Abstract】 **Objective** To evaluate the effects of recombinant luteinizing hormone (rLH) and human menopausal gonadotropins (hMG) supplementation on pregnancy outcomes for suboptimal ovarian responders undergoing follicular phase long protocol. **Methods** The data of infertile patients who underwent *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) for the first time with follicular phase long protocol from January 2017 to January 2020 in Reproductive Medicine Center of the First Affiliated Hospital of Nanjing Medical University Hospital were retrospectively cohort analyzed. Totally 2 336 patients with normal ovarian reserve were included in the study with suboptimal ovarian response to ovarian stimulation. According to the different exogenous LH supplementation, they were divided into hMG group ( $n=1\ 558$ ) and rLH group ( $n=778$ ). The clinical features and effects of ovulation induction were compared between the two groups and reproductive outcomes were compared in both fresh embryo transfer cycles and subsequent frozen-thawed embryo transfer (FET) cycles. Logistic regression analysis were performed to explore the relationship between different LH activity drugs supplementation and the cumulative live birth rate of suboptimal ovarian responders. **Results** The basic characteristics such as age, infertility type and diagnosis, body mass index and biomarkers of ovarian reserve were comparable between the two groups (all  $P>0.05$ ). Total dosage [(2 088.98±628.24) U] and duration [(12.22±2.29) d] of FSH used in the hMG group were significantly higher than those in the rLH group [(1 866.90±602.65) U,  $P<0.001$ ;

(11.89±2.37) d,  $P=0.001$ ). Total dosage [(537.30±484.49) U] and duration [(7.40±3.52) d] of LH used in the hMG group were significantly higher than those in the rLH group [(498.10±472.04) U, (5.67±3.78) d,  $P<0.001$ ]. The serum LH levels on the first day [(0.78±0.77) U/L] and the sixth day [(0.81±0.49) U/L] of gonadotropin stimulation in the hMG group were higher than those in the rLH group [(0.67±0.32) U/L,  $P<0.001$ ; (0.71±0.33) U/L,  $P=0.002$ ]. However, the serum LH level was comparable on the trigger day between the two groups without significant difference ( $P=0.303$ ). The levels of serum estradiol [(8 377.14±7 000.63) pmol/L] and progesterone [(3.84±2.18) nmol/L] on the trigger day were significantly higher in the hMG group than in the rLH group [(7 644.91±5 145.64) pmol/L,  $P=0.009$ ; (3.14±1.80) ng/L,  $P<0.001$ ]. The pregnancy outcomes including clinical pregnancy rates, abortion rates and live birth rates were comparable between the two groups in fresh embryo transfer cycles and the subsequent FET cycles (all  $P>0.05$ ). The cumulative pregnancy rate (CPR) [89.46% (696/778)] and the cumulative live birth rate (CLBR) [78.02% (607/778)] in the rLH group were significantly higher than those in the hMG group [84.60% (1 318/1 558),  $P=0.001$ ; 72.98% (1 137/1 558),  $P=0.008$ ]. Multivariate logistic regression analysis showed that age was a risk factor for CLBR ( $OR=0.930$ , 95%  $CI$ : 0.906–0.955,  $P<0.001$ ) and antral follicle count ( $OR=1.029$ , 95%  $CI$ : 1.005–1.054,  $P=0.018$ ), total number of oocytes retrieved ( $OR=1.064$ , 95%  $CI$ : 1.029–1.100,  $P<0.001$ ), the number of embryos transferred ( $OR=1.714$ , 95%  $CI$ : 1.293–2.272,  $P<0.001$ ), the stage of embryos transferred ( $OR=1.567$ , 95%  $CI$ : 1.243–1.975,  $P<0.001$ ), endometrial thickness on transfer day ( $OR=1.122$ , 95%  $CI$ : 1.077–1.170,  $P<0.001$ ) and rLH supplementation ( $OR=1.348$ , 95%  $CI$ : 1.101–1.651,  $P=0.004$ ) were protective factors for CLBR of suboptimal responders. **Conclusion** For suboptimal ovarian responders with normal ovarian reserve, rLH supplementation may achieve a higher CLBR than hMG supplementation in follicular phase long protocol.

**【 Key words 】** Suboptimal ovarian response; Recombinant luteinizing hormone; Human menopausal gonadotropins; Follicular phase long protocol; Cumulative live birth rate

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· 临床研究 ·

# 既往自然流产次数对首次 IVF/ICSI-ET 助孕患者妊娠结局的影响

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**【摘要】** 目的 探讨既往不同自然流产次数对首次体外受精/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) 患者妊娠结局的影响。方法 回顾性队列研究分析 2010 年 1 月 1 日至 2018 年 12 月 31 日期间在河南省人民医院生殖中心首次行 IVF/ICSI-ET 助孕患者的临床资料, 共纳入患者 12 912 例, 根据既往自然流产次数分为 0 次组 ( $n=10\,948$ )、1 次组 ( $n=1\,506$ )、2 次组 ( $n=345$ ) 及  $\geq 3$  次组 ( $n=113$ )。比较 4 组患者间的基本资料和助孕后妊娠结局, 并通过单因素、分类多因素 logistic 回归分析探讨既往自然流产次数对 IVF/ICSI-ET 患者妊娠结局的影响。结果 单因素 logistic 回归分析显示, 年龄、不孕年限、既往自然流产次数、子宫内膜厚度、移植胚胎数及移植优质胚胎数均是患者种植率、妊娠率、早期自然流产率和活产率的影响因素(子宫内膜厚度对早期自然流产率影响  $P=0.002$ , 余均  $P<0.001$ ); 胚胎移植类型、卵泡刺激素(follicle-stimulating hormone, FSH)、黄体生成素(luteinizing hormone, LH)、LH/FSH、抗苗勒管激素(anti-Müllerian hormone, AMH) 均对患者种植率、妊娠率和活产率有影响(AMH 对活产率影响  $P=0.002$ , 余均  $P<0.001$ ); 体质指数(body mass index, BMI) 是患者早期自然流产率和活产率的影响因素( $P=0.006$ ,  $P=0.002$ )。分类多因素 logistic 回归分析显示, 调整年龄、BMI、基础性激素(FSH、LH)、LH/FSH、AMH、周期类型、移植胚胎数、移植胚胎类型、移植优质胚胎数、子宫内膜厚度等混杂因素后, 以自然流产 0 次组为参照组, 自然流产  $\geq 3$  次组患者的种植率( $OR=0.63$ , 95%  $CI$ : 0.42~0.94,  $P=0.025$ ) 显著性降低; 自然流产 1 次组( $OR=1.56$ , 95%  $CI$ : 1.27~1.93,  $P<0.001$ )、2 次组( $OR=2.28$ , 95%  $CI$ : 1.61~3.23,  $P<0.001$ ) 和  $\geq 3$  次组( $OR=3.32$ , 95%  $CI$ : 1.89~5.82,  $P<0.001$ ) 患者再次发生早期自然流产的概率逐渐升高, 差异均有统计学意义; 自然流产 1 次组( $OR=0.80$ , 95%  $CI$ : 0.71~0.91,  $P<0.001$ )、2 次组( $OR=0.66$ , 95%  $CI$ : 0.52~0.84,  $P<0.001$ ) 和  $\geq 3$  次组( $OR=0.45$ , 95%  $CI$ : 0.29~0.67,  $P<0.001$ ) 患者的活产率显著降低, 差异均有统计学意义。结论 既往自然流产次数是影响 IVF/ICSI 助孕后种植率、早期自然流产率和活产率的独立影响因素, 随着既往自然流产次数增加, IVF/ICSI 助孕后种植率、活产率逐渐降低, 再次发生早期自然流产风险逐渐增加。



【关键词】 流产，自然； 受精，体外； 自然流产率； 妊娠结局  
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## **Influence of the number of previous spontaneous abortions on the pregnancy outcome of patients undergoing IVF/ICSI-ET**

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**【 Abstract 】 Objective** To explore the effect of previous different spontaneous abortion times on pregnancy outcomes of patients with the first *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET). **Methods** A retrospective cohort study was performed on the clinical data of patients with the first IVF/ICSI-ET in the Reproductive Center of Henan Provincial People's Hospital from January 1, 2010 to December 31, 2018. A total of 12 912 patients were included. According to the number of previous spontaneous abortions, the patients were divided into four groups: zero time group ( $n=10\,948$ ), 1 time group ( $n=1\,506$ ), 2 times group ( $n=345$ ) and  $\geq 3$  times group ( $n=113$ ). The basic data of patients and pregnancy outcomes after assisted pregnancy were compared among the four groups, and the influence of the number of previous spontaneous abortions on pregnancy outcomes of IVF/ICSI-ET patients was investigated by univariate and categorical multivariate logistic regression analysis. **Results** Univariate logistic regression analysis showed that age, infertility duration, previous spontaneous abortion times, endometrial thickness, the numbers of embryos transferred and high-quality embryos transferred were all influencing factors of implantation rate, pregnancy rate, early spontaneous abortion rate and live birth rate (all  $P<0.001$ , except for the influence of endometrial thickness on early spontaneous abortion rate  $P=0.002$ ). The types of embryo transferred, follicle-stimulating hormone (FSH) level, luteinizing hormone (LH) level, LH/FSH, and anti-Müllerian hormone (AMH) level all had effects on the implantation rate, the pregnancy rate, and the live birth rate (all  $P<0.001$ , except for the effect of AMH on the live birth rate  $P=0.002$ ). Body mass index (BMI) was the influencing factor of early spontaneous abortion rate and live birth rate ( $P=0.006$ ,  $P=0.002$ ). After adjusting for confounding factors, multiple regression analysis showed that with zero time group as the reference group, the implantation rate of  $\geq 3$  times group ( $OR=0.63$ , 95%  $CI$ : 0.42–0.94,  $P=0.025$ ) was significantly decreased; the early spontaneous abortion rate was significantly increased in 1 time group ( $OR=1.56$ , 95%  $CI$ : 1.27–1.93,  $P<0.001$ ), 2 times group ( $OR=2.28$ , 95%  $CI$ : 1.61–3.23,  $P<0.001$ ), and  $\geq 3$  times group ( $OR=3.32$ , 95%  $CI$ : 1.89–5.82,  $P<0.001$ ); the live birth rate was significantly reduced in 1 time group ( $OR=0.80$ , 95%  $CI$ : 0.71–0.91,  $P<0.001$ ), 2 times group ( $OR=0.66$ , 95%  $CI$ : 0.52–0.84,  $P<0.001$ ) and  $\geq 3$  times group ( $OR=0.45$ , 95%  $CI$ : 0.29–0.67,  $P<0.001$ ). **Conclusion** The number of previous early spontaneous abortions is an independent factor affecting the implantation rate, the early spontaneous abortion rate and the live birth rate for

patients undergoing IVF/ICSI-ET. With the increase of the number of previous early spontaneous abortions, the implantation rate and the live birth rate after IVF/ICSI were gradually decreased, and the risk of early spontaneous abortion gradually increased.

**【Key words】** Abortion, spontaneous; Fertilization *in vitro*; Spontaneous abortion rate; Pregnancy outcomes

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# 非活动性结核对不孕患者 IVF/ICSI-ET 助孕结局的影响

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**【摘要】** 目的 探讨非活动性结核对不孕患者首次行体外受精 (*in vitro* fertilization, IVF)/卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI)-胚胎移植 (embryo transfer, ET) 助孕结局的影响。方法 通过回顾性队列研究分析 2011 年 1 月至 2021 年 12 月期间于郑州大学第一附属医院生殖与遗传专科医院首次进行新鲜周期胚胎移植不孕患者 (15 412 例) 的病例资料, 应用倾向性评分匹配法 (propensity score matching, PSM) 按照 1:2 配比分为非活动结核组 (635 例) 和对照组 (1 270 例), 其中非活动结核组按部位分为肺结核亚组 (A 组, 378 例)、盆腔结核亚组 (B 组, 214 例) 及其他结核亚组 (C 组, 43 例), 按是否经过治疗分为治疗亚组 (377 例) 及非治疗亚组 (258 例), 对其助孕结局进行比较, 并分析影响因素。结果 经过 PSM 后非活动结核组和对照组基线资料差异均无统计学意义 (均  $P>0.05$ )。非活动结核组患者的受精率 [65.2% (5 207/7 991)] 显著高于对照组 [63.7% (9 889/15 524),  $P=0.027$ ], 但着床率 [41.9% (483/1 152)]、临床妊娠率 [58.4% (371/635)]、活产率 [46.5% (295/635)] 均显著低于对照

组 [48.8% (1112/2279),  $P<0.001$ ; 67.2% (853/1270),  $P<0.001$ ; 57.9% (735/1270),  $P<0.001$ ], 流产率 [20.5% (76/371)] 显著高于对照组 [13.8% (118/853),  $P=0.003$ ], 且内膜厚度 [ $(11.8\pm 2.6)$  mm] 小于对照组 [ $(12.5\pm 3.9)$  mm,  $P<0.001$ ]. 亚组分析 B 组优质胚胎率 [62.3% (1111/1784)] 显著低于 A 组 [66.5% (2027/3048),  $P=0.007$ ] 及对照组 [65.9% (6516/9889),  $P=0.007$ ], 差异均有统计学意义。治疗亚组的着床率 [46.6% (318/682)]、临床妊娠率 [64.5% (243/377)] 及活产率 [51.7% (195/377)] 均高于非治疗亚组 [35.1% (165/470),  $P<0.001$ ; 49.6% (128/258),  $P<0.001$ ; 38.8% (100/258),  $P=0.001$ ]. 此外, logistic 回归分析显示非活动性结核是影响临床妊娠、活产和流产 ( $OR=0.71$ , 95%  $CI$ : 0.58~0.87,  $P=0.002$ ;  $OR=0.65$ , 95%  $CI$ : 0.54~0.80,  $P<0.001$ ;  $OR=1.58$ , 95%  $CI$ : 1.15~2.19,  $P=0.045$ ) 的独立危险因素。结论 非活动性结核是不良助孕结局的独立危险因素, 非活动性结核不孕患者与非结核不孕患者相比首次接受 IVF/ICSI-ET 的助孕结局较差, 其中既往盆腔结核的患者更显著, 而结核患者行规律抗痨治疗有助于改善助孕结局。

【关键词】 不孕症; 受精, 体外; 胚胎移植; 非活动性结核

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## Effect of inactive tuberculosis on pregnancy outcome of IVF/ICSI-ET in infertile patients

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**【Abstract】 Objective** To explore the effect of inactive tuberculosis on the assisted reproductive outcome of the first *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) in infertile patients. **Methods** A retrospective cohort study was conducted to analyze the data of 15 412 infertile patients who underwent the first fresh-cycle embryo transfer in the Reproductive and Genetics Hospital of the First Affiliated Hospital of Zhengzhou University from January 2011 to December 2021. They were divided into inactive tuberculosis group (635 cases) and control group (1 270 cases) according to the ratio of 1 : 2 by propensity score matching (PSM). The inactive tuberculosis group was divided into three subgroups: tuberculosis (group A, 378 cases), pelvic tuberculosis (group B, 214 cases) and other tuberculosis (group C, 43 cases) according to the location. The inactive tuberculosis group was also divided into the treatment subgroup (377 cases) and the non-treatment subgroup (258 cases) according to whether they had undergone treatment. The assisted reproductive outcomes were compared and the influencing factors were analyzed. **Results** After PSM, the difference of the baseline data between the inactive tuberculosis group and control group was not statistically significant (all  $P>0.05$ ). The fertilization rate [65.2% (5 207/7 991)] of patients in the inactive tuberculosis group was significantly higher than that of control group [63.7% (9 889/15 524),  $P=0.027$ ], but the implantation rate [41.9% (483/1 152)], the clinical pregnancy rate [58.4% (371/635)] and the

live birth rate [46.5% (295/635)] were significantly lower than those of control group [48.8% (1 112/2 279),  $P<0.001$ ; 67.2% (853/1 270),  $P<0.001$ ; 57.9% (735/1 270),  $P<0.001$ ], and the miscarriage rate [20.5% (76/371)] was significantly higher than that of control group [13.8% (118/853),  $P=0.003$ ], and the endometrium thickness [(11.8 $\pm$ 2.6) mm] was thinner than that of control group [(12.5 $\pm$ 3.9) mm,  $P<0.001$ ]. For subgroup analysis, the high-quality embryo rate in group B [62.3% (1 111/1 784)] was significantly lower than that in group A [66.5% (2 027/3 048),  $P=0.007$ ] and control group [65.9% (6 516/9 889),  $P=0.007$ ], and the difference was statistically significant. The implantation rate [46.6% (318/682)], the clinical pregnancy rate [64.5% (243/377)] and the live birth rate [51.7% (195/377)] in the treatment group were higher than those in the non-treatment group [35.1% (165/470),  $P<0.001$ ; 49.6% (128/258),  $P<0.001$ ; 38.8% (100/258),  $P=0.001$ ]. In addition, logistic regression showed that inactive tuberculosis was an independent risk factor for clinical pregnancy, live birth, and miscarriage ( $OR=0.71$ , 95%  $CI$ : 0.58–0.87,  $P=0.002$ ;  $OR=0.65$ , 95%  $CI$ : 0.54–0.80,  $P<0.001$ ;  $OR=1.58$ , 95%  $CI$ : 1.15–2.19,  $P=0.045$ ). **Conclusion** Inactive tuberculosis is an independent risk factor for adverse assisted reproductive outcomes. Compared with non-tuberculosis infertile patients, the pregnancy outcomes of inactive tuberculosis infertile patients who received IVF/ICSI-ET for the first time are poorer, especially the patients with pelvic tuberculosis in the past. Regular anti-tuberculosis treatment for tuberculosis patients can help to improve pregnancy outcomes.

**【Key words】** Infertility; Fertilization *in vitro*; Embryo transfer; Inactive tuberculosis

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## 影响宫腔内夫精人工授精妊娠结局的多因素分析及预测模型建立

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**【摘要】** 目的 探讨影响宫腔内夫精人工授精妊娠结局的相关因素并建立预测模型。方法 回顾性队列研究分析 2017 年 1 月至 2020 年 12 月期间在河南省人民医院生殖中心行夫精人工授精治疗的 2 035 个周期的临床资料，按照治疗时间分为训练集（75%，1526 个周期）和验证集（25%，509 个周期），采用单因素分析和多元 logistic 回归分析筛选出影响临床妊娠率的相关预测因子，建立临床妊娠率的预测模型并绘制列线图。结果 单因素和多因素 logistic 回归分析显示，女方年龄 $\geq 37$  岁，临床妊娠率下降（ $OR=0.48$ ，95%  $CI$ : 0.22~1.06， $P=0.071$ ）；随着抗苗勒管激素（anti-Müllerian hormone, AMH）水平下降患者临床妊娠率下降（ $OR=1.05$ ，95%  $CI$ : 1.01~1.09， $P=0.028$ ）；不孕年限 $\geq 5$  年的患者临床妊娠率下降（ $OR=0.61$ ，95%  $CI$ : 0.38~0.97， $P=0.037$ ）；促排卵周期患者临床妊娠率高（ $OR=1.64$ ，95%  $CI$ : 1.18~2.27， $P=0.003$ ）。基于上述 4 个影响因素，建立列线图预测模型，曲线下面积（area under curve, AUC）为 0.62，模型预测能力中等。结论 宫腔内夫精人工授精中女方年龄 $< 37$  岁、AMH 水平高、不孕年限 $< 5$  年、使用促排卵者临床妊娠率较高。所建立的预测模型能够预测患者临床妊娠概率，可作为临床医师的参考。

**【关键词】** 授精，人工；临床妊娠率；年龄；不孕年限

## Multivariate analysis and prediction model establishment of intrauterine insemination pregnancy outcomes

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**【Abstract】** **Objective** To explore the related factors affecting the pregnancy outcomes of intrauterine insemination and to establish a predictive model. **Methods** The clinical data of 2 035 cycles of artificial insemination by husband sperm in Reproductive Center of Henan Provincial People's Hospital from January 2017 to December 2020 were retrospectively analyzed. According to the treatment time, they were divided into training sets (75%,  $n=1\ 526$ ) and validation sets (25%,  $n=509$ ). Univariate analysis and multivariate logistic regression were used to analyze the related factors affecting the clinical pregnancy rate, and a predictive model of clinical pregnancy rate was established according to the results of multivariate logistic regression analysis. **Results** Univariate and multivariate logistic regression analysis showed that pregnancy rate of women aged  $\geq 37$  years decreased ( $OR=0.48$ , 95%  $CI$ : 0.22–1.06,  $P=0.071$ ), the pregnancy rate decreased with the decrease of anti-Müllerian hormone (AMH,  $OR=1.05$ , 95%  $CI$ : 1.01–1.09,  $P=0.028$ ), the clinical pregnancy rate of infertility duration  $\geq 5$  years decreased ( $OR=0.61$ , 95%  $CI$ : 0.38–0.97,  $P=0.037$ ), the clinical pregnancy rate was high in the

stimulation cycle ( $OR=1.64$ , 95%  $CI$ : 1.18–2.27,  $P=0.003$ ). Based on the above four influencing factors, the nomogram prediction model was established, and an area under the curve (AUC) was 0.62, and the model prediction ability was moderate.

**Conclusion** The clinical pregnancy rate was higher in women with maternal age <37 years, high level of AMH, infertility duration <5 years and ovulation induction. The established prediction model can predict the clinical pregnancy probability of patients and can be used as a reference for clinicians.

**【Key words】** Insemination, artificial; Clinical pregnancy rate; Age; Infertility duration

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# 血清维生素 D 水平与卵巢血流动力学及卵巢储备功能相关性研究

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**【摘要】** 目的 分析血清维生素 D 水平与卵巢血流动力学及卵巢储备功能的相关性。方法 回顾性队列研究选取 2020 年 9 月至 2021 年 11 月期间哈尔滨医科大学附属第二医院妇产科收治的年龄 18~40 岁、性生活规律的女性为研究对象。收集患者年龄、身高、体质量等资料, 检测患者补充维生素 D 前后血清维生素 D、抗苗勒管激素 (anti-Müllerian hormone, AMH)、黄体生成素、卵泡刺激素等指标, 采用彩色多普勒超声仪器测量窦卵泡计数及早卵泡期双侧卵巢间质动脉血流阻力指数 (resistance index, RI)、搏动指数 (plusatility index, PI)。多重线性回归分析血清维生素 D 水平相关影响因素。结果 研究共纳入女性 218 例, 其中维生素 D 缺乏 137 例, 占 62.8%; 维生素 D 不足 39 例, 占 17.9%; 维生素 D 正常 42 例, 占 19.3%。多重线性回归分析显示, 血清维生素 D 水平与卵巢间质动脉血流 RI 之间存在负相关 ( $P=0.025$ ); 与其余指标之间均无相关性 (均  $P>0.05$ )。结论 血清维生素 D 水平在一定程度上影响了女性卵巢间质动脉血流 RI, 但与卵巢间质动脉血流 PI、血清 AMH 水平及其他卵巢储备功能相关指标并无明显关联。

**【关键词】** 维生素 D; 血流动力学; 卵巢储备功能; 抗苗勒管激素

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# Study on the relationship between vitamin D level and ovarian blood flow and ovarian reserve function

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**【Abstract】 Objective** To analyze the correlation between serum vitamin D level and ovarian artery blood flow index and ovarian reserve function in women.

**Methods** A retrospective cohort study was conducted. Women aged from 18 to 40 years who were admitted to the Department of Obstetrics and Gynecology of the Second Affiliated Hospital of Harbin Medical University from September 2020 to November 2021 and had regular sexual life were selected as subjects. The data of age, height and weight were collected. And the indexes of vitamin D, anti-Müllerian hormone (AMH), luteinizing hormone and follicle-stimulating hormone were detected in the laboratory. Color Doppler ultrasound was used to measure antral follicle count and bilateral ovarian interstitial artery blood stream resistance index (RI) and plusatility index (PI) in early follicular phase. Multiple linear regression was used to analyze the related factors of serum vitamin D level. **Results** A total of 218 women were included in the study, including 137 cases of vitamin D deficiency, accounting for 62.8%, 39 cases of vitamin D insufficiency, accounting for 17.9%, 42 cases of normal vitamin D, accounting for 19.3%. Multiple linear regression analysis showed that there was a negative correlation between serum vitamin D level and ovarian blood flow ( $P=0.024$ ), but no correlation with other indexes (all  $P>0.05$ ). **Conclusion** Serum vitamin D level affected ovarian interstitial artery blood flow RI to some extent, but had no significant correlation with ovarian interstitial artery blood flow PI, serum AMH level and other indexes related to ovarian reserve function.

**【Key words】** Vitamin D; Hemodynamics; Ovarian reserve; Anti-Müllerian hormone

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· 实验研究 ·

# 基于 ERK/Nrf2-ARE 通路探究枸杞多糖对七氟烷麻醉诱导雄性大鼠生殖毒性的拮抗作用机制

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**【摘要】** 目的 探究枸杞多糖 (Lycium barbarum polysaccharides, LBP) 对七氟烷麻醉诱导的雄性大鼠生殖毒性的作用, 分析其对细胞外信号调节激酶 (extracellular-signal-regulated kinase, ERK)/核因子 E2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)-抗氧化反应元件 (antioxidant response element, ARE) 信号通路的影响。方法 取 SD 雄性大鼠按计算机随机生成数字法分为空白对照组、模型组、LBP 低剂量组、LBP 高剂量组和阳性对照组, 除空白对照组外其余均以七氟烷麻醉诱导, 同时腹腔注射给药, 空白对照组和模型组予以等体积生理盐水, LBP 低、高剂量组分别予以 100 mg/kg、200 mg/kg LBP, 每天 1 次, 阳性对照组予以 10 mg/kg 维生素 E, 隔天 1 次, 14 d 后处死。计算各组大鼠睾丸与附睾的脏器指数; 检测睾丸组织标志酶酸性磷酸酶 (acid phosphatase, ACP)、碱性磷酸酶 (alkaline phosphatase, AKP)、乳酸脱氢酶 (lactate dehydrogenase, LDH) 含量; HE 染色观察大鼠睾丸组织病理学; 检测睾丸组织中超氧化物歧化酶 (superoxide dismutase, SOD)、丙二醛 (malondialdehyde, MDA) 含量; TUNEL 染色观察大鼠睾丸组织细胞凋亡率; Western blotting 检测大鼠睾丸组织内 Bax、Bcl-2 及 ERK/Nrf2-ARE 通路蛋白表达。结果 LBP 低、高剂量组和阳性对照组睾丸脏器指数 [ (0.39±0.04) %、(0.47±0.05) %、(0.62±0.05) % ] 和附睾脏器指数 [ (0.08±0.01) %、(0.11±0.01) %、(0.14±0.02) % ] 均比模型组 [ (0.33±0.03) %, (0.05±0.01) % ] 高 (均  $P<0.001$ ), ACP [ (122.13±5.39) U/g、(115.37±4.45) U/g、(109.74±4.73) U/g ]、LDH 含量 [ (260.43±15.18) U/g、(245.17±8.13) U/g、(236.19±10.23) U/g ] 均比模型组 [ (129.98±6.17) U/g、(279.89±18.41) U/g ] 低 (均  $P<0.001$ ), AKP 含量 [ (224.41±11.69) U/g、(247.59±12.17) U/g、(266.74±13.78) U/g ]、SOD 活性 [ (3.11±0.12) U·mg/蛋白、(4.05±0.14) U·mg/蛋白、(4.78±0.15) U·mg/蛋白 ] 均比模型组 [ (200.48±10.48) U/g、(2.02±0.09) U·mg/蛋白 ] 高 (均  $P<0.001$ ), MDA 含量 [ (14.86±1.41) nmol·mg/蛋白、(10.39±1.22) nmol·mg/蛋白、(5.25±0.47) nmol·mg/蛋白 ] 均较模型组 [ (18.36±1.99) nmol·mg/蛋白 ] 低 (均  $P<0.001$ ), 睾丸细胞凋亡率均较模型组低 (均  $P<0.001$ ), 且呈 LBP 剂量依赖性 (均  $P<0.001$ )。模型组大鼠生精



小管变薄，生精细胞明显减少，部分曲精管内仅残留少量精原细胞；给药后，LBP 低、高剂量组和阳性对照组生精小管结构比较完整，各级生精细胞排列有序，数量增多，空泡减少。模型组大鼠睾丸组织中 Bcl-2、p-ERK1/2、Nrf2、HO-1、NQO1 蛋白水平较空白对照组高，Bax 蛋白水平较空白对照组低（均  $P<0.05$ ）；LBP 低、高剂量组 Bcl-2、p-ERK1/2、Nrf2、HO-1、NQO1 蛋白水平较模型组高，Bax 蛋白水平较模型组低（均  $P<0.05$ ），且呈 LBP 剂量依赖性（ $P<0.05$ ）。结论 LBP 对七氟烷麻醉诱导的雄性大鼠生殖毒性有拮抗作用，可能与抑制 ERK/Nrf2-ARE 通路有关。

【关键词】 枸杞多糖； 七氟烷； 麻醉诱导； 生殖毒性； 睾丸； 凋亡

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### Study on the mechanism of Lycium barbarum polysaccharide on reproductive toxicity induced by sevoflurane anesthesia in male rats based on ERK/Nrf2-ARE pathway

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【Abstract】 **Objective** To explore the effect of Lycium barbarum polysaccharide (LBP) on sevoflurane anesthesia-induced reproductive toxicity in male rats, and to analyze its effect on extracellular signal-regulated kinase (ERK)/nuclear factor E2-related factor 2 (Nrf2)-antioxidant response element (ARE) signaling pathway. **Methods** SD male rats were randomly divided into blank control group, model group, low-dose LBP group, high-dose LBP group and positive control group. Except for the blank control group, the rest were induced by sevoflurane anesthesia and administered by intraperitoneal injection at the same time. The model group was given equal volume of normal saline; the LBP low- and high-dose groups were given 100 mg/kg and 200 mg/kg LBP, once a day, respectively. The positive control group was given 10 mg/kg vitamin E, once every other day. After 14 d of the experiment, all rats were sacrificed. The organ indexes of testis and epididymis of rats in each group were calculated. The contents of testis tissue marker enzymes acid phosphatase (ACP), alkaline phosphatase (AKP) and lactate dehydrogenase (LDH) were detected. HE staining was used to observe the testicular tissue disease of rats. The contents of superoxide dismutase (SOD) and malondialdehyde (MDA) in testis tissue were detected. TUNEL staining was used to observe the apoptosis rate of rat testis tissue. Western blotting was used to detect Bax, Bcl-2 and ERK/Nrf2-ARE pathway protein expression level. **Results** In the low-dose and high-dose LBP groups and positive control group, the testicles [(0.39±0.04)%, (0.47±0.05)%, (0.62±0.05)%] and epididymal organ index [(0.08±0.01)%, (0.11±0.01)%, (0.14±0.02)%] were higher than those of the model group [(0.33±0.03)%, (0.05±0.01)%, all  $P<0.001$ ], ACP [(122.13±5.39) U/g, (115.37±4.45) U/g, (109.74±4.73) U/g] and LDH content [(260.43±15.18) U/g, (245.17±8.13) U/g, (236.19±10.23) U/g] were lower than those in the model group

[(129.98±6.17) U/g, (279.89±18.41) U/g, all  $P<0.001$ ], the AKP content [(224.41±11.69) U/g, (247.59±12.17) U/g, (266.74±13.78) U/g] and SOD activity [(3.11±0.12) U·mg/protein, (4.05±0.14) U·mg/protein, (4.78±0.15) U·mg/protein] were higher than those in the model group [(200.48±10.48) U/g, (2.02±0.09) U·mg/protein, all  $P<0.001$ ], MDA content [(14.86±1.41) nmol·mg/protein, (10.39±1.22) nmol·mg/protein, (5.25±0.47) nmol·mg/protein] was lower than that in the model group [(18.36±1.99) nmol·mg/protein, all  $P<0.001$ ], the apoptosis rate of testicular cells was relatively low (all  $P<0.001$ ) and showed a LBP dose-dependent relationship (all  $P<0.001$ ). The seminiferous tubule of the model group became thinner, and spermatid were significantly reduced, and only a small amount of spermatogonium remained in some seminiferous tubules. After administration, the structure of seminiferous tubule in the low- and high-dose LBP groups and the positive control group was relatively complete, and spermatid at all levels were arranged in order, the number increased, and vacuoles decreased. The levels of Bcl-2, p-ERK1/2, Nrf2, HO-1, and NQO1 proteins in the testicular tissue of the model group were higher than those of the blank control group, while the levels of Bax protein were lower than those of the blank control group (all  $P<0.05$ ), the protein levels of Bcl-2, p-ERK1/2, Nrf2, HO-1, and NQO1 in the low- and high-dose LBP groups were higher than those in the model group, while the protein levels of Bax were lower than that in the model group (all  $P<0.05$ ), and showed a LBP dose-dependent (all  $P<0.05$ ). **Conclusion** LBP has an antagonistic effect on sevoflurane anesthesia-induced reproductive toxicity in male rats, which may be related to the inhibition of ERK/Nrf2-ARE pathway.

**【Key words】** Lycium barbarum polysaccharide; Sevoflurane; Anesthesia induction; Reproductive toxicity; Testis; Apoptosis

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• 实验研究 •

## 依托孕烯/炔雌醇复方阴道环体外 释放方法学研究

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**【摘要】** 目的 研制出具有良好缓释性能的依托孕烯(etonogestrel, ENG)/炔雌醇(ethinyl estradiol, EE)复方阴道环, 并对其体外释放测定方法学开展研究, 确立与实时释放方法具有良好相关性的加速释放方法。方法 以乙烯-醋酸乙烯共聚物(ethylene-vinyl acetate copolymer, EVA)为基质, 以热熔挤出法制备ENG/EE 复方阴道环, 建立基于摇瓶法的体外实时释放测定方法和加速释放测定方法, 考察该复方阴道环的体外释放行为及释放机制, 并对其实时释放经时过程和加速释放经时过程的相关性进行分析。结果 所得阴道环外观圆整, 表面光滑, 在优选出的体外实时释放条件(释放介质: 200 mL 纯水, 37 °C 恒温水浴振荡器中 60 r/min 振摇)中缓慢释药, 第 21 天 ENG 和 EE 累计释放量分别为 54.39% 和 46.80%, 在优选出的体外加速条件(释放介质: 200 mL 0.6% 十二烷基硫酸钠水溶液, 55 °C 下 60 r/min 振摇)下药物释放经时过程及其机制与实时释放条件下的拟合结果相关系数均大于 0.99。结论 本研究研制的 ENG/EE 复方阴道环的体外缓释效果显著, 所建立的加速释放方法与实时释放方法相关性良好, 可供此类阴道环产品的质量评价研究及体外释放研究方法指南的制定提供有益参考。

**【关键词】** 依托孕烯; 炔雌醇; 阴道环; 实时释放; 加速释放; 相关性

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# **Methodological study on *in vitro* release of etonogestrel/ethinyl estradiol compound vaginal ring**

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**【 Abstract 】 Objective** To develop an etonogestrel (ENG)/ethinyl estradiol (EE) compound vaginal ring with good sustained-release properties, studying its *in vitro* release assay methodology, and establishing an accelerated release method with good correlation with real-time release methods. **Methods** Ethylene-vinyl acetate copolymer (EVA) was used as the matrix to prepare ENG/EE compound vaginal ring by hot melt extrusion method, and an *in vitro* real-time release assay method and an accelerated release assay method based on shake flask method were established. The *in vitro* release behavior and release mechanism of ENG/EE compound vaginal ring were investigated, and the correlation between real-time release and accelerated release over time was analyzed. **Results** The obtained vaginal ring had a round appearance and a smooth surface, and the drug was slowly released under the optimal real-time release conditions *in vitro* (release medium: 200 mL of pure water, shaking at 60 r/min in a constant temperature water bath shaker at 37 °C), and the cumulative release of ENG and EE on the 21st day were 54.39% and 46.80%, respectively. The correlation coefficients of drug release and its mechanism under the optimized *in vitro* accelerated conditions (release medium: 200 mL of 0.6% sodium dodecyl sulfate aqueous solution, shaking at 60 r/min at 55 °C) with the results under real-time release conditions were all greater than 0.99. **Conclusion** The ENG/EE compound vaginal ring obtained in this study has a significant *in vitro* sustained-release effect, and the established accelerated release conditions have a good correlation with real-time release conditions, which can provide a useful reference for the quality evaluation research of such vaginal ring products and the formulation of guidelines for *in vitro* release research methods.

**【 Key words 】** Etonogestrel; Ethinyl estradiol; Vaginal ring; Real-time release; Accelerated release; Correlation

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• 临床报道 •

# 生长激素预处理对卵巢储备功能低下患者 IVF/ICSI-ET 助孕结局的影响

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**【摘要】** 目的 探讨生长激素 (growth hormone, GH) 预处理在卵巢储备功能低下女性体外受精/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) 的疗效。方法 采用回顾性队列研究, 分析 2018 年 10 月至 2019 年 10 月期间在北京大学第三医院生殖医学中心接受 IVF/ICSI-ET 助孕, 行拮抗剂方案控制性卵巢刺激 (controlled ovarian stimulation, COS), 且基于波塞冬标准 3 组及 4 组的卵巢储备功能低下患者的临床资料。根据患者是否应用 GH 预处理, 分为 GH 组 ( $n=103$ ) 及对照组 ( $n=197$ )。GH 组促排卵前接受 2 U/d GH 皮下注射 4 周, 促排卵期间剂量调整为 4 U/d, 继续使用至扳机日, 对照组未使用 GH, 分析比较两组的临床结局。结果 女方年龄、不孕年限、体质指数 (body mass index, BMI)、抗苗勒管激素 (anti-Müllerian hormone, AMH)、基础窦卵泡计数 (antral follicle count, AFC)、基础卵泡刺激素 (follicle-stimulating hormone, FSH) 组间比较差异均无统计学意义 (均  $P>0.05$ )。促性腺激素 (gonadotropin, Gn) 使用时间、Gn 用量、人绒毛膜促性腺激素 (human chorionic hormone, hCG) 注射日雌二醇水平及子宫内膜厚度组间差异均无统计学意义 (均  $P>0.05$ )。GH 组获卵数与对照组相比差异无统计学意义 ( $P>0.05$ )。GH 组的可利用胚胎数 [ $(2.62\pm 2.41)$  枚] 显著高于对照组 [ $(1.51\pm 1.56)$  枚], 差异有统计学意义 ( $P<0.001$ )。GH 组 56 个新鲜移植周期, 对照组 106 个新鲜移植周期, 两组移植日子宫内膜厚度、移植胚胎数组间差异均无统计学意义 (均  $P>0.05$ )。GH 组与对照组新鲜移植周期临床妊娠率、流产率、活产率差异均无统计学意义 (均  $P>0.05$ )。结论 促排卵前 4 周开始 GH 预处理并持续至扳机日可增加卵巢储备功能低下患者拮抗剂方案的可利用胚胎数。

**【关键词】** 生长激素; 生殖技术, 辅助; 卵巢储备功能低下; 卵巢低反应; 波塞冬标准

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**Effect of growth hormone pretreatment on IVF/ICSI-ET assisted pregnancy outcomes in patients with poor ovarian reserve**

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**【Abstract】 Objective** To investigate the effect of growth hormone (GH) pretreatment on *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) in women with poor ovarian reserve. **Methods** A retrospective cohort study was conducted to analyze the clinical data of women who underwent IVF/ICSI-ET with gonadotropin-releasing hormone (GnRH) antagonist protocol in Reproductive Medicine Center of Peking University Third Hospital from October 2018 to October 2019. Patients with poor ovarian reserve belong POSEIDON group 3 or POSEIDON group 4 were included as the research objects and were divided into GH group ( $n=103$ ) and control group ( $n=197$ ) by pretreated with GH or not. GH group received 2 U/d subcutaneous injection of GH for 4 weeks before ovulation induction, and the dosage was adjusted to 4 U/d until the trigger day during ovulation induction. GH was not used in control group. The clinical outcomes of the two groups were analyzed and compared. **Results** There were no significant differences in general condition between GH group and control group including age, infertility duration, body mass index (BMI), anti-Müllerian hormone (AMH), basal follicle-stimulating hormone (FSH) and antral follicle count (AFC, all  $P>0.05$ ). No significant differences were found in the duration of gonadotropin (Gn) used, total dosage of Gn used, estrogen levels and the endometrial thickness on human chorionic hormone (hCG) injection day between the two groups (all  $P>0.05$ ). Furthermore, no statistically significant difference was found in the number of oocytes retrieved between GH group and control group ( $P>0.05$ ). The number of available embryos in GH group ( $2.62\pm2.41$ ) was significantly higher than that in control group ( $1.51\pm1.56$ ,  $P<0.001$ ). There were 56 fresh embryo transfer cycles in GH group and 106 fresh embryo transfer cycles in control group. There were no statistically significant differences in endometrial thickness on fresh embryo transfer day and the number of embryos transferred between GH group and control group (all  $P>0.05$ ). No statistically significant differences were found in clinical pregnancy rate, miscarriage rate and live delivery rate after fresh embryo transferred between the two groups (all  $P>0.05$ ). **Conclusion** GH pretreatment for 4 weeks before controlled ovarian stimulation and continued use till the trigger day may improve number of the available embryos in poor ovarian reserve patients with GnRH antagonist.

**【Key words】** Growth hormone; Reproductive technology, assisted; Poor ovarian reserve; Poor ovarian response; POSEIDON criteria

**Fund program:** Capital Special Fund for Health Development and Scientific Research (2014-14091)

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• 临床报道 •

## “短时取样法”用于非侵入性胚胎植入前遗传学检测效能的前瞻性研究

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**【摘要】** 目的 探讨“短时取样法”在非侵入性胚胎植入前遗传学检测(non-invasive preimplantation genetic testing, ni-PGT)中的检测效能。方法 采用前瞻性研究分析方法,对2021年3月至2022年6月期间就诊于湘潭市中心医院生殖中心行胚胎植入前非整倍体遗传学检测(preimplantation genetic testing for aneuploidy, PGT-A)患者的囊胚进行外滋养层细胞(trophectoderm, TE)活检,同时收集囊胚培养液(spent culture medium, SCM)。根据SCM收集方法的不同,分为直接收集法与“短时取样法”,分析比较两种取样方法ni-PGT的检测结果与PGT-A结果的符合率。结果 本研究收集36对夫妇的108个囊胚,均行TE活检及收集SCM,其中直接收集法59例、“短时取样法”49例。直接收集法诊断胚胎倍性的曲线下面积(area under curve, AUC, 0.628)小于“短时取样法”(0.785)。结论 “短时取样法”诊断胚胎倍性的效能相较于直接收集法更优。

**【关键词】** 无创胚胎植入前遗传学检测; 胚胎植入前遗传学检测; “短时取样法”; 二代测序

基金项目: 湖南省出生缺陷协同防治科技重大专项(2019SK1010)

### Efficiency of "short time sampling" in noninvasive preimplantation genetic testing: a prospective study

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**【Abstract】** **Objective** To explore the efficiency of "short time sampling" for noninvasive preimplantation genetic testing (ni-PGT). **Methods** A prospective study was conducted. The blastocysts of patients who were treated by preimplantation genetic testing for aneuploidy (PGT-A) in the Reproductive Center of Xiangtan Central Hospital from March 2021 to June 2022 were biopsied, meanwhile the spent culture medium (SCM) were collected. According to the

different sampling methods for SCM, they were divided into two groups, direct sampling method and "short time sampling". The coincidence rate between ni-PGT and PGT-A was analyzed and compared statistically. **Results** Totally 108 blastocysts from 36 couples were biopsied and SCMs were collected, including 59 cases of direct collection and 49 cases of "short time sampling". The area under curve (AUC) of direct collection method for diagnosing embryo ploidy was lower than that of "short time sampling" (0.628 vs. 0.785). **Conclusion** The efficiency of "short time sampling" in diagnosing embryo ploidy is better than that of direct collection method.

**【 Key words 】** Non-invasive preimplantation genetic testing; Preimplantation genetic testing; Short time sampling; Next generation sequencing

**Fund program:** Major Project of Cooperative Prevention and Control of Birth Defects in Hunan Province (2019SK1010)

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· 临床报道 ·

## 宫腔镜下子宫黏膜下肌瘤切除术后妊娠情况分析

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**【摘要】** 目的 分析不孕症或复发性流产患者宫腔镜下子宫黏膜下肌瘤切除术后妊娠结局、影响因素及妊娠期并发症情况。方法 回顾 2010 年 1 月至 2020 年 12 月期间因不孕症或复发性流产在北京大学第三医院妇产科生殖医学中心行宫腔镜下子宫黏膜下肌瘤切除术患者的临床资料, 队列研究分析患者年龄、肌瘤分型、大小、数目和位置与术后妊娠的关系, 并探讨妊娠期相关并发症情况。结果 共纳入 212 例患者, 0 型、1 型、2 型、混合型肌瘤比例分别为 9.4% (20/212)、33.5% (71/212)、51.4% (109/212) 和 5.7% (12/212), 切除单个肌瘤者占 85.4% (181/212), 切除肌瘤直径 $\leq 2$  cm 者占 79.3% (168/212); 切除肌瘤主要位于前壁和后壁分别占比 31.6% (67/212) 和 30.2% (64/212), 剪刀切除占 25.9% (55/212), 双极电切占 72.2% (153/212)。术后随访 88 例 (41.5%) 患者妊娠, 术后妊娠率随时间推移呈下降趋势, 术后 1 年内妊娠率为 77.2% (68/88)。logistic 回归分析显示术后是



否妊娠与年龄有关( $P<0.001$ ),而与肌瘤分型、大小、数目和部位无关(均 $P>0.05$ );术后妊娠的患者中,无妊娠期和分娩期子宫破裂发生,5例(5.7%)患者胎盘异常附着,其中3例胎盘植入,1例胎盘粘连,1例中央型前置胎盘。5例患者中2例既往有宫腔粘连松解史,4例患者既往有 $\geq 2$ 次子宫肌瘤切除史。结论 不孕症或复发性流产患者子宫黏膜下肌瘤切除术后妊娠率1年内最高,应结合肌瘤位置及大小决定术后是否避孕及避孕时间,多次宫腔手术史者孕期发生胎盘附着异常风险升高。

【关键词】 宫腔镜; 子宫肌瘤切除术; 妊娠; 子宫黏膜下肌瘤; 胎盘植入

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### **Analysis of pregnancy outcome after hysteroscopic submucosal myomectomy**

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【Abstract】 **Objective** To analyze the pregnancy outcome, influencing factors and pregnancy complications after hysteroscopic submucosal myomectomy in patients with infertility or recurrent abortion. **Methods** The clinical data of patients who underwent hysteroscopic submucosal myomectomy in Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital from January 2010 to December 2020 were reviewed. The relationship between age, myoma classification, size, number and location and postoperative pregnancy was retrospectively cohort analyzed, and the related complications during pregnancy were discussed. **Results** A total of 212 patients underwent surgery during the study period. The proportions of type 0, type 1, type 2 and mixed submucosal myoma were 9.4% (20/212), 33.5% (71/212), 51.4% (109/212) and 5.7% (12/212), respectively. Totally 85.4% (181/212) of patients underwent hysteroscopic resection of a single submucosal myoma, and the size of submucosal myoma of 79.3% (168/212) patients were  $\leq 2$  cm in diameter. Submucosal myoma were mainly located in the anterior and posterior wall, accounted for 31.6% (67/212) and 30.2% (64/212), respectively. Scissors removal accounted for 25.9% (55/212), and bipolar electroresection accounted for 72.2% (153/212). Totally 88 patients (41.5%) got pregnancy after hysteroscopic submucosal myomectomy. The postoperative pregnancy rate showed a downward trend over time, and the pregnancy rate in the first year after operation was 77.2% (68/88). Logistic analysis showed that pregnancy was related to age ( $P<0.001$ ), but not to the type, size, number and location of submucosal myoma (all  $P>0.05$ ). Among the patients with postoperative pregnancy, there was no uterine rupture during pregnancy and delivery. Five cases (5.7%) had abnormal placental attachment, including 3 cases of placental implantation, 1 case of placental adhesion and 1 case

of central placenta previa. Among the 5 patients, there were 2 cases with previous intrauterine adhesion and 4 cases with  $\geq 2$  times of myomectomy. **Conclusion** The pregnancy rate of patients with infertility or recurrent abortion after submucosal myomectomy is the highest within the first year. The location and size of submucosal myoma should be combined to determine whether contraception and contraception time after operation. Those with a history of multiple intrauterine surgery may have abnormal placental attachment during pregnancy.

**【Key words】** Hysteroscopy; Myomectomy; Pregnancy; Submucosal myoma; Placenta accrete

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· 现场调查 ·

## 蒙古族地区 1951 年至 2005 年间出生的汉族和蒙古族女性月经初潮年龄变化趋势研究

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**【摘要】** 目的 研究中国蒙古族地区 1951 年至 2005 年期间出生的汉族和蒙古族女性月经初潮年龄的变化及趋势。方法 通过横断面整群抽样调查方法, 在规范调查流程和质量控制标准下, 于 2003 年至 2019 年在通辽地区的 3 个旗县对 16~46 岁汉族及蒙古族女性人群进行回顾性调查, 获得 1951 年至 2005 年 55 年间

出生女性月经初潮年龄的基础数据,以每年、每5年、每10年为节点,分析其变化情况及规律。结果 本研究共完成46 928例(汉族24 450例,蒙古族22 478例)的调查,调查有效率为96.09%(46 928/48 836)。1951年至2005年55年间出生女性月经初潮发生年龄逐渐提前;平均月经初潮年龄,在以每年为节点的分析中,汉族和蒙古族分别由1951年的(16.22±0.52)岁和(15.86±1.24)岁变化为2005年的(12.37±1.15)岁和(12.33±0.98)岁,分别提前3.85岁和3.54岁(平均每年分别提前0.84个月和0.77个月),变化趋势表现出与年代呈显著负相关(均 $P<0.0001$ );在以每5年为节点的分析中,汉族和蒙古族分别由1951年至1955年的(15.54±1.45)岁和(15.53±1.48)岁变化为2001年至2005年的(12.41±0.97)岁和(12.47±0.96)岁,分别提前3.13岁和3.06岁(平均每5年分别提前3.41个月和3.34个月);在以每10年为节点的分析中,汉族和蒙古族分别由1951年至1960年的(15.79±0.95)岁和(15.53±1.33)岁变化为2001年至2005年的(12.41±0.97)岁和(12.47±0.96)岁,分别提前3.38岁和3.06岁(平均每10年分别提前6.76个月和6.12个月);相同出生年代的汉族与蒙古族女性月经初潮发生年龄接近,在1951年至1965年15年间、1966年至1970年、1971年至1990年20年间、1991年至2000年10年间分别集中在15~16岁、14~15岁、13~14岁、12~13岁;在2001年至2005年的汉族和蒙古族出生者月经初潮年龄发生在11岁、12岁、13岁分别占26.79%(457/1 706)、73.27%(1 250/1 706)、92.85%(1 584/1 706)和23.25%(653/2 809)、62.01%(1 742/2 809)、90.14%(2 532/2 809)。结论 1951年至2005年55年间出生的汉族和蒙古族女性月经初潮年龄均呈明显提前趋势,民族间趋于一致。建议在8~9岁开始开展青春期教育,重视月经初潮发生年龄提前的变化规律。

【关键词】 月经初潮; 青春期发育; 青少年; 蒙古族; 月经初潮年龄; 青春期教育

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## Study on the trend of menarche age in Han and Mongolian women born from 1951 to 2005 in Mongolian region

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【Abstract】 **Objective** To study the trend of menarche age in Han and Mongolian women born from 1951 to 2005 in Mongolian region. **Methods** A cross-sectional cluster sampling survey method was adopted, From 2003 to 2019, a retrospective survey was carried out in three banners/counties in Tongliao region on the female population of Han and Mongols nationalities aged 16 to 46 and conducted under standardized survey procedures and quality control standards. The

basic data of menarche age of women born between 1951 and 2005 were obtained. The changes and rules were analyzed by taking 1 year, 5 years and 10 years as nodes.

**Results** Totally 46 and conducted under standardized survey procedures and quality control standards 928 people (24 450 Han and 22 478 Mongolian) were recruited, the survey response rate was 96.09% (46 928/48 836). In one-year-period analysis, the menarche age gradually decreased from 1951 to 2005. The mean menarche age of Han and Mongolian women changed from (16.22±0.52) years and (15.86±1.24) years in 1951 to (12.37±1.15) years and (12.33±0.98) years in 2005, respectively. The mean menarche age of Han and Mongolian women decreased 3.85 years and 3.54 years. The trend of the mean menarche age's change showed a significant negative correlation with the years (all  $P<0.000\ 1$ ). In five-year-period analysis, the mean menarche age of Han and Mongolian women changed from (15.54±1.45) years and (15.53±1.48) years from 1951 to 1955 to (12.41±0.97) years and (12.47±0.96) years from 2001 to 2005, the mean menarche age decreased 3.13 years (3.41 months ahead of schedule every 5 years on average) and 3.06 years (3.34 months ahead of schedule every 5 years on average) in Han and Mongolian women respectively. In ten-year-period analysis, the mean menarche age of Han and Mongolian women changed from (15.79±0.95) years and (15.53±1.33) years from 1951 to 1960 to (12.41±0.97) years and (12.47±0.96) years from 2001 to 2005, the mean menarche age decreased 3.38 years (6.76 months ahead of schedule every 10 years on average) and 3.06 years (6.12 months ahead of schedule every 10 years on average) in Han and Mongolian women respectively. During the 15 years from 1951 to 1965, 1966 to 1970, 1971 to 1990, and 1991 to 2000, they were concentrated at the ages of 15–16, 14–15, 13–14, and 12–13, respectively. The proportion of women at 11 years, 12 years and 13 years menarche age were 26.79% (457/1 706), 73.27% (1 250/1 706), and 92.85% (1 584/1 706) during 2001—2005 in Han women, while the proportion were 23.25% (653/2 809), 62.01% (1 742/2 809), and 90.14% (2 532/2 809) in Mongolian women. **Conclusion** The menarche age decreased in Han and Mongolian women from 1951 to 2005, and the ethnic groups tended to be the same. It is recommended to start adolescent education at the age of 8–9 years and pay attention to the changing pattern of early onset of menarche.

**【Key words】** Menarche; Adolescent development; Adolescent; Mongolian nationality; Menarche age; Adolescent education

**Fund program:** National Basic Science and Technology Work Special Project (2013FY110500, 2006FY230400, 2003DEB5J047)

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· 综述 ·

# 人子宫内膜类器官的研究进展及应用

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**【摘要】** 子宫内膜类器官 (endometrium organoids, EOs) 是干细胞自组织形成的类似子宫内膜的三维培养物。EOs 可以保留原始组织的生物学特性并且保持基因稳定, 是一种新型体外模拟子宫内膜生理结构和功能的理想研究模型。随着生物技术和类器官培养方法的发展, EOs 不仅可以用于子宫内膜发育研究, 而且可用于妇科疾病模型、药物筛选、个体化诊疗及再生医学等研究领域。本文将从 EOs 的研究进展及应用前景等方面进行概述, 以期推广 EOs 在基础和临床研究的应用。

**【关键词】** 子宫内膜; 类器官; 三维培养; 妇科疾病; 药物筛选; 个性化医疗; 再生医学

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## Research progress and application of human endometrium organoids

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**【Abstract】** Endometrium organoids (EOs) are formed three-dimensional culture by self-organizing stem cells, which is similar to the endometrium in structure and function. EOs remain the biological characteristics of the original tissue and maintain gene stability, which are ideal research model to simulate the physiological structure and function of the endometrium *in vitro*. With the development of biotechnology and organoid culture methods, EOs can be used not only in endometrial development research, but also in gynecological disease models, drug screening, personalized diagnosis and treatment, and regenerative medicine. In order to popularize the EOs for the basic and clinical research, this review summarizd the research progress and application prospects of EOs.

**【Key words】** Endometrium; Organoids; Three-dimensional culture; Gynecologic diseases; Drug screening; Personalized medicine; Regenerative medicine

**Fund program:** National Natural Science Foundation of China (81901437, 82171619)

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· 综述 ·

## 能量不足对女性生殖健康影响的研究进展

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**【摘要】** 女性生殖功能的发育和维持需要大量能量, 而生殖过程并非机体必需的生命活动。当机体处于能量供应缺乏状态, 即能量摄入不足和(或)能量消耗过多时, 则会出现能量的重新分配, 导致生殖功能降低, 出现下丘脑-垂体-卵巢(hypothalamic-pituitary-ovary, HPO)轴不同程度的抑制, 表现为排卵障碍、月经失调和不孕症等。长期能量不足状态下可引起体脂率下降, 而脂肪组织在维系营养与生殖中发挥重要作用, 影响月经初潮的发动和周期的维持。女运动员三联征和神经性厌食患者都是长期能量不足和低体脂的典型例子, 目前以减少运动消耗和增加饮食摄入使体脂率升高作为生殖功能康复的必要条件。本文就以上两种模型对能量不足对女性生殖健康影响的研究进展进行综述。

**【关键词】** 能量代谢; 功能性下丘脑性闭经; 生殖健康; 女运动员三联征; 神经性厌食症

### Research progress of the influence of energy deficiency on female reproductive health

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**【Abstract】** Women need amounts of energy to develop and maintain normal reproductive function which is not necessary physiological activity for body. When body is in situation of low energy availability, namely deficient energy intake and (or) excessive energy expend, the energy redistribution will happen accompanied with

reduced reproduction function. It can manifest as inhibition of hypothalamic-pituitary-ovary axis to different extents and ovulation dysfunction, menstrual disturbance and infertility as clinical symptoms. Long term energy deficiency can result in decrease of body fat, while the adipose tissue play key role in the relationship between nutrition and reproduction, thus exerting an influence on menarche initiation and menstrual cycle maintenance. The female athlete triad and anorexia nervosa are two typical examples of pathological situation under energy deficiency and low body fat over long term. Now, in order to restore body fat, we consider decreasing exercise consumption and increasing diet intake to increase body fat rate as necessary conditions for reproductive rehabilitation. In this review, we will focus on the influences of energy deficiency and low body fat on female reproductive health.

**【Key words】** Energy metabolism; Functional hypothalamic amenorrhea; Reproductive health; Female athlete triad syndrome; Anorexia nervosa

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· 综述 ·

## 单细胞测序技术在生殖医学中的应用及研究进展

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**【摘要】** 近年来单细胞测序技术快速发展, 以所需细胞少、高通量、高灵敏度的优势, 应用于人体各组织细胞的基因组测序、转录组测序, 助力细胞间相互作用、细胞异质性的研究。在婚育观的改变、社会、环境等复杂因素的影响下, 不孕不育的发病率逐年增高, 如何保护人类生育力成为社会热点。单细胞测序技术在辅助生殖中的应用, 从基因层面、表观遗传修饰更精准地揭示了生殖细胞的发育、成熟、衰老规律, 阐释早期胚胎发育规律, 解密生殖疾病的分子调控研究机制。本文

就单细胞测序技术在生殖领域的应用进展作一综述,为进一步探索人类生殖系统发育轨迹、病理改变、分子调控机制、遗传诊断等方面提供参考。

【关键词】 生殖医学; 卵母细胞; 精子; 胚胎发育; 单细胞测序技术

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## Application and research progress of single cell sequencing technology in reproductive medicine

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【Abstract】 In recent years, single cell sequencing technology has developed rapidly. With the advantages of few cells needed, high throughput and high sensitivity, it has been applied to genome sequencing and transcriptome sequencing of human tissues and cells to facilitate the research of cell interaction and cell heterogeneity. Under the influence of the complex factors such as the change of marriage and childbirth, social and environmental factors, the incidence rate of infertility has increased year by year. How to protect human fertility has become a social hot spot. The application of single cell sequencing technology in assisted reproduction reveals the development, maturation and aging laws of germ cells more accurately, explains the law of early embryonic development, decrypts the molecular regulation research mechanism of reproductive diseases from the genetic level and epigenetic modification. This article reviewed the application progress of single cell sequencing technology in the field of reproduction, in order to provide a reference for further exploring the development track, pathological changes, genetic diagnosis and molecular regulation mechanism of human reproductive system.

【Key words】 Reproductive medicine; Oocytes; Sperm; Embryonic development; Single cell sequencing technology

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· 综述 ·



# 玻璃化冷冻保存对卵母细胞表观遗传修饰及转录组的影响

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**【摘要】** 卵母细胞玻璃化冷冻已经成为女性生育力保存的一线方案, 在辅助生殖中得到广泛运用。卵母细胞是胚胎发育的基础, 在胚胎发育早期表观遗传重编程和母源-合子转换 (maternal-to-zygotic transition, MZT) 中发挥重要作用, 是个体发育的关键。卵母细胞表观遗传修饰和转录组对玻璃化冷冻诱导的应激非常敏感, 作为一种外界强刺激, 玻璃化冷冻保存可能对卵母细胞的表观遗传修饰和转录组产生不良影响。本文主要对玻璃化冷冻程序对卵母细胞表观遗传修饰和转录组的影响进行综述, 为玻璃化冷冻技术的优化提高提供理论基础。

**【关键词】** 卵母细胞; 玻璃化冷冻; 表观遗传学; 转录组

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## Effects of vitrification on epigenetic modification and transcriptome of oocytes

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**【Abstract】** Oocyte vitrification has developed as a first-line solution for female fertility preservation, which is widely used in assisted reproductive technology. As the basis of embryonic development, oocytes play an important role in early embryonic development, including epigenetic reprogramming and maternal-to-zygotic transition (MZT). They deserve the key to individual development. Oocyte epigenetic modification and transcriptome are very sensitive to stress induced by vitrification. Vitrification cryopreservation may have adverse effects on the epigenetic modification and transcriptome of oocytes as a strong external stimulus. Through the paper, we mainly reviewed the effects of vitrification on epigenetic modification and transcriptome of oocytes, hoping to provide a theoretical basis for the optimization and improvement of vitrification technology.

**【Key words】** Oocyte; Vitriification; Epigenetics; Transcriptome

**Fund program:** National Key R&D Program of China (2017YFC1002003);  
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· 综述 ·

## miRNA 在胚胎植入免疫调控中的研究进展

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**【摘要】** 胚胎植入是妊娠过程的起始阶段, 囊胚必须黏附并入侵接受性母体子宫内膜, 以获得氧气和营养的供应; 但胎儿是一种半同种异体移植物, 一旦进入子宫必然会遭到母体的免疫排斥, 因此建立并维持母-胎免疫耐受对植入成功至关重要。微小 RNAs (microRNAs, miRNAs) 是一类内源性的非编码 RNA, 通过调控靶基因的转录后表达, 从而参与人体内众多的生理和病理活动。目前已有大量的研究证实, miRNAs 在胚胎植入中具有重要作用, 同时也能调控母体免疫系统, 当 miRNAs 表达失调时, 通过调控免疫细胞和免疫分子参与妊娠并发症。此外, 母-胎界面的免疫耐受性在着床中起着至关重要的作用。本文对 miRNAs 在胚胎植入免疫调控中的相关研究进展作一综述。

**【关键词】** 微小 RNAs; 胚胎植入; 杀伤细胞, 自然; 巨噬细胞; T 淋巴细胞; 主要组织相容性复合物; 妊娠

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**Research progress of miRNA in immune regulation of embryo implantation**

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**【Abstract】** Embryo implantation is the initial stage of the gestation process where the blastocyst must adhere to and invade the receptive endometrium in order to receive oxygen and nutrients; but the fetus is a semi-allogeneic graft that will inevitably be immunologically rejected by the mother once it enters the uterus, therefore, establishing and maintaining maternal-fetal immune tolerance is essential for a successful implantation. MicroRNAs (miRNAs) are a class of endogenous non-coding RNAs, and involved in numerous physiological and pathological activities in the body by regulating the post-transcriptional expression of target genes. A large number of studies have confirmed that miRNAs have an important role in embryo implantation and also regulate the maternal immune system, which is involved in pregnancy complications by modulating immune cells and immune molecules when miRNAs are dysregulated in expression. In addition, immune tolerance at the maternal-fetal interface plays a crucial role in implantation. This paper reviews the progress of research on the immune regulation of miRNAs in the process of embryo implantation.

**【Key words】** MicroRNAs; Embryo implantation; Killer cell, natural; Macrophages; T-lymphocytes; Major histocompatibility complex; Pregnancy

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• 综述 •

## 多囊卵巢综合征临床、代谢表型及远期并发症 与抑郁、焦虑关系的研究进展

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**【摘要】** 多囊卵巢综合征 (polycystic ovary syndrome, PCOS) 是育龄期妇女常见的生殖内分泌疾病。PCOS 患者易发心理障碍, 其中尤以抑郁、焦虑的发病率最高。PCOS 与抑郁、焦虑的相关性是近年研究的热点问题, 研究表明 PCOS 临床、代谢表型及远期并发症所致的生化改变和心理压力可能解释了抑郁、焦虑产生的机制。本文对 PCOS 表型及远期并发症与抑郁、焦虑发生的相关研究展开综述, 总结现有的研究结果, 以期厘清 PCOS 对抑郁、焦虑的潜在影响因素, 为后续研究和临床工作提供帮助。

**【关键词】** 多囊卵巢综合征; 抑郁; 焦虑; 表型; 并发症  
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## **Progress on depression and anxiety in polycystic ovary syndrome: impact of clinical and metabolic phenotypes and long-term complications**

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**【Abstract】** Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder in women of childbearing age. Patients with PCOS are more likely to have psychological disorders such as anxiety and depression. In recent years, researchers have explored the link between PCOS and depression and anxiety. The biochemical changes and psychological stress experienced by PCOS patients caused by different clinical and metabolic phenotypes and long-term complications may account for the high levels of depression and anxiety experienced by women with PCOS risk. The purpose of this review was to summarize the present findings on PCOS phenotype and long-term complications related to depression and anxiety, to clarify the factors that may contribute to depression and anxiety, and to formulate future study directions and clinical practice.

**【Key words】** Polycystic ovary syndrome; Depression; Anxiety; Phenotype; Complications

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