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Reviews

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·临床研究·

囊胚二次活检对胚胎植入前遗传学检测患者临床结局的影响

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【摘要】　目的　探究囊胚二次活检对胚胎植入前遗传学检测（preimplantation genetic testing，PGT）患者临床妊娠和新生儿结局的影响。方法　回顾性队列研究分析了河南省人民医院生殖医学中心于 2019 年 1 月至 2022 年 12 月期间行一次活检 PGT 和二次活检 PGT 后助孕患者（分别为 453 例、60 例）的临床妊娠和新生儿结局。采用 2∶1 倾向性评分匹配（propensity score matching，PSM）方法对两组的女方年龄、体质量指数（body mass index，BMI）、不孕年限进行匹配，比较两组 PGT 患者实验室指标及移植助孕结局和新生儿结局相关指标。同时依据 PGT 类型对二次活检 PGT 组进行亚组分析，分为胚胎植入前非整倍体遗传学检测（preimplantation genetic testing for aneuploidy，PGT-A）亚组、胚胎植入前染色体结构异常遗传学检测（preimplantation genetic testing for structural rearrangements，PGT-SR）亚组、胚胎植入前单基因遗传学检测（preimplantation genetic testing for monogenic，PGT-M）亚组，两两比较其二检率、扩增成功率、可移植率等指标。结果　PSM 后，两组 PGT 患者间女方年龄、女方 BMI、不孕类型、促排卵方案、PGT 类型及实验室相关指标的差异均无统计学意义（均 $P>0.05$）；同时，二次活检胚胎的种植率、临床妊娠率、活产率均略降低，流产率略增高，但差异均无统计学意义（均 $P>0.05$）；然而，二次活检 PGT 组患者的第 3 天可利用胚胎率［87.50%（434/496）］明显高于一次活检 PGT 组［82.19%（812/980），$P=0.020$］，而囊胚形成数［4.00（2.25，6.75）］明显少于一次活检 PGT 组［5.50（3.00，8.00），$P=0.028$］；同时，二次活检胚胎的染色体整倍体率［35.9%（28/78）］低于一次活检胚胎［49.3%（226/458），$P=0.028$］，且异常率［9.0%（7/78）］高于一次活检胚胎［0.9%（4/458），$P<0.001$］，差异均有统计学意义。二次活检 PGT 组非整倍体率和多条染色体嵌合体率高于一次活检 PGT 组，但差异均无统计学意义（均 $P>0.05$）。新生儿出生体质量、胎龄、性别比例、低出生体质量

儿、巨大儿、小于胎龄儿、大于胎龄儿、出生缺陷发生率两组间差异均无统计学意义（均 $P>0.05$）。二次活检 PGT 组亚组之间两两比较，其二检率、扩增成功率、可移植率的差异均无统计学意义（均 $P>0.05$）。结论　对于第一次活检失败的患者，经过二次活检行 PGT 后的临床妊娠率、活产率和新生儿出生体质量、出生缺陷发生率等与一次活检 PGT 患者相当。

【关键词】　囊胚；　倾向性匹配；　二次活检；　胚胎植入前遗传学检测；　新生儿结局

基金项目：河南省医学科技攻关计划联合共建项目（LHGJ20220045）

Effect of the second biopsy on the clinical outcomes of patients with preimplantation genetic testing

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【Abstract】　Objective　To investigate the effect of rebiopsy blastocyst on clinical pregnancy and neonatal outcomes in patients with preimplantation genetic testing (PGT) before embryo implantation. **Methods**　A retrospective cohort study analyzed the clinical pregnancy and neonatal outcomes of one biopsy and rebiopsy patients (453 and 60 patients, respectively) with PGT in the Reproductive Medicine Center of Henan Provincial People's Hospital from January 2019 to December 2022. The 2∶1 propensity score matching (PSM) method was used to match the age, body mass index (BMI) and infertility duration of women in the two groups, and the laboratory indexes and related indexes of transplant fertility and neonatal outcomes of PGT patients were compared between the two groups. The rebiopsy patients with PGT were divided into PGT for aneuploidy (PGT-A) subgroup, PGT for structural rearrangements (PGT-SR) subgroup and PGT for monogenic (PGT-M) subgroup according to PGT types, and the rebiopsy rate, the success rate of amplification and the rate of transferrable embryo were compared between each two subgroups. **Results**　After PSM, there were no significant differences in women's age, female body mass index, infertility type, ovulation induction program, PGT type and laboratory-related indexes between the two groups (all $P>0.05$). At the same time, the implantation rate, the clinical pregnancy rate and the live birth rate of rebiopsy embryos decreased, and the miscarriage rate increased, but the differences were not statistically significant (all $P>0.05$). The rate of day 3 available embryo in the rebiopsy PGT group [87.50% (434/496)] was significantly increased, and the number of blastocyst [4.00 (2.25,6.75)] was significantly decreased compared with one biopsy PGT group [82.19% (812/980), $P=0.020$; 5.50 (3.00,8.00), $P=0.028$]. Then the chromosomal euploidy rate of the rebiopsy embryo [35.9% (28/78)] decreased and the abnormality rate [9.0% (7/78)] increased in the rebiopsy PGT group compared with one biopsy PGT group [49.3% (226/458), $P=0.028$; 0.9% (4/458), $P<0.001$], and the differences were statistically significant. The aneuploidy rate and multi-chromosome mosaic rate in the rebiopsy PGT group were higher than

those in the one biopsy PGT group, but the difference was not statistically significant (all *P*>0.05). There were no significant differences in birth weight, gestational age, sex ratio, low birth weight infants, macrosomia, small-for-gestational-age infants, large-for-gestational-age infants, and incidence of birth defects between the two groups (all *P*>0.05). There was no significant difference in the rebiopsy rate, the success rate of amplification and the rate of transferrable embryo between the subgroups of the PGT group (all *P*>0.05). **Conclusion** For patients who fail the first biopsy, the clinical pregnancy rate, the live birth rate, the neonatal birth weight, and the birth defect incidence rate after the second biopsy of PGT are comparable to those of the patients with the first biopsy of PGT.

【**Key words**】 Blastocyst; Propensity score matching; Secondary biopsy; Preimplantation genetic testing; Neonatal outcomes

Fund program: Henan Provincial Medical Science and Technology Research Program (LHGJ20220045)

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·临床研究·

阴道微生物群失调对冻融胚胎移植患者妊娠结局的影响：一项回顾性队列研究

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【摘要】 目的 探讨阴道微生物群失调对全胚胎冷冻首次行冻融胚胎移植（frozen-thawed embryo transfer， FET）患者妊娠结局及单胎妊娠活产 FET 患者围产期结局的影响。方法 采用回顾性队列研究收集 2021 年 1 月至 2022 年 12 月期间于郑州大学第三附属医院生殖医学科全胚胎冷冻首次行 FET 患者共 2 299 个周期的临床资料，根据移植前阴道微生物群优势菌类型分为 3 组：对照组（优势菌为乳酸杆菌即革兰阳性杆菌，1 849 个周期）、革兰阴性杆菌组（191 个周期）和革兰阳性球菌组（259 个周期）。比较各组基线数据、妊娠结局。选取符合纳排

标准的单胎妊娠活产 FET 患者，进一步分析各组的围产期结局。主要观察指标为活产率、流产率及早产率。多因素 logistic 回归模型矫正主要观察指标的混杂因素，分析阴道微生物群优势菌类型与活产率、流产率及早产率的关系。结果　对照组、革兰阴性杆菌组和革兰阳性球菌组移植日子宫内膜厚度差异具有统计学意义[分别为（9.38±1.58） mm、（9.56±1.70） mm、（9.84±1.74） mm，*P*<0.001]。内膜准备方案中，革兰阳性球菌组降调节+人工周期患者占比高于对照组，差异具有统计学意义［13.13% （34/259）、7.46% （138/1 849），*P*<0.016 7］。妊娠结局中，对照组、革兰阴性杆菌组和革兰阳性球菌组 3 组间活产率差异具有统计学意义[分别为 49.86%（922/1 849）、49.21%（94/191）、41.70%（108/259），*P*=0.048]，组间两两比较显示，革兰阳性球菌组活产率低于对照组，组间差异具有统计学意义（*P*<0.016 7）。其余妊娠结局及单胎妊娠活产 FET 患者围产期结局差异均无统计学意义（均 *P*>0.05）。多因素 logistic 回归模型矫正女方年龄、不孕年限、基础卵泡刺激素、抗苗勒管激素、单胚胎移植占比、单囊胚移植占比、移植日内膜厚度、内膜准备方案后，革兰阳性球菌是 FET 后活产的独立危险因素（a*OR*=0.73，95% *CI*：0.55~0.95，*P*=0.021）。结论　胚胎移植前阴道微生物群优势菌为革兰阳性球菌可能与首次 FET 患者活产率降低相关，而与单胎妊娠活产 FET 患者围产期结局无明显相关性。

【关键词】 生殖技术，辅助； 胚胎移植； 妊娠结局； 阴道微生物群失调； 活产率

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Effect of vaginal microbiota disorder on pregnancy outcomes in frozen-thawed embryo transfer patients: a retrospective cohort study

Liu Manman, Zhang Hebo, Xu Shilian, Zhang Rui, Huang Jiangdi, Yang Ruxue, Zhou Liang, Ren Bingnan, Zhang Junwei, Liu Zhaozhao, Zhang Wenjuan, Guan Yichun

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【**Abstract**】 **Objective** To explore the effect of vaginal microbiota disorder on pregnancy outcomes in the first-time frozen-thawed embryo transfer (FET) patients and perinatal outcomes in single pregnancy live delivery patients. **Methods** The clinical data of 2 299 cycles of FET patients in the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University from January 2021 to December 2022 were collected in a retrospective cohort study. According to the types of dominant bacteria in the vaginal microbiota before transplantation, they were divided into three groups: control group (dominant bacteria were Lactobacillus, which was Gram positive bacteria, 1 849 cycles), the Gram negative bacilli group (191 cycles), and the Gram positive cocci group (259 cycles). Baseline data and pregnancy outcomes were compared among the three groups. The perinatal outcomes of select single pregnancy live birth FET patients who met the inclusion criteria were further analyzed among the three groups. The main observation indicators were live birth rate, miscarriage rate, and preterm birth rate. A multivariate logistic regression model was used to control confounding factors in

the main observation indicators, and to analyze the relationship between dominant bacterial types in the vaginal microbiota and live birth rate, miscarriage rate, and preterm birth rate. **Results** The difference in endometrial thickness on the day of transplantation among control group, Gram negative bacilli group, and Gram positive cocci group was statistically significant [(9.38±1.58) mm, (9.56±1.70) mm, and (9.84±1.74) mm, respectively, *P*<0.001]. In the endometrium preparation methods, the proportion of down-regulation+artificial cycle patients in the Gram positive cocci group was higher than that in control group, and the difference was statistically significant [13.13% (34/259) and 7.46% (138/1 849), respectively, *P*<0.016 7]. In the pregnancy outcomes, there was a statistically significant difference in live birth rate among control group, Gram negative bacilli group, and Gram positive cocci group [49.86% (922/1 849), 49.21% (94/191) and 41.70% (108/259), respectively, *P*=0.048]. The live birth rate of the Gram positive cocci group was lower than that of control group, and the difference between the two groups was statistically significant (*P*<0.016 7). There were no statistically significant differences in other pregnancy outcomes and perinatal outcomes of single pregnancy live birth FET patients (all *P*>0.05). The multivariate logistic regression model corrected for female age, infertility years, basal follicle stimulating hormone, anti-Müllerian hormone, proportion of single embryo transfer, proportion of single blastocyst transfer, endometrial thickness on transfer day, and endometrial preparation methods, Gram positive cocci were independent risk factors for live brith after FET transplantation (a*OR*=0.73, 95% *CI*: 0.55−0.95, *P*=0.021). **Conclusion** The dominant bacteria in the vaginal microbiota before embryo transfer are Gram positive cocci, which may be related to a decrease in live birth rate in first-time FET patients, but not significantly related to the perinatal outcomes.

【 Key words 】 Reproductive techniques, assisted; Embryo transfer; Pregnancy outcome; Vaginal microbiota disorder; Live birth rate

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应用自然周期与激素替代疗法行首次冻融胚胎移植的年轻患者临床结局分析

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【摘要】 目的　分析应用自然周期（natural cycle， NC）与激素替代疗法（hormone replacement therapy，HRT）行首次冻融胚胎移植（frozen-thawed embryo transfer， FET）的<35 岁患者的临床结局。方法　回顾性队列研究分析 2016 年 1 月至 2021 年 6 月期间在郑州大学第一附属医院生殖医学中心接受首次 FET 助孕的年轻不孕症患者 4 814 例，根据内膜准备方案的不同分为 NC 组和 HRT 组，使用倾向性评分匹配（propensity score matching，PSM）法按 1∶1 的比例匹配两组的基线数据后，比较基线特征、妊娠结局及围产期结局，通过单因素及多因素 logistic 回归分析调整影响活产率的混杂因素后，根据窦卵泡计数（antral follicle count， AFC）、移植胚胎数和移植优质胚胎数进一步分层，分别分析 NC 和 HRT 对活产率的影响。结果　PSM 前，纳入 NC 组 2 131 例，HRT 组 2 683 例，两组间的女方年龄、男方年龄、体质量指数（body mass index， BMI）、基础卵泡刺激素（basal follicle-stimulating hormone， bFSH）、抗苗勒管激素（anti-Müllerian hormone， AMH）、AFC、转化日子宫内膜厚度、移植胚胎数差异均存在统计学意义（均 *P*<0.05），两组间的移植优质胚胎数和移植胚胎类型差异均无统计学意义（均 *P*>0.05）；PSM 后，纳入 NC 组和 HRT 组各 1 441 例，两组患者的女方年龄、男方年龄、BMI 等基线特征差异均无统计学意义（均 *P*>0.05），NC 组的活产率［50.66%（730/1 441）］和临床妊娠率［60.31%（869/1 441）］显著高于 HRT 组［44.69%（644/1 441），*P*=0.001； 54.27%（782/1 441），*P*=0.001］，极低出生体质量儿发生率 NC 组［0.34%（3/871）］显著低于 HRT 组［1.69%（13/769），*P*=0.006］，余各项指标两组差异均无统计学意义（均 *P*>0.05）。把 bFSH、AMH、AFC、转化日子宫内膜厚度、移植胚胎数及移植优质胚胎数纳入多因素 logistic 回归模型矫正混杂因素后，结果显示 NC 为影响首次 FET 周期活产的独立保护因素（*aOR*=1.280，95% *CI*：1.103~1.486，*P*=0.001）。分层分析结果显示，在 AFC<11、11~20，移植胚胎数为 2 及移植优质胚胎数为 2 的人群中，NC 组的活产率［49.03%（151/308），49.09%（349/711），56.38%（442/784），57.85%（350/605）］显著高于 HRT 组［36.36%（120/330），*P*=0.001；43.14%（286/663），*P*=0.027；48.97%（379/774），*P*=0.003；48.68%（294/604），*P*=0.001］。结论　对于年轻 FET 助孕患者，NC-FET 比 HRT-FET 有更高的活产率和临床妊娠率。

【关键词】 自然周期； 激素替代疗法； 冻融胚胎移植； 临床结局； 活产率

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Analysis of the first frozen-thawed embryo transfer clinical outcomes in young patients applying natural cycle and hormone replacement therapy

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【Abstract】 Objective To analyze the clinical outcomes of the first frozen-thawed embryo transfer (FET) in patients <35 years old applying natural cycle (NC) and hormone replacement therapy (HRT). **Methods** A retrospective cohort study was conducted to analyze 4 814 young infertility patients who underwent the first FET in Reproductive Medicine Center of the First Affiliated Hospital of Zhengzhou University from January 2016 to June 2021. According to different endometrial preparation protocols, they were divided into 2 groups: NC group and HRT group, who were matched the baseline data using 1∶1 propensity score matching (PSM). After the matching, the two groups of their baseline data, pregnancy outcomes and perinatal outcomes were compared, and then we adjusted the confounding factors which affect live birth rate by univariate and multivariate logistic regression analysis. Based on antral follicle count (AFC), number of embryos transferred and number of high-quality embryos transferred, the effect of NC and HRT on the live birth rate were further analyzed. **Results** Before PSM, 2 131 patients in NC group and 2 683 patients in HRT group were included. The differences in female age, male age, body mass index (BMI), basal follicle-stimulating hormone (bFSH), anti-Müllerian hormone (AMH), AFC, endometrial thickness on conversion day, and number of embryos transferred were all statistically significant between the two groups (all $P<0.05$). And the differences in number of high-quality embryos transferred and type of embryos transferred between the two groups were not statistically significant (all $P>0.05$). After PSM, 1 441 patients in each of NC group and HRT group were included, and there were no significant differences in their baseline characteristics such as female age, male age and BMI between the two groups (all $P<0.05$). The live birth rate [50.66% (730/1 441)] and the clinical pregnancy rate [60.31% (869/1 441)] in NC group were significantly higher than those in HRT group [44.69% (644/1 441), $P=0.001$; 54.27% (782/1 441), $P=0.001$], and the incidence of very low birth weight in NC group was significantly lower than that in HRT group, and there were no statistical significances in other indicators between the two groups (all $P>0.05$). After adjusting confounders including bFSH, AMH, AFC, endometrial thickness on conversion day, number of embryos transferred and high-quality embryos transferred using multivariate logistic regression analysis, the results showed that NC was an independent protective factor for live birth rate in the first FET cycle (*aOR*=1.280, 95% *CI*: 1.103-1.486, $P=0.001$). Stratified analysis showed that those

with AFC<11, AFC 11-12, 2 embryos transferred and 2 high-quality embryos tranferred in NC group had significantly higher live birth rate [49.03% (151/308), 49.09% (349/711), 56.38% (442/784), 57.85% (350/605)] than those in HRT group [36.36% (120/330), *P*=0.001; 43.14% (286/663), *P*=0.027; 48.97% (379/774), *P*=0.003; 48.68% (294/604), *P*=0.001]. **Conclusion** NC-FET had higher live birth rate and clinical pregnancy rate than HRT-FET in young patients.

【Key words】 Natural cycle; Hormone replacement therapy; Frozen-thawed embryo transfer; Clinical outcome; Live birth rate

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·临床研究·

基于波塞冬标准的卵巢低反应人群胚胎非整倍体率分析

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【摘要】 目的 基于波塞冬标准分析卵巢低反应（poor ovarian response，POR）人群的胚胎非整倍体率，探究卵巢储备评估指标对卵子质量的预测价值。方法 基于2017年1月至2020年12月期间于山东大学附属生殖医院生殖遗传科行胚胎移植前非整倍体筛查（preimplantation genetic testing for aneuploidies，PGT-A）助孕的患者临床资料，进行回顾性病例对照研究。根据年龄和卵巢储备水平参照波塞冬标准分为POR 1组，即非高龄非预期POR组［年龄<35岁，抗苗勒管激素（anti-Müllerian hormone， AMH）≥1.2 μg/L，获卵数≤9枚，258个周期］；POR 2组，即高龄非预期POR组（年龄≥35岁，AMH≥1.2 μg/L，获卵数≤9枚，397个周期）；POR 3组，即非高龄低储备组（年龄<35岁，AMH<1.2 μg/L，获卵数≤9 枚，99个周期）；POR 4组，即高龄低储备组（年龄≥35岁，

AMH<1.2 μg/L，获卵数≤9 枚，377 个周期）。以年龄为匹配因素，选取卵巢储备及卵巢反应均正常女性设立非 POR 组作为对照（非 POR 1 组、非 POR 2 组、非 POR 3 组和非 POR 4 组，AMH≥1.2 μg/L，获卵数>9 枚）。根据各组样本量差异，对非高龄组进行 1∶2 倾向性评分匹配（propensity score matching，PSM；POR 1 组比非 POR 1 组；POR 3 组比非 POR 3 组），高龄组进行 1∶1 PSM（POR 2 组比非 POR 2 组；POR 4 组比非 POR 4 组）。胚胎整倍体率和非整倍体率作为主要观察指标，获卵数、MⅡ（成熟卵子）数、双原核（two pronuclei， 2PN）数、检测囊胚数、胚胎整倍体数、非整倍体数、嵌合体胚胎数/率作为次要观察指标。结果　POR 1~4 组的获卵数［7.0（6.0，9.0）枚、7.0（5.0，8.0）枚、6.0（4.0，9.0）枚和 5.0（3.0，7.0）枚］和检测囊胚数［3.0（2.0，4.0）枚、2.0（1.0，3.0）枚、3.0（2.0，4.0）枚和 2.0（1.0，3.0）枚］均显著少于同龄非 POR 1~4 组［获卵数：16.0（13.0，20.0）枚、14.0（11.0，17.0）枚、16.0（13.0，20.0）枚、13.0（11.0，17.0）枚，均 *P*<0.001；检测囊胚数：4.0（3.0，6.0）枚、3.0（2.0，5.0）枚、4.0（3.0，6.0）枚、3.0（2.0，5.0）枚，均 *P*<0.001］。非 POR 4 组在校正重复取卵周期、PGT-A 指征、促排卵方案和促性腺激素用量后，POR 4 组胚胎非整倍体率显著高于非 POR 4 组（*OR*=1.252，95% *CI*：1.053~1.488，*P*=0.011），POR 1 组、2 组、3 组患者与相应的非 POR 1、2、3 组相比，胚胎非整倍体率差异均无统计学意义（均 *P*>0.05）。结论　高龄（≥35 岁）女性卵巢储备异常降低不仅减少了获卵数，而且因影响卵子质量进而导致胚胎整倍体率下降、非整倍体率上升；而非高龄（<35 岁）女性卵巢储备降低主要影响获卵数。

【关键词】 胚胎植入前非整倍体遗传学检测； 抗苗勒管激素； 非整倍体；卵巢低反应； 波塞冬标准

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Blastocyst aneuploidy rates in poor ovarian response patients according to the POSEIDON criteria

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【Abstract】 **Objective** To compare the aneuploidy rate of embryos between poor ovarian response (POR) patients and women with normal ovarian reserve stratified by age, and to eliminate the influence of ovarian reserve on embryo quality. **Methods** This was a retrospective case-control study of patients who underwent preimplantation genetic testing for aneuploidies (PGT-A) at the Department of Reproduction and Genetics in Hospital for Reproductive Medicine, Shandong University from January 2017 to December 2020. According to the

POSEIDON criteria, POR patients were divided into group 1 [age<35 years, anti-Müllerian hormone (AMH)≥1.2 μg/L, number of oocytes retrieved≤9, 258 cycles], group 2 (age≥35 years, AMH≥1.2 μg/L, number of oocytes retrieved≤9, 397 cycles), group 3 (age<35 years, AMH<1.2 μg/L, number of oocytes retrieved≤9, 99 cycles) and group 4 (age≥35 years, AMH<1.2 μg/L, number of oocytes retrieved≤9, 377 cycles). The aneuploidy rate of the blastocysts in each group was compared with age-matched control women with normal ovarian reserve and normal ovarian response (non-POR 1 group, non-POR 2 group, non-POR 3 group and non-POR 4 group, AMH≥1.2 μg/L, number of oocytes retrieved>9). Based on the difference in sample size of POR groups and control groups, a 1∶2 propensity score matching (PSM) analysis was performed between the <35 years old POR groups and age-matched control groups (POR 1 group *vs*. non-POR 1 group, POR 3 group *vs.* non-POR 3 group) and a 1∶1 PSM analysis was performed between the ≥35 years old POR groups and age-matched control groups (POR 2 group *vs.* non-POR 2 group, POR 4 group *vs.* non-POR 4 group). The main outcomes were the rates of euploid and aneuploid embryo, the secondary outcomes were the numbers of oocytes retrieved, metaphaseⅡ oocytes, two pronuclei, embryos biopsied, euploid embryos, aneuploid embryos and mosaic embryos per cycle. **Results** The number of oocytes retrieved and embryos biopsied embryos in POR 1−4 groups was significantly decreased compared with non-POR 1−4 groups [No. of oocytes retrieved: 7.0 (6.0, 9.0) *vs*. 16.0 (13.0, 20.0), 7.0 (5.0, 8.0) *vs.* 14.0 (11.0, 17.0), 6.0 (4.0, 9.0) *vs.* 16.0 (13.0, 20.0), 5.0 (3.0, 7.0) *vs.* 13.0 (11.0, 17.0), all *P*<0.001; No. of embryos biopsied: 3.0 (2.0, 4.0) *vs.* 4.0 (3.0, 6.0), 2.0 (1.0,3.0) *vs.* 3.0 (2.0, 5), 3.0 (2.0, 4.0) *vs.* 4.0 (3.0, 6.0), 2.0 (1.0, 3.0) *vs.* 3.0 (2.0, 5.0), all *P*<0.001]. After adjusting for repeated egg retrieval, PGT-A indications, ovarian stimulation protocol and total dosage of gonadotrophin, the embryo aneuploidy rate in group 4 POR patients was significantly higher than controls (*OR*=1.252, 95% *CI*:1.053−1.488, *P*=0.011). However, no differences were identified in embryo aneuploidy rate between POR patients in groups 1, 2, 3 and corresponding controls, respectively (all *P*>0.05). **Conclusion** The ovarian reserve adversely affects the quantity and quality of oocytes in advanced age POR women (≥35 years old). Decreased ovarian reserve in young women (<35 years old) mainly affects the number of oocytes retrieved.

【**Key words**】 Preimplantation genetic testing for aneuploidy; Anti-Müllerian hormone; Aneuploidy; Poor ovarian response; POSEIDON criteria

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多囊卵巢综合征患者外周血 PD-1、PD-L1 表达水平及其与细胞因子相关性研究

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【摘要】 目的 探讨多囊卵巢综合征（polycystic ovary syndrome，PCOS）患者外周血程序性细胞死亡蛋白 1（programmed cell death protein 1，PD-1）和其配体 PD-L1 表达水平与细胞因子相关性。方法 利用 GEO 数据库中 GSE54248 数据集筛选出 PCOS 中差异表达 PD-1/PD-L1 通路相关基因，对其进行 GO 和 KEGG 通路富集分析。采用病例对照研究，选取 2022 年 1 月至 2023 年 6 月期间在新疆医科大学第一附属医院生殖医学中心就诊的 105 例 PCOS 患者（记为 PCOS 组）和 109 例非 PCOS 患者（记为对照组）作为研究对象，利用 QBPlex 流式高通量多因子检测技术检测两组外周血 PD-L1、PD-L2、PD-1 和细胞因子表达水平。采用 Pearson 法进行相关性分析。结果 PCOS 组患者外周血中 PD-1 水平[2.890（0.020，4.540）ng/L]显著低于对照组[3.370（2.460，4.360）ng/L，*P*=0.008]；PD-L1 水平[9.820（8.860，10.880）ng/L]显著低于对照组[10.410（9.700，11.160）ng/L，*P*=0.001]；PD-L2 表达水平在两组间差异无统计学意义（*P*>0.05）。在 GSE54248 数据集筛选出 26 个差异表达基因，主要富集在 PD-1/PD-L1 通路、1 型 T 辅助细胞（T helper cell 1，Th1）和 2 型 T 辅助细胞（T helper cell 2，Th2）分化、参与炎症反应的细胞因子的产生等通路。与对照组相

比较，PCOS 组患者外周血中白细胞介素（interleukin，IL）-5、IL-9、IL-25、IL-10、生长刺激表达基因 2（growth stimulation expressed gene 2，ST-2）和颗粒酶 B（Granzyme B）浓度显著降低，IL-8、IL-1RA 和肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）浓度显著升高，差异均具有统计学意义（均 $P<0.05$）。PD-1 与 IL-1RA、ST-2 和 TNF-α 水平呈正相关（$r=0.270$，$P=0.005$；$r=0.213$，$P=0.029$；$r=0.291$，$P=0.003$），与 IL-9、IL-25 和 Granzyme B 水平呈负相关（$r=-0.322$，$P<0.001$；$r=-0.211$，$P=0.031$；$r=-0.369$，$P<0.001$）。PD-L1 与 IL-9、IL-25 和 Granzyme B 水平呈正相关（$r=0.254$，$P=0.009$；$r=0.330$，$P<0.001$；$r=0.340$，$P<0.001$），与 IL-10 水平呈负相关（$r=-0.373$，$P=0.009$）。结论　PCOS 患者外周血 PD-1 和 PD-L1 下调表达，可能与 Th1/Th2 细胞因子失衡相关，是治疗 PCOS 的潜在分子生物标志物。

【关键词】　多囊卵巢综合征；　程序性细胞死亡蛋白 1；　程序性细胞死亡蛋白配体 1；　细胞因子

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Expression levels of PD-1 and PD-L1 in peripheral blood and their correlation with cytokines in patients with polycystic ovary syndrome

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【 Abstract 】　Objective　To investigate the association between programmed cell death protein 1 (PD-1) and its ligand PD-L1 and cytokines in patients with polycystic ovary syndrome (PCOS). **Methods**　Using the GSE54248 dataset from the GEO database, differentially expressed PD1/PD-L1 pathway-related genes in PCOS were identified and subjected to GO and KEGG pathway enrichment analysis. In this case-control study, totally 105 patients with PCOS (named PCOS group) and 109 non-PCOS patients (named control group) who were treated at the Reproductive Assisted Reproduction Center of the First Affiliated Hospital of Xinjiang Medical University from January 2022 to June 2023 were recruited. The QBPlex flow cytometry high-throughput multiplex assay was utilized to assess the peripheral blood levels of PD-L1, PD-L2, PD-1, and cytokines in PCOS group and control group. Pearson's method was used for correlation analysis. **Results**　In PCOS group, the PD-1 level in peripheral blood [2.890 (0.020, 4.540) ng/L] was significantly lower than that of control group [3.370 (2.460, 4.360) ng/L, $P=0.008$], the PD-L1 level [9.820 (8.860, 10.880) ng/L] was lower than that in control group [10.410 (9.700, 11.160) ng/L, $P=0.001$]. There was no significant difference in the expression level of PD-L2 between the two groups ($P>0.05$). From the GSE54248 dataset, 26 differentially expressed genes were identified, primarily enriched in the PD-1/PD-L1 pathway, Th1 and Th2 cell differentiation, and pathways associated

with the production of cytokines involved in inflammatory responses. Compared with control group, PCOS group exhibited a significant decrease in the peripheral blood concentrations of interleukin (IL)-5, IL-9, IL-25, IL-10, growth stimulation expressed gene 2 (ST-2), and Granzyme B, and a significant increase in IL-8, IL-1RA, and tumor necrosis factor-α (TNF-α) levels, with all differences being statistically significant (all $P<0.05$). PD-1 exhibited positive correlations with the levels of IL-1RA, ST-2, and TNF-α ($r=0.270$, $P=0.005$; $r=0.213$, $P=0.029$; $r=0.291$, $P=0.003$), while it exhibited negative correlations with the levels of IL-9, IL-25, and Granzyme B ($r=-0.322$, $P<0.001$; $r=-0.211$, $P=0.031$; $r=-0.369$, $P<0.001$). PD-L1 demonstrated positive correlations with the levels of IL-9, IL-25, and Granzyme B ($r=0.254$, $P=0.009$; $r=0.330$, $P<0.001$; $r=0.340$, $P<0.001$), and a negative correlation with IL-10 level ($r=-0.373$, $P=0.009$). **Conclusion** The expression of PD-1 and PD-L1 in the peripheral blood of PCOS patients is down-regulated, which may be associated with an imbalance in Th1/Th2 cytokines and serve as potential molecular biomarkers for the treatment of PCOS.

【**Key words**】 Polycystic ovary syndrome; Programmed cell death 1; Programmed cell death ligand 1; Cytokines

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·循证医学·

囊胚活检中透明带开孔时机对临床结局影响的系统评价

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【摘要】 目的 系统比较滋养外胚层活检技术中同步透明带开孔与提前开孔的临床效果，为建立标准囊胚活检程序提供循证医学证据。方法 计算机检索PubMed、Cochrane Library、Embase、Web of Science、中国生物医学文献数据库、中国期刊全文数据库、维普中文科技期刊数据库和万方数据库，检索时限均为建库至2023年8月。检索两种透明带开孔时机应用效果比较的研究文献，主要评价指标为临床妊娠率和活产率，次要评价指标包括活检成功率、整倍体囊胚率和

流产率。采用 R4.2.2 软件 meta 程序包进行 meta 分析。结果　共纳入 6 篇原始研究，包括 12 223 枚活检胚胎，2 374 个移植周期。meta 分析结果显示，同步开孔组的临床妊娠率（*RR*=1.22，95% *CI*：1.14~1.30，*P*<0.01）和活产率（*RR*=1.22，95% *CI*：1.12~1.32，*P*<0.01）均高于提前开孔组。两组间的活检成功率（*RR*=1.38，95% *CI*：0.30~6.25，*P*=0.68）、整倍体囊胚率（*RR*=0.98，95% *CI*：0.83~1.15，*P*=0.81）和流产率（*RR*=1.06，95% *CI*：0.77~1.47，*P*=0.73）差异均无统计学意义。结论　同步透明带开孔囊胚活检方案在临床妊娠率和活产率方面优于提前开孔，受纳入研究样本量及质量的限制，透明带开孔时机对临床效果的影响还需更多高质量的研究。

【关键词】 Meta 分析；　透明带开孔时机；　囊胚活检

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Systematic evaluation of the effect of timing of zona pellucida opening in blastocyst biopsy on clinical outcomes

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【Abstract】 **Objective** To systematically compare the clinical effects of simultaneous zona pellucida opening and prehatching in ectodermal biopsy techniques and to provide evidence-based medical evidence for the establishment of standard blastocyst biopsy procedure. **Methods** We systematically searched PubMed, Cochrane Library, Embase, Web of Science, CBM, CNKI, VIP and Wanfang Data published until August 2023. We searched the literatures for studies that compared the effects of two zona pellucida opening. Primary evaluation measures included clinical pregnancy rate and live birth rate, and secondary evaluation indicators included biopsy success rate, euploid blastocyst rate, and miscarriage rate. Meta-analysis was performed using the R4.2.2 software meta package. **Results** Six studies, including 12 223 biopsy embryos and 2 374 transfer cycles were subjected to analysis. The results of meta-analysis showed that the clinical pregnancy rate (*RR*=1.22, 95% *CI*: 1.14−1.30, *P*<0.01) and the live birth rate (*RR*=1.22, 95% *CI*: 1.12−1.32, *P*<0.01) in the simultaneous zona pellucida opening group were significantly higher than those in the prehatching group, and there were no significant differences between the two groups in biopsy success rate (*RR*=1.38, 95% *CI*: 0.30−6.25, *P*=0.68), euploid blastocyst rate (*RR*=0.98, 95% *CI*: 0.83−1.15, *P*=0.81) and miscarriage rate (*RR*=1.06, 95% *CI*: 0.77−1.47, *P*=0.73). **Conclusion** Stimultaneous zona pellucida opening blastocyst biopsy protocol is better than prehatching in terms of clinical pregnancy rate and live birth rate. Due to the limitation of sample size and quality of included studies, more high-quality studies are needed on the effect of zona pellucida opening timing on clinical outcomes.

【Key words】 Meta-analysis; Timing of zona pellucida opening; Blastocyst biopsy

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·临床报道·

卵泡周围血流参数与 IVF-ET 卵泡发育、胚胎质量和妊娠结局的相关性分析

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【摘要】 目的 分析卵泡周围血流参数与体外受精-胚胎移植（*in vitro* fertilization and embryo transfer，IVF-ET）卵泡发育、胚胎质量和妊娠结局的相关性。方法 回顾性病例对照研究分析 2020 年 10 月至 2022 年 10 月期间驻马店市中心医院生殖医学科收治的 112 例接受 IVF-ET 的不孕患者资料。使用阴道彩色多普勒超声测量卵泡周围血流参数，即动脉收缩期峰值流速/舒张末期血流速度比值（peak systolic velocity/end diastolic velocity，S/D）、阻力指数（resistance index，RI）、搏动指数（pulsatility index，PI）、收缩期最大血流速度（peak systolic velocity，PSV）。共提取 1 156 个卵泡，依照卵泡发育情况划分为优质卵泡组（*n*=208）和非优质卵泡组（*n*=948），依照胚胎质量划分为优质胚胎组（*n*=161）和非优质胚胎组（*n*=995），依照妊娠结局划分为妊娠组（*n*=37）和未妊娠组（*n*=75），比较不同组间的 S/D、RI、PI、PSV。对比不同卵泡周围血流 PSV 峰速间相关指标，以 Pearson 法分析非优质卵泡组、非优质胚胎组、未妊娠组中 PSV 与卵泡发育、胚胎质量、妊娠结局的相关性。结果 优质卵泡组 PSV［（11.26±0.94）cm/s］明显较非优质卵泡组高［（10.31±0.78）cm/s，*P*<0.001］，两组间 S/D、RI、PI 差异均无统计学意义（均 *P*>0.05）。优质胚胎组 PSV

［（13.38±1.19）cm/s］明显较非优质胚胎组高［（12.02±0.85）cm/s，*P*<0.001］，优质胚胎组、非优质胚胎组间 S/D、RI、PI 比较，差异均无统计学意义（均 *P*>0.05）。妊娠组 PSV［（15.14±1.25） cm/s］明显较未妊娠组［（8.27±0.75） cm/s，*P*<0.001］高，妊娠组、未妊娠组间 S/D、RI、PI 比较，差异均无统计学意义（均 *P*>0.05）。不同卵泡周围血流 PSV 峰速间年龄、不孕年限、体质量指数、基础卵泡刺激素水平、促性腺激素（gonadotropin，Gn）用量、Gn 使用时间对比差异均无统计学意义（均 *P*>0.05），而优质卵泡数、优质胚胎数、血 β-人绒毛膜促性腺激素（β-human chorionic gonadotropin，β-hCG）水平组间比较差异有统计学意义［PSV<9 cm/s：（1.05±0.23）个、（0.73±0.14）个、（3.05±0.61） U/L；PSV 9~10 cm/s：（1.35±0.35）个、（0.85±0.16）个、（22.14±5.78） U/L；PSV>10 cm/s： （2.01±0.41）个、（1.12±0.20）个、（71.33±8.63） U/L；均 *P*<0.001］；采用 Pearson 进行相关性分析，结果显示非优质卵泡组、非优质胚胎组、未妊娠组中 PSV 与卵泡直径、胚胎质量评分、血 β-hCG 水平呈正相关（*r*=0.767，*P*<0.001；*r*=0.750，*P*<0.001；*r*=0.700，*P*<0.001）。结论 卵泡周围血流参数 PSV 与 IVF-ET 卵泡发育、胚胎质量、妊娠结局具有相关性，可为临床评定卵泡发育、胚胎质量、妊娠结局提供重要参考。

【关键词】 受精，体外； 胚胎移植； 卵泡发育； 胚胎质量； 妊娠结局； 收缩期最大血流速度

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Correlation analysis of perifollicular blood flow parameters with IVF-ET follicular development, embryo quality and pregnancy outcome

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【Abstract】 Objective To analyze the correlation of perifollicular blood flow parameters with follicle development, embryo quality and pregnancy outcome in *in vitro* fertilization and embryo transfer (IVF-ET). **Methods** A retrospective case-control study was conducted to analyze the data of 112 infertile patients who underwent IVF-ET admitted to the Department of Reproductive Medicine of Zhumadian Central Hospital from October 2020 to October 2022. Perifollicular blood flow parameters [peak systolic velocity/end diastolic velocity (S/D), resistance index (RI), pulsatility index (PI) and peak systolic velocity (PSV)] were measured by vaginal color doppler ultrasound. A total of 1 156 follicles were extracted, they were divided into high-quality follicle group (*n*=208), and non-high-quality follicle group (*n*=948) according to follicle development, high-quality embryo group (*n*=161) and non-high-quality embryo group (*n*=995) according to embryo quality, pregnant group (*n*=37) and non-pregnant group (*n*=75) according to pregnancy outcome. The S/D, RI, PI and PSV of the groups were compared. The correlation indexes of PSV

peak velocity among different perifollicular blood flow were compared, and the correlation between PSV and follicle development and embryo quality in non-high-quality follicle group, non-high-quality embryo group and non-pregnant group was analyzed by Pearson method. **Results** PSV in high-quality follicle group [(11.26±0.94) cm/s] was significantly higher than that in non-high-quality follicle group [(10.31±0.78) cm/s, *P*<0.001], but there were no significant differences in S/D, RI and PI between high-quality follicle group and non-high-quality follicle group (all *P*>0.05). PSV was significantly higher in the high-quality embryo group [(13.38±1.19) cm/s] than in the non-high-quality embryo group [(12.02±0.85) cm/s, *P*<0.001], but there were no significant differences in S/D, RI and PI between high-quality embryo group and non-high-quality embryo group (all *P*>0.05). PSV of pregnant group [(15.14±1.25) cm/s] was significantly higher than that of non-pregnant group [(8.27±0.75) cm/s, *P*<0.001], and there were no significant differences in S/D, RI and PI between pregnant group and non-pregnant group (all *P*>0.05). There were no statistically significant differences in age, infertility duration, body mass index, basal follicle-stimulating hormone level, total dosage and duration of gonadotropin used among different perifollicular blood flow PSV peak velocity (all *P*>0.05), but there were statistically significant differences in the number of high-quality follicles, the number of high-quality embryos and the level of β-human chorionic gonadotropin (β-hCG) [<9 cm/s: 1.05±0.23, 0.73±0.14, (3.05±0.61) U/L;9−10 cm/s: 1.35±0.35, 0.85±0.16, (22.14±5.78) U/L; >10 cm/s: 2.01±0.41, 1.12±0.20, (71.33±8.63) U/L; all *P*<0.001]. Pearson correlation analysis showed that PSV was positively correlated with follicle diameter, embryo quality score and blood β-hCG level (*r*=0.767, *P*<0.001; *r*=0.750, *P*<0.001; *r*=0.700, *P*<0.001) in non-high-quality follicle group, non-high-quality embryo group,non-pregnant group. **Conclusion** Perifollicular blood flow parameter PSV is correlated with IVF-ET follicle development, embryo quality and pregnancy outcome, which can provide an important reference for clinical evaluation of follicle development, embryo quality and pregnancy outcome.

【Key words】 Fertilization *in vitro*; Embryo transfer; Follicle development; Embryo quality; Pregnancy outcome; Peak systolic velocity

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·临床报道·

宫腔粘连分离术对冻融胚胎移植后产科结局的影响因素分析

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【摘要】 目的　分析宫腔粘连分离术（transcervical resection of adhesion，TCRA）对冻融胚胎移植（frozen-thawed embryo transfer， FET）后患者产科并发症的影响及其相关因素。方法　采用回顾性队列研究，收集 2015 年 4 月至 2022 年 5 月期间在南京医科大学附属妇产医院生殖医学中心行自体卵母细胞 FET 治疗并至少活产 1 名新生儿患者的临床资料。根据宫腔情况分为 3 组，对照组：正常宫腔形态（712 例）；宫腔粘连（intrauterine adhesion，IUA）组：IUA 患者未行 TCRA 治疗（45 例）；TCRA 组：IUA 患者行 TCRA 治疗（51 例）。通过倾向性评分匹配（propensity score matching， PSM）探讨 3 组患者宫腔情况与产科并发症的关系，并通过多因素 logistic 回归方法分析与 TCRA 相关的产科并发症的危险因素，采用校准曲线、受试者工作特征（receiver operating characteristic， ROC）曲线对构建的多因素 logistic 回归模型的效能进行评估。结果　①在 PSM 前，3 组间子宫内膜厚度、有无瘢痕子宫、妊娠次数、分娩次数、流产次数、人工流产次数和移植胚胎数的差异均有统计学意义（均 *P*<0.05）；在 PSM 后，基线特征在各组间达到平衡，TCRA 组和 IUA 组的胎盘植入性疾病（placenta accreta spectrum disorders， PAS）发生率［48.8%（20/41）；45.2%（19/42）］显著高于相应的对照组［24.7%（18/73），*P*=0.016；22.8%（18/79），*P*=0.019］。②多因素 logistic 回归分析显示子宫内膜厚度（*OR*=0.79，95% *CI*：0.69~0.90，*P*<0.001）、妊娠次数（2 次，*OR*=2.25，95% *CI*：1.33~3.82，*P*=0.003）、子宫内膜准备方案（促性腺激素释放激素激动降调节联合激素替代疗法，*OR*=2.29，95% *CI*：1.16~4.52，*P*=0.017）、瘢痕子宫（*OR*=2.19，95% *CI*：1.39~3.45，*P*<0.001）和宫腔情况（IUA 和 TCRA，*OR*=2.11，95% *CI*：1.07~4.17，*P*=0.031；*OR*=2.70，95% *CI*：1.37~5.31，*P*=0.004）是 PAS 发生的独立预测因子。③预测 PAS 发生的多因素 logistic 回归模型的 ROC 曲线下面积为 0.732（95% *CI*：0.686~0.778），并且校准曲线的结果经过内部验证表明预测风险和实际结果之间具有良好一致性（*P*=0.540），表现出良好的区分度和校准度。结论　TCRA 术后患者的前置胎盘、产后出血、胎膜早破等产科并发症的发病率与正常宫腔形态患者相同。然而，TCRA 显著增加了采用 FET 助孕治疗的 IUA 患者发生 PAS 的风险。

【关键词】 宫腔粘连；　宫腔粘连分离术；　冻融胚胎移植；　产科并发症；胎盘植入

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Analysis of influencing factors of intrauterine adhesion separation on obstetric outcomes after frozen-thawed embryo transfer

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【Abstract】 **Objective** To analyze the impact of transcervical resection of adhesion (TCRA) on obstetric complications in patients after frozen-thawed embryo transfer (FET) and its associated factors. **Methods** A retrospective cohort study was conducted by collecting clinical data from patients who underwent autologous oocyte FET treatment and gave birth to at least one live newborn at the Reproductive Medicine Center of Nanjing Women and Children's Healthcare Hospital from April 2015 to May 2022. Based on the uterine condition, patients were divided into three groups: control group with normal uterine morphology (712 cases); the intrauterine adhesion (IUA) group consisting of IUA patients who did not undergo TCRA surgery (45 cases); the TCRA group, which included IUA patients who received TCRA treatment (51 cases). The relationship between uterine conditions and obstetric complications among the three groups was investigated using propensity score matching (PSM). Multivariate logistic regression analysis was applied to identify risk factors associated with obstetric complications related to TCRA. The performance of the constructed multivariate logistic regression model was evaluated using calibration curves and receiver operating characteristic (ROC) curves. **Results** 1) Before PSM, statistically significant differences were observed among the three groups regarding endometrial thickness, the presence of a scarred uterus, numbers of pregnancies, deliveries, miscarriages, induced abortions, and transferred embryos (all $P<0.05$). After PSM, baseline characteristics were balanced across the groups. The rates of placenta accreta spectrum disorders (PAS) in the TCRA group [48.8% (20/41)] and the IUA group [45.2% (19/42)] were significantly higher than those in control group [24.7% (18/73), $P=0.016$; 22.8% (18/79), $P=0.019$]. 2) Multivariable logistic regression analysis revealed that endometrial thickness (*OR*=0.79, 95% *CI*: 0.69–0.90, $P<0.001$], number of pregnancies (2 times, *OR*=2.25, 95% *CI*: 1.33–3.82, $P=0.003$), endometrial preparation protocol (gonadotropin-releasing hormone agonist plus hormone replacement therapy, *OR*=2.29, 95% *CI*: 1.16–4.52, $P=0.017$), the presence of a scarred uterus (*OR*=2.19, 95% *CI*: 1.39–3.45, $P<0.001$), and uterine cavity conditions (IUA and TCRA, *OR*=2.11, 95% *CI*: 1.07–4.17, $P=0.031$; *OR*=2.70, 95% *CI*: 1.37–5.31, $P=0.004$) were independent predictors of PAS occurrence. 3) The area under the ROC curve for this model was 0.732 (95% *CI*: 0.686–0.778). Calibration curve results, after internal validation, showed good consistency between predicted risks and actual outcomes, demonstrating good discriminative ability and calibration ($P=0.540$). **Conclusion** The incidence of obstetric complications such as placenta previa, postpartum hemorrhage, and premature rupture of membranes in patients who underwent TCRA surgery was comparable to that of patients with a normal uterine morphology. However, TCRA significantly increased the risk of PAS in patients with IUA undergoing FET assisted reproductive treatment.

【Key words】 Intrauterine adhesion; Transcervical resection of adhesion; Frozen-thawed embryo transfer; Obstetric complications; Placenta accreta

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·临床报道·

胚胎移植患者饮水量对膀胱充盈时间影响的生存分析研究：一项随机对照试验

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【摘要】 目的 探讨饮水量对胚胎移植患者术前膀胱充盈时间的影响。方法 收集 2023 年 2 月至 6 月期间于广东省妇幼保健院生殖健康与不孕症科拟行体外受精-胚胎移植的患者 189 例。运用随机数字表将患者随机分为 A、B、C 3 组，各组样本量依次为 61 例、64 例和 64 例，分别给予术前饮水 300 mL、500 mL 和 700 mL。于饮水后 45 min 开始，每 15 min 进行腹部超声监测，共 1~5 次，记录膀胱充盈时间和膀胱容量。采用 Kaplan-Meier 法比较 3 组患者膀胱充盈时间的差异，并采用多因素 Cox 回归分析膀胱充盈时间的影响因素。结果 A、B、C 组患者饮水后 105 min 累积膀胱充盈率分别为 57.4%（35/61）、90.6%（58/64）和 98.4%（63/64），膀胱充盈中位生存时间（95% *CI*）为 105.0（89.9~120.1）min、60.0（55.4~64.7） min 和 60.0（55.4~64.6） min。Kaplan-Meier 成对比较结果显示，A 组膀胱充盈时间长于 B 组和 C 组（均 *P*<0.001），B 组膀胱充盈中位生存时间与 C 组之间差异无统计学意义（*P*>0.05）。按年龄分层分析结果显示，低龄层（<35 岁）患者膀胱充盈中位生存时间 A 组［90.0（75.2~104.8）min］长于 B 组［60.0（55.8~64.2） min，*P*<0.001］和 C 组［60.0（55.1~64.8）min，*P*<0.001］，B 组与 C 组之间差异无统计学意义（*P*>0.05）；高龄层（≥35 岁）患者膀胱充盈中位生存时间 A 组与 B 组之间差异无统计学意义（*P*>0.05），C 组［60.0（59.1~70.9） min］短于 A 组（105.0 min，*P*<0.001）和 B 组［75.0（64.3~85.7） min，*P*=0.027］。多因素 Cox 回归分析结果显示，以 A 组为参考类别，B、C 组的风险比（hazard ratio，*HR*）分别为 2.71、3.23，95% *CI* 分

别为1.78~4.21、2.10~4.96，均 *P*<0.001；高龄 *HR*为0.69，95% *CI*为0.49~0.99，*P*=0.044。结论　饮水量和年龄为胚胎移植患者膀胱充盈时间的独立影响因素。胚胎移植患者宜术前75 min饮水500 mL，并对高龄患者适当增加饮水量或延长饮水后膀胱准备时间。

【关键词】　胚胎移植；　生殖技术，辅助；　超声；　饮水量；　膀胱

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Survival analysis of the effect of water intake on bladder filling time in embryo transfer patients: a randomized control trial

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【Abstract】　Objective　To investigate the effect of water intake on bladder filling time before embryo transfer. **Methods**　A total of 189 patients were collected from February to June 2023 who were to undergo embryo transfer in Guangdong Women and Children Hospital. The patients were divided into group A (*n*=61), group B (*n*=64) and group C (*n*=64) using a random number table and they were respectively given 300 mL, 500 mL and 700 mL water to drink. Abdominal ultrasound was performed every 15 min, a total of 1–5 times, from 45 min after drinking water until the bladder filling. The bladder filling time and bladder volume were collected. Kaplan-Meier method was used to compare the difference of bladder filling time among the three groups. The multivariate Cox regression was used to analyze factors of bladder filling time. **Results**　The cumulative bladder filling rates of group A, group B and group C at 105 min after drinking water were 57.4% (35/61), 90.6% (58/64) and 98.4% (63/64), respectively, and the median survival time (95% *CI*) of bladder filling was 105.0 (89.9–120.1) min, 60.0 (55.4–64.7) min and 60.0 (55.4–64.6) min, respectively. Pairwise comparison of Kaplan-Meier analysis revealed that the bladder filling time of group A was longer than that of group B and group C (*P*<0.001), and there was no statistically significant difference between group B and group C (*P*>0.05). The results of age-stratification analysis showed that the bladder filling time of younger patients in group A [90.0 (75.2–104.8) min] was longer than that in group B [60.0 (55.8–64.2) min, *P*<0.001] and group C [60.0 (55.1–64.8) min, *P*<0.001], and there was no statistical significance between group B and group C (*P*>0.05); the bladder filling time of older patients in group C [60.0 (59.1–70.9) min] was shorter than that in group A [105.0 (89.9–120.1) min, *P*<0.001] and group B [75.0 (64.3–85.7) min, *P*=0.027], there was no statistical significance between group A and group B (*P*>0.05). Multivariate Cox regression analysis showed that taking group A as reference, the hazard ratio (*HR*, 95% *CI*) of groups B and C were 2.71 (1.78–4.21) and 3.23 (2.10–4.96), both *P*<0.001. The *HR* (95% *CI*) of the elderly patients was 0.69 (0.49–0.99), *P*=0.044. **Conclusion**　Water intake and age

are independent factors affecting bladder filling time in embryo transfer patients. Patients are recommended to drink 500 mL of water 75 min before embryo transfer and appropriately increase the amount of water or extend the bladder preparation time after drinking water for elderly patients.

【 **Key words** 】 Embryo transfer; Reproductive techniques, assisted; Ultrasonography; Drinking; Bladder

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·临床报道·

辅助生育夫妇的男性年龄与精液质量的关联：一项横断面研究

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【摘要】 目的 探讨辅助生育夫妇的男性年龄与精液质量及精子 DNA 碎片化指数（DNA fragmentation index，DFI）的关联性。方法 采用横断面研究，收集 2020 年 1 月至 2023 年 8 月期间在武汉大学人民医院生殖医学中心因非男性因素行辅助生殖技术助孕治疗的 3 361 例男性的临床资料。使用计算机辅助精液分析系统分析精液质量参数，使用精子核染色体结构检测分析 DFI。将受试者按年龄分为 20~29 岁（A 组）、30~39 岁（B 组）和 40~59 岁（C 组）3 组。采用多元线性回归和限制性立方样条（restricted cubic spline， RCS）法分析年龄与精液质量参数及 DFI 之间的关联。结果 共纳入研究对象共 3 361 例，年龄为（34.86±5.34）岁。B 组和 C 组的精子前向运动率［（40.17±18.16）%、（37.83±16.96）%］及精子总活动率［（55.27±21.37）%、（53.09±21.14）%］显著低于 A 组[（43.78±18.16）%、（58.29±20.24）%]；精子浓度[（78.96±63.04）×10^6/mL、（91.93±72.28）×10^6/mL]及 DFI[（19.18±12.18）%、（21.73±12.52）%]显著高于 A 组［（71.75±57.44）×10^6/mL，（16.31±10.04）%］，差异均有统计学意义（均 P<0.001）。C 组的精液量［（2.94±1.42） mL］ 显著低于 A 组［（3.28±1.43） mL］和 B 组［（3.15±1.58） mL］，差异均有统计学意义（均

P<0.05）。在调整了文化程度、体质量指数、吸烟、饮酒、禁欲天数后，多元线性回归结果显示：与 A 组相比，B 组年龄与精子前向运动率（β=−3.055，95% CI：−4.879~−1.231）、精子总活动率（β=−2.366，95% CI：−4.516~−0.216）呈负相关，与精子浓度（β=7.752，95% CI：1.398~4.106）、DFI 呈正相关（β=2.744，95% CI：1.526~3.961）。与 A 组相比，C 组年龄与精液量（β=−0.379，95% CI：−0.565~−0.192）、精子前向运动率（β=−5.507，95% CI：−7.714~−3.301）、精子总活动率（β=−4.932 ，95% CI：−7.532~−2.331）呈负相关，与精子浓度（β=17.288，95% CI：9.604~24.973）、DFI（β=5.226，95% CI：3.753~6.699）呈正相关。RCS 分析结果显示，年龄与精液量存在显著线性剂量-反应关系（$P_{非线性检验}$=0.424），精液量随年龄增长而下降（P<0.001）；年龄与精子浓度、精子前向运动率、精子总活动率及 DFI 呈非线性剂量-反应关系（$P_{非线性检验}$=0.003、$P_{非线性检验}$<0.001、$P_{非线性检验}$<0.001、$P_{非线性检验}$=0.004）。结论　非男性因素行辅助生殖助孕术的男性中，年龄超过 30 岁与精液量、精子前向运动率及精子总活动率下降，与精子浓度及 DFI 上升显著相关。

【关键词】　年龄因素；　精液分析；　不育症；　限制性立方样条

Association between male age and semen quality in assisted reproductive technology cycles: a cross-sectional study

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【**Abstract**】　**Objective**　To investigate the correlation between the age of men and the quality of semen, as well as the DNA fragmentation index (DFI) in assisted reproduction couples. **Methods**　A cross-sectional study was conducted, collecting clinical data from 3 361 men who underwent assisted reproductive technology for fertility treatment at the Reproductive Medicine Center of Wuhan University People's Hospital from January 2020 to August 2023 due to non-male factors. Computer-assisted semen analysis system (CASA) was used to analyze semen quality parameters, and DFI was measured by Sperm Chromatin Structure Assay (SCSA). Patients were categorized into three groups based on age: 20−29 years (group A), 30−39 years (group B), and 40−59 years (group C). Multiple linear regression and restricted cubic spline (RCS) were used to analyze the correlation between age and semen quality parameters as well as DFI. **Results**　The study included 3 361 participants with an average age of (34.86±5.34) years. In groups B and C, sperm progressive motility [(40.17±18.16)%, (37.83±16.96)%] and total motility [(55.27±21.37)%, (53.09±21.14)%] were significantly lower than those in group A [(43.78±18.16)%, (58.29±20.24)%], sperm concentration [(78.96±63.04)×10^6/mL, (91.93±72.28)×10^6/mL] and DFI [(19.18±12.18)%, (21.73±12.52)%] were significantly higher than those in group A [(71.75±57.44)×10^6/mL, (16.31±10.04)%], semen volume was significantly lower in group C [(2.94±1.42) mL] than in groups B and A [(3.28±1.43) mL, (3.15±1.58) mL], with statistically significant differences (all P<0.05). After adjusting for education

level, body mass index, smoking, alcohol consumption, and abstinence days, the results of multiple linear regression showed that compared with group A, the age of group B was negatively associated with sperm progressive motility (β=−3.055, 95% *CI*: −4.879−−1.231) and total motility (β=−2.366, 95% *CI*:−4.516−−0.216), while positively associated with sperm concentration (β=7.752, 95% *CI*: 1.398−4.106) and DFI (β=2.744, 95% *CI*: 1.526−3.961). Compared with group A, the age of group C was negatively correlated with semen volume (β=−0.379, 95% *CI*: −0.565−−0.192), sperm progressive motility (β=−5.507, 95% *CI*: −7.714−−3.301), and total motility (β=−4.932, 95% *CI*: −7.532−−2.331), while positively correlated with sperm concentration (β=17.288, 95% *CI*: 9.604−24.973) and DFI (β=5.226, 95% *CI*: 3.753−6.699). The results of RCS analysis indicated a significant linear dose-response relationship between age and semen volume ($P_{\text{non-linearity}}$=0.424), showing a decline in semen volume with increasing age (P<0.001). Non-linear dose-response relationships were observed between age and sperm density ($P_{\text{non-linearity}}$=0.003), sperm progressive motility ($P_{\text{non-linearity}}$<0.001), total motility ($P_{\text{non-linearity}}$<0.001), and DFI ($P_{\text{non-linearity}}$=0.004). **Conclusion** In men undergoing assisted reproductive technology for fertility treatment due to non-male factors, age greater than 30 years is significantly associated with a decrease in semen volume, sperm progressive motility, and total motility, as well as an increase in sperm density and DFI.

【**Key words**】 Age factors; Semen analysis; Male infertility; Restricted cubic spline

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·临床报道·

屈螺酮炔雌醇在早发性卵巢功能不全患者诱导卵泡发育作用的研究

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【摘要】 目的 探讨屈螺酮炔雌醇在早发性卵巢功能不全（premature ovarian insufficiency， POI）患者诱导卵泡恢复生长发育的作用。方法 随机对照临床研究分析中国人民解放军总医院第七医学中心妇产医学部生殖医学科和第六医学中心妇产科 2021 年 12 月至 2022 年 11 月期间 130 例进行辅助生殖助孕治疗的 POI 患者的临床资料。受试者中心随机分组法进行分配隐藏，无盲法。试验组给予屈螺酮炔雌醇预处理，对照组不做处理。比较两组主要观察指标卵泡恢复生长率，次要观察指标预处理前后雌二醇、卵泡刺激素水平、获卵数、获卵人数占比等胚胎实验室相关指标。结果 试验组卵泡恢复生长率［50.77%（33/65）］明显高于对照组［15.38%（10/65）］，差异有统计学意义（*P*<0.001，率差=35.38%，95% *CI*：19.44%~48.98%）。试验组预处理后卵泡刺激素水平［17.70（8.15，27.00） U/L］较预处理前明显下降［30.30（25.95， 48.05） U/L，*P*<0.001］，雌二醇水平［24.00（15.00， 90.47） ng/L］较预处理前［15.00（15.00， 24.00） ng/L，*P*<0.001］明显升高，差异均具有统计学意义。结论 屈螺酮炔雌醇可有效抑制 POI 患者升高的卵泡刺激素水平，提高雌二醇水平，增加诱导排卵治疗中卵巢恢复卵泡生长发育的概率。

【关键词】 早发性卵巢功能不全； 口服避孕药； 药物诱导； 卵泡发育

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Study on the effects of drospirenone and ethinylestradiol in inducing follicular development in patients with premature ovarian insufficiency

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【Abstract】 **Objective** To investigate the effect of drospirenone and ethinylestradiol in the treatment of ovulation induction in patients with premature ovarian insufficiency (POI). **Methods** A randomized controlled clinical study analyzed the clinical data of 130 POI patients who underwent assisted reproductive

treatment at the Department of Reproductive Medicine, Department of Obstetrics and Gynecology, the Seventh Medical Center and Department of Obstetrics and Gynecology, the Sixth Medical Center of Chinese people's Liberation Army General Hospital from December 2021 to November 2022. The subject-centered randomization method was used to conceal the allocation, and there was no blinding. The patients in experimental group was given drospirenone and ethinylestradiol as pretreatment, while control group was not treated. The main observation indicator of the follicle recovery growth rate and the secondary observation indicators of estradiol and follicle-stimulating hormone (FSH) levels before and after pretreatment, the number of eggs retrieved, the proportion of eggs retrieved, and other embryo laboratory-related indicators were compared between the two groups. **Results** The recovery rate of follicular growth in the experimental group was significantly higher than that in control group, and the difference was statistically significant [50.77% (33/65) *vs.* 15.38% (10/65), $P<0.001$, rate difference =35.38%, 95% *CI*: 19.44%–48.98%]. The levels of FSH [17.70 (8.15, 27.00) U/L] decreased significantly and estradiol [24.00 (15.00, 90.47) ng/L] increased significantly in the experimental group after preconditioning with spironolone ethinylestradiol compared with those before preconditioning [30.30 (25.95, 48.05) U/L, $P<0.001$; 15.00 (15.00, 24.00) ng/L, $P<0.001$], the differences were statistically significant. **Conclusion** The spironolone ethinylestradiol can effectively inhibit the level of FSH and increase the level of estradiol in patients with POI, and increase the probability of ovarian growth and development during ovulation induction therapy.

【Key words】 Primary ovarian insufficiency; Oral contraceptive; Drug induction; Follicular development

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·综述·

子宫内膜异位症患者冻融胚胎移植内膜准备方案的研究进展

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【摘要】 子宫内膜异位症（endometriosis， EMS）是育龄女性的常见疾病，也是人类辅助生殖技术的常用指征之一。随着玻璃化冷冻技术的发展，冻融胚胎移植（frozen-thawed embryo transfer， FET）成为体外受精技术的重要组成部分。影响 FET 成功的因素包括胚胎质量、子宫内膜容受性及胚胎与内膜的同步性。其中内膜准备是胚胎着床和活产的关键步骤。EMS 被认为是影响子宫内膜容受性的重要病因。目前针对 EMS 患者 FET 内膜准备方案研究较少并存在争议。本文通过分析现有文献，对 EMS 患者 FET 内膜准备方案的妊娠结局、母婴并发症进行综述，为临床决策提供参考。

【关键词】 子宫内膜异位症； 妊娠结局； 冻融胚胎移植； 子宫内膜准备

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Research progress on endometrial preparation for frozen-thawed embryo transfer cycles in patients with endometriosis

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【Abstract】 Endometriosis (EMS) is a common disease afflicting females of reproductive age and a common indication of human assisted reproductive technology. With the development of technology of vitrification, frozen-thawed embryo transfer (FET) has become an essential component of *in vitro* fertilization. The factors that affect the success of FET include embryo quality, endometrial receptivity, and synchronization between embry and endometrium. The preparation of the endometrium is a key step in embryo implantation and live birth. EMS is considered as an important cause affecting endometrial receptivity. At present, there are few studies and controversies on the FET endometrial preparation plan for EMS patients. This article reviews the pregnancy outcomes and maternal infant complications of FET endometrial preparation in EMS patients by analyzing existing literature, providing reference for clinical decision-making.

【Key words】 Endometriosis; Pregnancy outcome; Frozen-thawed embryo transfer; Endometrial preparation

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·综述·

辅助生殖技术中年轻低预后患者不良妊娠结局的非预期因素分析

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【摘要】 卵巢低反应会引起不良妊娠结局，是目前生殖领域亟须解决的难题之一。造成卵巢低反应患者不良妊娠结局的因素较多，除可预知因素如年龄、子宫因素及医源性因素外，我们也应重视那些非预期的因素如促排卵不当、基因缺陷、环境因素、不良生活习惯、体质量指数等，为提高年轻低预后患者的活产率提供临床指导。本文将从卵巢刺激方案、基因缺陷、体质量指数以及其他非预期影响因素进行阐述。

【关键词】 生殖技术，辅助； 卵巢低反应； 年轻女性； 波塞冬标准；低预后

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Unexpected factors of adverse pregnancy outcomes in young patients with low prognosis in assisted reproductive technology

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【Abstract】 Poor ovarian response is one of the urgent problems in the reproductive field, which may lead to poor pregnancy outcomes. There are many factors that may lead to poor pregnancy outcomes in patients with poor ovarian response. In addition to predictable factors such as age, uterine factors and iatrogenic factors, we should also pay attention to those unexpected factors such as improper ovulation promotion, genetic defects, environmental factors, bad living habits, body mass index, etc, and provide clinical guidance for improving the live birth rate of young patients with low prognosis. This article will elaborate on several aspects including ovarian stimulation regimen, genetic defects, body mass index, and other unexpected influencing factors.

【Key words】 Reproductive techniques, assisted; Poor ovarian response; Young women; POSEIDON criteria; Low prognosis

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·综述·

子宫腺肌病转录组学研究进展

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【摘要】 子宫腺肌病是一种常见的妇科疾病，临床表现主要为盆腔疼痛、异常子宫出血和生殖障碍，目前尚无统一的评估标准及治疗方案，因此了解子宫腺肌病相关的分子机制至关重要。转录组学从整体水平解释了基因组的功能元件，揭示了特定生物学过程中的分子机制。近年来，随着转录组学研究技术飞速发展，已有多项研究基于转录组学探讨了子宫腺肌病病理生理机制，识别了子宫腺肌病的生物标志物和潜在治疗靶点，为子宫腺肌病的诊断及治疗提供了新视角。本文就转录组测序技术在子宫腺肌病中的应用研究进展进行综述。

【关键词】 子宫腺肌病； 转录组学； 微阵列； RNA 测序； 单细胞 RNA 测序； 子宫内膜容受性阵列

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Research progress of transcriptomic study in adenomyosis

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【Abstract】 Adenomyosis is a common gynecological disease with the main clinical manifestations of pelvic pain, abnormal uterine bleeding and reproductive disorders. At present, there is no unified evaluation criteria and treatment plan for adenomyosis, so it is important to understand the molecular mechanism of adenomyosis. Transcriptomics explains the functional elements of the genome at a global level and reveals the molecular mechanisms in specific biological processes.

In recent years, with the rapid development of transcriptomics analysis technology, a number of studies have explored the molecular mechanism of adenomyosis based on transcriptomics, identified biomarkers and potential therapeutic targets of adenomyosis, and provided a new perspective for the diagnosis and treatment of adenomyosis. This review focuses on the latest research advances in transcriptome analysis in adenomyosis.

【Key words】 Adenomyosis; Transcriptome analysis; Microarray; RNA sequencing; Single-cell RNA sequencing; Endometrial receptivity array

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·综述·

葡萄糖转运蛋白对子宫内膜蜕膜化影响的研究进展

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【摘要】 葡萄糖转运蛋白（glucose transporters，GLUTs）在子宫内膜中广泛表达，介导葡萄糖摄取，调控子宫内膜基质细胞的能量代谢及蜕膜免疫代谢等过程，并与蜕膜化过程中重要的信号通路相互作用，影响胚胎植入。本文将对蜕膜化过程中 GLUTs 的表达及其作用机制作一综述，以期为不孕症及妊娠相关疾病的防治提供理论依据。

【关键词】 葡萄糖转运蛋白； 子宫内膜基质细胞； 蜕膜化； 胚胎植入
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Research progress on the role of glucose transporters in regulating decidualization

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【Abstract】 Glucose transporters (GLUTs) are widely expressed in the endometrium, mediate glucose uptake, and regulate energy metabolism of endometrial stromal cells, as well as decidual immune metabolism and other related processes. GLUTs also interact with important signaling pathways during decidualization, affecting embryo implantation. In this paper, the aspects of GLUTs expression and mechanism during decidualization are reviewed in order to provide a theoretical basis for the prevention and treatment of infertility and pregnancy-related diseases.

【Key words】 Glucose transporter; Endometrial stromal cells; Decidualization; Embryo implantation

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·综述·

PCOS 患者妊娠期过量睾酮影响男性子代生殖发育的机制研究进展

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【摘要】 多囊卵巢综合征患者典型特征之一是体内高雄激素分泌。其妊娠期母体过量睾酮水平不仅影响女性后代生殖健康，也影响男性后代生殖健康。本文主要针对 PCOS 患者妊娠期母源性睾酮暴露影响男性胎儿生殖发育及精子发生的机制进行综述，为妊娠期高雄激素影响男性后代生殖健康的机制研究与临床干预提供参考。

【关键词】 睾酮； 精子发生； 多囊卵巢综合征； cAMP 反应元件结合蛋白

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Excessive prenatal testosterone of patients with polycystic ovarian syndrome affects the reproductive system of male offspring: a review

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【Abstract】 High androgen levels are one of the typical features of patients with polycystic ovarian syndrome. Excessive prenatal testosterone not only affects the reproductive health of female offspring, but also affects male reproductive health. This article reviews the mechanisms of excessive prenatal testosterone affecting reproductive development and spermatogenesis on male offspring. This article aims to provide reference for the mechanism research and clinical intervention of excessive prenatal testosterone affecting reproductive health of male offspring.

【Key words】 Testosterone; Spermatogenesis; Polycystic ovarian syndrome; cAMP response element binding protein

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·综述·

人类精子代谢和表观遗传调控通过影响精子活力导致男性不育的研究进展

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【摘要】 精子作为男性体内高度分化的单倍体生殖细胞，是生命遗传信息传递的重要载体，其结构完整是正常受精的条件，也是正常代谢产生能量和完成表观遗传的基础。精子代谢被认为是精子运动的“供能站”，保证精子发生、成熟、过活化和精卵结合等生命活动正常进行，代谢异常会直接影响精子活力造成男性不育。而精子表观遗传是一种通过父系遗传来影响后代胚胎发育和繁殖的过程，包括 DNA 甲基化、染色质重塑和精子携带的小 RNA 等多种调控方式，它们可在一定程度上影响能量产生，进而导致精子活力和男性生育力下降。因此，精子代谢和表观遗传在维持精子活力方面有着不可分割的联系，本文就人类精子结构、代谢和表观遗传调控方面进行综述，以期为与它们相关的精子活力异常导致的男性不育症相关研究提供理论参考。

【关键词】 氧化磷酸化； 活性氧； 组蛋白； DNA 甲基化； 精子代谢

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Advances in the study of human sperm metabolism and epigenetic regulation causing male infertility by influencing sperm motility

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【Abstract】 As a highly differentiated haploid germ cell in male body, sperm is an important carrier of life genetic information transmission, and its structural integrity is the condition of normal insemination, and also the basis of normal metabolism to produce energy and complete epigenetic inheritance. Sperm metabolism is considered to be the "energy supply station" of sperm movement, which ensures the normal life activities such as spermatogenesis, maturation, over-activation and sperm-egg union. Abnormal metabolism will directly affect the sperm vitality and cause male infertility. Sperm epigenetic inheritance is a process that affects the embryonic development and reproduction of offspring through paternal inheritance, including DNA methylation, chromatin remodeling and small RNA carried by sperm and other regulatory modes, which can also affect energy production to a certain extent, thereby leading to the decline of sperm motility and male fertility. Therefore, sperm metabolism and epigenetics are inextricably related to the maintenance of sperm motility. In this paper, the structure, metabolism and

epigenetic regulation of human sperm are reviewed in order to provide theoretical reference for the research on male infertility caused by abnormal sperm motility.

【Key words】 Oxidative phosphorylation; Reactive oxygen species; Histone; DNA methylation; Sperm metabolism

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