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自身免疫性疾病合并不孕症的患者管理专家共识（2024 年）

中国医师协会生殖医学专业委员会

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【摘要】　自身免疫性疾病（autoimmune diseases，AIDs）患者助孕和妊娠均面临较大的风险，对 AIDs 患者在助孕和围妊娠期时进行规范化管理，对降低助孕和妊娠不良风险至关重要。本共识对常见的 AIDs 及自身抗体与不孕症的关系、AIDs 如何影响妊娠、妊娠如何影响 AIDs 病情、如何为 AIDs 合并不孕症的患者提供孕前咨询、AIDs 合并不孕症患者辅助生育过程中如何使用抗凝药物几个方面进行了分析总结，旨在为多学科合作共同管理 AIDs 及自身抗体阳性合并不孕症的患者提供借鉴。

【关键词】　自身免疫性疾病；　自身抗体；　不孕症；　管理

基金项目：国家重点研发计划（2021YFC2700605）；北京大学第三医院临床重点项目（BYSYZD2023003）

Expert consensus on autoimmune diseases and infertility management (2024)

Reproductive Medicine Professional Committee of Chinese Medical Doctor Association
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【Abstract】　Patients with autoimmune diseases (AIDs) face greater risks in assisted reproductive treatment and gestation. Standardized management of AID patients during the assisted reproduction and peri pregnancy period is crucial for reducing the AID assisted pregnancy risk and improving the outcome. This consensus analyzes and summarizes the relationship between several common AIDs and auto-antibodies and infertility, how AIDs affect pregnancy, how pregnancy affects AIDs' condition, how to provide preconception consultation for patients with AIDs and infertility, and how to use antithrombotic drugs in the assisted

reproduction process of AID patients with infertility. It aims to provide a reference for multidisciplinary cooperation in the management of patients with AIDs and autoantibody positive and infertility.

【**Key words**】 Autoimmune disease; Autoantibody; Infertility; Management

Fund program: National Key Research and Development Program (2021YFC2700605); Peking University Third Hospital Clinical Key Project (BYSYZD2023003)

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·中医药在不孕不育中的应用专栏·

中医药在不孕不育中的应用专栏导读

不孕症是一个全球性的健康问题，它不仅影响着患者的身心健康，也给家庭带来了巨大的压力和困扰。据统计，全球有10%~15%的夫妇面临不孕问题。而在中国，不孕症的发病率呈逐年上升趋势，已成为影响人口出生率的重要因素之一。

中医药学作为中国重要的卫生资源，在多途径治疗生殖障碍疾病、改善不孕症患者妊娠结局方面，具有悠久的历史和深厚的应用基础，在临床中具有独特的优势。中医药以整体观念为指导，结合历代医家不断完善不孕症的辨证论治系统，形成调周法、分期论治等多样性的诊疗思路，在实践应用时可以与西医诊治手段灵活结合来减轻西药的不良反应、增强西药疗效，还可以改善卵巢储备功能，提高优质卵子率、受精率、卵裂率和优质胚胎率，改善子宫内膜容受性，进而提高妊娠率、活产率及优生儿成功率。中医药治疗不孕症的手段多样，包括中药内服、外敷、针灸、艾灸等，这些方法可以单独应用或综合运用，以满足不同的治疗场景和治疗需求。同时，中医药治疗还具有不良反应小、安全性高的优点，为不孕症患者提供了安全有效的治疗手段。

本期中医药在不孕不育中的应用专栏邀请了中医生殖领域的专家就中医药治疗生殖障碍疾病的作用及机理、针灸治疗卵巢储备功能减退的靶标、针刺促卵泡发育和排卵的机制等进行阐述，展示了中医药对于慢性子宫内膜炎、反复种植失败、复发性流产患者妊娠结局的改善作用，并探讨电针改善多囊卵巢综合征患者胚胎移植结局的作用机制及中医药干预肠道菌群影响多囊卵巢临床机制，旨在为中医药改善生殖障碍性疾病提供更多的应用范式。

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温阳化浊方对不明原因复发性流产患者妊娠结局的影响

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【摘要】　目的　探讨温阳化浊方对不明原因复发性流产（unexplained recurrent spontaneous abortion，URSA）患者妊娠结局的影响。方法　采用回顾性队列研究方法，收集2018年11月至2022年3月期间就诊于天津中医药大学第一附属医院生殖中心和天津医科大学总医院妇产科240例再次妊娠的脾肾阳虚证URSA患者的临床资料，按照是否于孕前3个月至孕后8~12周规律口服温阳化浊方治疗，分为中药组（120例）及对照组（120例）。比较两组妊娠结局、围产期结局及产科并发症。多因素logistic回归分析温阳化浊方对妊娠结局的影响。结果　中药组活产率[86.67%（104/120）]、持续妊娠率[90.00%（108/120）]均高于对照组[71.67%（86/120），*P*=0.004；75.00%（90/120），*P*=0.002]，早期流产率[10.08%（12/119）]低于对照组[25.86%（30/116），*P*=0.002]，差异均有统计学意义。两组间围产期结局及产科并发症发病率差异均无统计学意义（均*P*>0.05）。多因素logistic回归分析显示，应用温阳化浊方能显著改善URSA患者的活产率（*OR*=8.818，95% *CI*：3.556~21.871，*P*<0.001）和持续妊娠率（*OR*=11.261，95% *CI*：4.262~29.751，*P*<0.001）。结论　孕前及孕期使用温阳化浊方治疗可显著提高脾肾阳虚证URSA患者的活产率及持续妊娠率，改善URSA患者的妊娠结局。

【关键词】　妊娠结局；　中医学；　温阳化浊方；　不明原因复发性流产；　活产率

基金项目：天津市教委科研计划项目（2022KJ164）

Effect of Wenyang Huazhuo recipe on pregnancy outcomes in patients with unexplained recurrent spontaneous abortion

Qiu Yunhuan[1], Ma Saihua[1], Ma Tiantian[1], Chen Yiran[1], Wang Baojuan[1], Dong Rong[1], Li Xiaozhou[2], Ju Duan[2], Xia Tian[1]

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【Abstract】 **Objective** To observe the effect of Wenyang Huazhuo recipe (WYHZ) on pregnancy outcomes in patients with unexplained recurrent spontaneous abortion (URSA). **Methods** A retrospective cohort study was used and 240 cases of pregnancy URSA patients with spleen kidney yang deficiency syndrome at the Reproductive Center, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine and Department of Gynaecology and Obstetrics, General Hospital of Tianjin Medial University from November 2018 to March 2022 were recruited. The patients were assigned to WYHZ group (120 cases) and control group (120 cases) based on whether accepting oral WYHZ from 3 months before pregnancy to 8–12 weeks after pregnancy regularly. Pregnancy outcomes, perinatal period outcomes and obstetric complications were compared between the two groups. Multivariate logistic regression were used to analyze the effect of WYHZ on pregnancy outcome. **Results** The live birth rate and the clinical pregnancy rate in WYHZ group [86.67% (104/120), 90.00% (108/120)] were higher than those in control group [71.67% (86/120), *P*=0.004; 75.00% (90/120), *P*=0.002]. The early abortion rate in WYHZ group [10.08% (12/119)] was lower than that in control group [25.86% (30/116), *P*=0.002], the differences were statistically significant. There were no significant differences in perinatal outcome and incidence rate of obstetric complications between the two groups (all *P*>0.05). Multivariate logistic regression analysis showed that the application of WYHZ significantly improved the live birth rate (*OR*=8.818, 95% *CI*: 3.556-21.871, *P*<0.001) and sustained pregnancy rate (*OR*=11.261, 95% *CI*: 4.262-29.751, *P*<0.001) in URSA patients. **Conclusion** WYHZ using before and during pregnancy can significantly improve the live birth rate and the clinical pregnancy rate of URSA patients with syndrome of yang deficiency of spleen and kidney, and improve their pregnancy outcomes.

【Key words】 Pregnancy outcome; Traditional Chinese Medicine; Wenyang Huazhuo recipe; Unexplained recurrent spontaneous abortion; Live birth rate

Fund program: Tianjin Education Commission Research Program Project (2022KJ164)

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温阳化浊方治疗慢性子宫内膜炎对反复种植失败患者妊娠结局的影响：一项随机对照研究

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【摘要】 目的　研究温阳化浊方联合抗生素治疗对反复种植失败（recurrent implantation failure，RIF）合并慢性子宫内膜炎（chronic endometritis，CE）患者妊娠结局的影响。方法　采用随机对照研究，纳入2020年2月至2021年1月期间就诊于天津中医药大学第一附属医院生殖医学科的脾肾阳虚型RIF合并CE患者60例，按照随机数字表法1∶1分为对照组和中药组，每组各30例。对照组予口服多西环素+甲硝唑治疗14 d，中药组在此基础上加用温阳化浊方口服治疗3个月经周期，两组在治疗结束后行冻融胚胎移植。比较两组妊娠结局、内膜转化日/排卵日子宫内膜厚度和形态、子宫内膜血流分支及血流相关指数，CE转阴率及治疗结束当周期黄体中期的子宫内膜组织CD138、血管内皮生长因子（vascular endothelial growth factor，VEGF）及同源框基因A10（homeobox A10，HOXA10）的表达。通过单因素logistic回归分析持续妊娠率的影响因素。结果　中药组的持续妊娠率［46.67%（14/30）］和胚胎种植率［54.05%（20/37）］高于对照组［20.00%（6/30），*P*=0.028；31.71%（13/41），*P*=0.046］，两组临床妊娠率、生化妊娠率和早期流产率差异均无统计学意义（均*P*>0.05）。治疗后，中药组A型子宫内膜比例[66.67%（18/27）]高于对照组[33.33%（10/30），*P*=0.017］，血流动力指数（2.29±0.76）及收缩期峰值速度/舒张末期流速（5.52±1.24）均低于对照组（2.86±0.92，*P*=0.015；6.44±1.43，*P*=0.012）。两组治疗后CE转阴率差异无统计学意义（*P*>0.05）。与对照组[（33.37±11.46）ng/L，2.06±0.89]相比，中药组黄体中期子宫内膜VEGF[（64.52±10.14）ng/L，*P*<0.001］与*HOX*A10（3.67±1.27，*P*<0.001）表达增加。单因素logistic回归分析结果显示子宫内膜血流是影响RIF合并CE持续妊娠的独立因素（*OR*=2.956，95% *CI*：1.072~8.148，*P*=0.036）。结论　温阳化浊方能够增加脾肾阳虚型RIF合并CE患者的子宫内膜血供，提高子宫内膜容受性，改善妊娠结局。

【关键词】 妊娠结局；　反复种植失败；　慢性子宫内膜炎；　温阳化浊方；　子宫内膜容受性

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Effect of treatment of Wenyang Huazhuo recipe for chronic endometritis on pregnancy outcomes in patients with repeated implant failure: a randomized controlled study

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【**Abstract**】 **Objective** To study the effect of the addition of Wenyang Huazhuo recipe(WYHZ) to antibiotics for the treatment of chronic endometritis (CE) on the pregnancy outcome of patients with recurrent implantation failure (RIF). **Methods** Totally 60 patients with spleen-kidney yang deficiency RIF combined with CE were selected who attended the Reproductive Center of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine from February 2020 to January 2021. They were randomly divided into control group and Traditional Chinese Medicine (TCM) group in a 1∶1 ratio using a random number table method. Thirty patients in control group were treated with oral doxycycline and metronidazole for 14 d, and 30 patients in TCM group were treated with the addition of WYHZ for three menstrual cycles. The patients underwent frozen-thawed embryo transfer during the next menstrual cycle at the end of treatment. We compared pregnancy outcomes, ultrasound endometrial thickness, morphology, endometrial flow branches, flow-related index, and endometrial tissue CD138, vascular endothelial growth factor (VEGF) and homeobox A10 (HOXA10) mRNA between the two groups. The influencing factors of persistent pregnancy rate was analyzed by univariate logistic regression. **Results** The continuous pregnancy rate [46.67% (14/30)] and the embryo implantation rate [54.05% (20/37)] in the TCM group were higher than those in control group [20.00% (6/30), P=0.028; 31.71% (13/41), P=0.046], and the differences of clinical pregnancy rate, biochemical pregnancy rate, and early miscarriage rate were not statistically significant (all P>0.05). After treatment, the proportion of type A endometrium in the TCM group [66.67% (18/27)] was higher than that in control group [33.33% (10/30), P=0.017], and the hemodynamic index (2.29±0.76) and systolic/diastolic (5.52±1.24) values were lower than those in control group (2.86±0.92, P=0.015; 6.44±1.43, P=0.012). There was no statistically significant difference in the CE negative rate between the two groups after treatment (P>0.05), and the expression level of VEGF [(33.37±11.46) ng/L *vs*. (64.52±10.14) ng/L, P<0.001] and *HOX*A10 (2.06±0.89 *vs*. 3.67±1.27, P<0.001) in the mid-luteal endometrium was increased in the TCM group after treatment compared with control group. In univariate logistic regression analysis, the results showed that endometrial blood flow was an independent factor affecting persistent pregnancy of RIF with CE (OR=2.956, 95% CI: 1.072-8.148, P=0.036). **Conclusion** WYHZ is able to improve the endometrial blood supply of patients

with RIF combined with CE, increase their endometrial receptivity, and improve their pregnancy outcome.

【**Key words**】 Pregnancy outcome; Repeated implantation failure; Chronic endometritis; Wenyang Huazhuo recipe; Endometrial receptivity

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·中医药在不孕不育中的应用专栏·

基于 DNA 甲基化探讨电针改善痰湿型 PCOS 患者胰岛素抵抗及 IVF-ET 妊娠结局的作用机制

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【摘要】 目的 基于 *INSR* 基因甲基化以及胰岛素代谢信号通路探讨电针改善痰湿型多囊卵巢综合征（polycystic ovary syndrome，PCOS）患者胰岛素抵抗及体外受精-胚胎移植（*in vitro* fertilization and embryo transfer，IVF-ET）妊娠结局的作用机制。方法 采用前瞻性随机对照研究，纳入 2020 年 1 月至 2022 年 12 月期间于山东中医药大学附属医院生殖与遗传科就诊拟行 IVF-ET 助孕的痰湿型 PCOS 患者 100 例，采用随机数字表法均分为电针治疗（试验组）50 例，伪针刺激（对照组）50 例，采用固定拮抗剂方案促排卵，两组患者分别于取卵前 1 个月经周期经净始予电针治疗和伪针刺激，每周 2 次，直至扳机日。收集颗粒细胞。观察比较两组患者痰湿证候积分、胰岛素抵抗指数（homeostasis model assessment- insulin resistance，HOMA-IR）、促性腺激素（gonadotropin，Gn）的用量及使用时间、获卵数、受精率、优质胚胎数、临床妊娠率、流产率和活产率。采用亚硫酸氢盐扩增子测序测定颗粒细胞中 *INSR* 基因启动子区甲基化水

平的变化；实时荧光定量 PCR 和 Western blotting 测定 *INSR*、*PI*3K、*GLUT*4 mRNA 和蛋白的含量。结果　试验组治疗后痰湿证候积分（15.23±1.57）、HOMA-IR（2.82±0.39）较治疗前（21.65±3.61、3.34±0.56）明显降低，差异均具有统计学意义（*P*<0.001，*P*=0.014）。试验组治疗前后证候积分差值（-5.76±2.86）、HOMA-IR 差值（-2.67±0.06）的绝对值明显大于对照组（-1.64±0.84、-0.11±0.04），差异均具有统计学意义（*P*<0.001，*P*=0.021）。试验组患者 Gn 用量［（2 119.53±338.28） U］及使用时间［（10.16±1.25） d］较对照组［（2 405.65±434.20） U、（10.94±1.46） d］明显减少（*P*=0.005，*P*=0.026），优质胚胎数[（3.54±1.04）枚]较对照组[（2.66±1.87）枚]明显增多（*P*=0.014），受精率[66.91%（552/825）]、临床妊娠率[63.27%（31/49）]和活产率[51.02%（25/49）]较对照组[60.20%（475/789）、41.67%（20/48）、31.25%（15/48）]明显升高，差异均具有统计学意义（*P*=0.005，*P*=0.033，*P*=0.048）；两组患者的获卵数、早期流产率差异均无统计学意义（均 *P*>0.05）。试验组患者颗粒细胞中 *INSR* 基因启动子区 38、47、56、59、94、143 位点甲基化水平较对照组明显降低，差异均具有统计学意义（均 *P*<0.05），两组患者 71、74、154、156、162 位点甲基化水平差异均无统计学意义（均 *P*>0.05）。与对照组相比，试验组患者卵巢颗粒细胞中 *INSR*、*PI*3K、*GLUT*4 基因 mRNA 和蛋白表达均上调，差异均有统计学意义（均 *P*<0.05）。结论　电针可能是通过降低痰湿型 PCOS 患者 *INSR* 基因启动子区甲基化水平，使 *INSR*、*PI*3K、*GLUT*4 基因表达上调，从而改善患者胰岛素抵抗，提高其胚胎的质量，最终改善妊娠结局。

【关键词】　多囊卵巢综合征；　电针治疗；　甲基化；　痰湿；　胰岛素抵抗

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Mechanism of electroacupuncture on improving insulin resistance and IVF-ET pregnancy outcome in polycystic ovary syndrome patients with phlegm-damp syndrome based on DNA methylation

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【Abstract】　Objective　To study the mechanism of electroacupuncture (EA) on improving insulin resistance and *in vitro* fertilization and embryo transfer (IVF-ET) pregnancy outcome in polycystic ovary syndrome (PCOS) patients with phlegm-damp syndrome based on DNA methylation and insulin metabolism signaling pathway. **Methods**　In this prospective randomized controlled study, 100 PCOS patients with phlegm-damp syndrome who underwent IVF-ET in Department of Reproduction and Genetics in Affiliated Hospital of Shandong University of Traditional Chinese Medicine from January 2020 to December 2022 were enrolled and divided into a treatment group (EA therapy) and control group (placebo needling) by random number table, 50 patients in each group. Fixed antagonist

regimen was used to promote ovulation in the two groups. Patients received EA therapy and placebo needling respectively twice a week from the menstrual cycle before oocyte retrieval till human chorionic gonadotrophin injection day. The granulosa cells were collected. The improvement of phlegm and dampness syndrome, homeostasis model assessment insulin resistance (HOMA-IR), dosage and number of days of gonadotropins (Gn) used, number of oocytes retrieved and high-quality embryos, fertilization rate, clinical pregnancy rate, early miscarriage rate and live birth rate of patients in the two groups were compared. Bisulfite amplicon sequencing was used to evaluate the methylation levels of the *INSR* gene promoter region in ovarian granulosa cells of patients in the two groups. Real-time polymerase chain reaction and Western blotting technology were used to detect the expression of *INSR*, *PI*3K and *GLUT*4. **Results** The phlegm-dampness score (15.23±1.57) and HOMA-IR (2.82±0.39) of the experimental group after treatment were significantly lower than those before treatment (21.65±3.61 and 3.34±0.56), and the differences were statistically significant (P<0.001, P=0.014). The differences of the phlegm-dampness score (-5.76±2.86) and HOMA-IR (-2.67±0.06) before and after treatment in the experimental group were significantly greater than those in control group (-1.64±0.84, -0.11±0.04), and the differences were all statistically significant (P<0.001, P=0.021). In the experimental group, the dosage of Gn used by patients [(2 119.53±338.28) U] and the duration of Gn used [(10.16±1.25) d] were significantly reduced compared with control group [(2 405.65±434.20) U, P=0.005; (10.94±1.46) d, P=0.026], and the number of high-quality embryos (3.54±1.04) was significantly increased compared with control group (2.66±1.87, P=0.014). Fertilization rate [66.91% (552/825)], clinical pregnancy rate [63.27% (31/49)] and live birth rate [51.02% (25/49)] were significantly higher in the experimental group than in control group [60.20% (475/789), 41.67% (20/48), 31.25% (15/48)], and the differences were all statistically significant (P=0.005, P=0.033, P=0.048). There were no significant differences in the number of oocytes retrieved and early abortion rate between the two groups (all P>0.05). The methylation levels of *INSR* gene promoter sites 38, 47, 56, 59, 94 and 143 in the experimental group were significantly lower than those in control group (all P<0.05), but there were no significant differences in methylation levels of sites 71, 74, 154, 156 and 162 between the two groups (all P>0.05). Compared with control group, the mRNA and protein expression of *INSR*, *PI*3K and *GLUT*4 was up-regulated in the experimental group (all P<0.05). **Conclusion** EA may improve IR by down-regulating *INSR* methylation levels and up-regulating *INSR*, *PI*3K and *GLUT*4 expression, thereby enhancing the quality of embryos and improving the pregnancy outcome in PCOS patients.

【Key words】 Polycystic ovary syndrome; Electroacupuncture; Methylation; Phlegm dampness; Insulin resistance

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·中医药在不孕不育中的应用专栏·

中医药干预肠道菌群影响多囊卵巢综合征机制研究进展

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【摘要】 多囊卵巢综合征（polycystic ovary syndrome，PCOS）作为常见的妇科疾病，其发病机制与肠道菌群息息相关。本文通过总结中医药干预肠道菌群治疗 PCOS 的多靶点、多途径，以期从慢性炎症、氧化应激、高雄激素血症及糖脂代谢异常 4 个方面为临床上的诊疗提供新思路。

【关键词】 多囊卵巢综合征；　肠道菌群；　中医药

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Research progress on the mechanism of the effect of Traditional Chinese Medicine intervention on intestinal microbiota on polycystic ovary syndrome

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【Abstract】 Polycystic ovary syndrome (PCOS) is a common gynecological disease, and its pathogenesis is closely related to the intestinal microbiota. This article summarizes the multi-target and multi-pathway of Traditional Chinese Medicine intervention in the treatment of PCOS with intestinal microbiota, in order

to provide new ideas for clinical diagnosis and treatment from four aspects: chronic inflammation, oxidative stress, hyperandrogenism and abnormal glucose and lipid metabolism.

【**Key words**】 Polycystic ovary syndrome; Intestinal microbiota; Traditional Chinese Medicine

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·中医药在不孕不育中的应用专栏·

中医药治疗排卵障碍性疾病的作用及机理研究

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【摘要】 排卵障碍性疾病是导致不孕不育的重要因素，严重影响人类生殖健康。近年来国内外专家学者对中西医结合诊治排卵障碍性疾病进行了有益的探索，在寻找有效诊疗手段和预防途径方面取得了可喜的成果。中医药在整体辨证、未病先防和既病防变等理念指导下，辨病与辨证相结合，体现了中医药个体精准治疗的优势特色，同时，中西医结合治疗相互取长补短，达到了减毒增效的作用。本文主要探讨了中医药诊治排卵障碍性疾病的特点和作用机理，为揭示中医药治疗排卵障碍性疾病的疗效机制提供了借鉴。

【关键词】 中医药； 排卵障碍性疾病； 不孕症

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Study on the role and mechanism of Traditional Chinese Medicine in the treatment of ovulatory disorder

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【**Abstract**】 Diseases of ovulatory disorder are an important factor leading to infertility and seriously affecting human reproductive health. In recent years, experts and scholars at home and abroad have carried out useful explorations of combining Chinese and Western medicine in the diagnosis and treatment of ovulation disorders, and have achieved promising results in searching for effective diagnostic and treatment methods and ways of prevention. Under the guidance of the concepts of holistic diagnosis, prevention of diseases before they occur and prevention of changes in existing diseases, Traditional Chinese Medicine combines the identification of diseases with the identification of evidence, reflecting the advantageous characteristics of Traditional Chinese Medicine in individual and precise treatment. At the same time, Traditional Chinese Medicine treatment and modern medicine combine to complement each other and achieve the effect of reducing toxicity and increasing effectiveness. This article mainly discusses the characteristics and mechanism of Traditional Chinese Medicine in treating ovulation disorders, and also provides a reference for further revealing the efficacy mechanism of Traditional Chinese Medicine in treating ovulation disorders.

【**Key words**】 Traditional Chinese Medicine; Ovulatory disorder; Infertility

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·中医药在不孕不育中的应用专栏·

卵巢储备功能减退的针灸治疗靶标研究进展

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【摘要】 卵巢储备功能减退（diminished ovarian reserve， DOR）是指在绝经前提前出现的卵泡数量减少和卵母细胞质量下降，其发病机制尚未完全明确，临床治疗亦缺乏高效的手段，俨然成为生殖医学界亟待解决的难题。针灸由于操作方便、疗效好、见效快等优点，在全世界逐渐被推广用于妇科疾病的治疗。随着组学技术的飞速发展，DOR 发病相关的分子靶标（蛋白质、核酸、受体等）被逐渐识别。本综述拟从针灸治疗 DOR 靶标的角度进行总结，以期为针灸治疗 DOR 的临床效果提供可靠依据。

【关键词】 卵巢储备功能减退； 针灸； 分子靶标

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Research progress on therapeutic targets of acupuncture and moxibustion for diminished ovarian reserve

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【Abstract】 Diminished ovarian reserve (DOR) refers to the decrease in the number of follicles and the quality of oocytes that appear prematurely before menopause. The pathogenesis of DOR is not yet fully understood, and clinical treatment lacks efficient methods, making it an urgent problem to be solved in the field of reproductive medicine. Acupuncture and moxibustion has been gradually popularized in the world for the treatment of gynecological diseases due to its advantages such as convenient operation, good curative effect and quick effect. With the rapid development of omics technology, molecular targets related to DOR pathogenesis (proteins, nucleic acids, receptors, etc.) are gradually recognized. In this review, we plan to make a summary from the perspective of the target of acupuncture and moxibustion treatment of DOR, in order to provide a reliable basis for the clinical treatment of DOR.

【Key words】 Diminished ovarian reserve; Acupuncture and moxibustion; Molecular target

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·中医药在不孕不育中的应用专栏·

针刺促卵泡发育和排卵的机制研究

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【摘要】　女性患者卵泡发育与排卵障碍是不孕症的主要原因，而针刺在促卵泡发育和排卵中具有显著疗效和独特优势，本文通过总结相关文献发现针刺促卵泡发育与排卵的机制主要涉及以下五个方面：改善下丘脑-垂体-卵巢轴功能；调节卵巢局部稳态；调节糖脂代谢，纠正内分泌紊乱；调整系统和局部交感神经；调节情绪障碍。本文总结上述机制以期为卵泡发育及排卵障碍相关疾病的基础研究及临床治疗提供理论参考，同时也对针刺促卵泡发育与排卵的研究提出了一些思考。

【关键词】　针刺；　多囊卵巢综合征；　不孕症；　卵泡发育；　排卵障碍

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Research of mechanism of acupuncture promoting follicular development and ovulation

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【**Abstract**】 Follicular development and ovulation disorders are the main causes of infertility in female patients, and acupuncture shows significant efficacies and unique advantages in promoting follicular development and ovulation. By summarizing relevant literature, this article illustrates the mechanism of acupuncture in promoting follicular development and ovulation from the following five aspects: improving the function of the hypothalamus-pituitary-ovary axis; regulating local ovarian homeostasis; regulating glucose and lipid metabolism and correcting endocrine disorders; adjusting sympathetic nerve system and regional sympathetic nerves; regulating emotional disorders. This article provides theoretical reference for basic research and clinical treatment of diseases related to follicular development and ovulation disorders, and also comes up with some thoughts on the study of acupuncture promoting follicular development and ovulation.

【**Key words**】 Acupuncture; Polycystic ovary syndrome; Infertility; Follicular development; Ovulation disorder

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·实验研究·

褪黑素通过 SIRT3/SOD2 途径改善高龄卵巢功能减退女性颗粒细胞线粒体功能和减轻氧化应激

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【摘要】 目的 研究褪黑素在体外培养中改善高龄卵巢功能减退女性颗粒细胞线粒体功能、减轻氧化应激状态的作用及可能机制。方法 收集在 2022 年 3 月

至 6 月期间在郑州大学第二附属医院生殖医学中心接受辅助生殖技术助孕患者取卵后废弃的卵泡液，提取壁层颗粒细胞，按患者年龄分为高龄组（年龄≥38 岁，6 例）和年轻对照组（年龄<35 岁，6 例）。使用透射电子显微镜观察颗粒细胞的线粒体超微结构，通过 ATP 检测试剂盒检测细胞内 ATP，实时荧光定量 PCR 检测线粒体 DNA（mitochondrial DNA，mtDNA）拷贝数，JC-1 荧光探针检测线粒体膜电位，MitoSOX™ Red 线粒体氧化物指示剂检测活性氧含量，Western blotting 法检测 SIRT3、SOD2 的蛋白表达。将高龄组的颗粒细胞样本根据随机数字表法分为褪黑素处理组和空白对照组（各 5 例），检测在体外培养颗粒细胞时添加褪黑素 1 μmol/L 后线粒体上述检测指标与空白对照组的差异。转染 siRNA 下调颗粒细胞内 SIRT3，检测褪黑素添加前后上述检测指标并与阴性对照组比较。结果　高龄组颗粒细胞的线粒体超微结构与年轻对照组相比存在明显差异，线粒体结构显示不清，线粒体嵴少见且不规律排列，ATP 水平（*P*=0.012）、mtDNA 拷贝数（*P*=0.005）和线粒体膜电位（*P*=0.009）显著低于年轻对照组，活性氧含量显著增加（*P*=0.003），SIRT3 和 SOD2 水平显著降低（*P*<0.001 和 *P*=0.002），差异均有统计学意义。经褪黑素体外培养后，线粒体超微结构有所恢复，ATP 水平（*P*<0.001）、mtDNA 拷贝数（*P*=0.038）和线粒体膜电位（*P*=0.002）高于空白对照组，SIRT3 和 SOD2 水平高于空白对照组（*P*=0.011 和 *P*=0.031），活性氧含量低于空白对照组（*P*<0.001），差异均有统计学意义。siRNA 转染后的颗粒细胞 SIRT3 的表达显著下调（*P*<0.001）。经褪黑素处理后，细胞内 ATP 水平、mtDNA 拷贝数和线粒体膜电位均低于未下调 SIRT3 的阴性对照组（*P*<0.001、*P*=0.001、*P*<0.001），活性氧含量高于阴性对照组（*P*<0.001），差异均有统计学意义。结论　在体外培养中添加褪黑素可以改善高龄卵巢功能减退女性颗粒细胞的线粒体功能和氧化应激状态。褪黑素除了直接抗氧化作用，还可通过调节 SIRT3 和 SOD2 水平来降低活性氧含量。

【关键词】　褪黑素；　颗粒细胞；　衰老；　线粒体；　氧化应激；　活性氧

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Improving mitochondrial function and alleviating oxidative stress in aged women with ovarian insufficiency: the role of melatonin through the SIRT3/SOD2 pathway

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【**Abstract**】　**Objective**　To investigate the potential effects of melatonin on improving mitochondrial function and reducing oxidative stress in granulosa cells in aged women with ovarian insufficiency *in vitro*, as well as explore the underlying mechanisms. **Methods**　Granulosa cells were extracted from waste follicular fluid obtained from patients undergoing assisted reproductive technology at the Reproductive Medicine Center of the Second Affiliated Hospital of Zhengzhou University from March to June 2022. According to the age of the patients, they were divided into two groups: the aged group (age ≥38 years old, 6 cases) and the young control group (age <35 years old, 6 cases). The mitochondrial ultrastructure of the

granulosa cells was examined using transmission electron microscopy. Intracellular ATP levels were measured using an ATP detection kit, while mitochondrial DNA (mtDNA) copy number was assessed using real-time fluorescence quantitative PCR. Mitochondrial membrane potential was evaluated using the JC-1 fluorescent probe, reactive oxygen species (ROS) content was measured using the MitoSOX™ Red mitochondrial oxide indicator, and protein expressions of SIRT3 and SOD2 were determined using Western blotting. According to the random number table method, samples from the aged group were randomly allocated to either the melatonin treatment group or blank control group (5 cases in each group) to assess the impact of *in vitro* melatonin treatment on the aforementioned mitochondrial parameters. SIRT3 in granular cells was down-regulated by transfection of siRNA, and the above indexes were detected before and after melatonin addition and compared with the negative control group. **Results** In comparison to the young group, the aged group exhibited distinct differences in the ultrastructure of granulosa cell mitochondria. Specifically, the mitochondrial structure appeared unclear, with sparse and irregularly arranged ridges. Furthermore, significant reductions were observed in ATP levels (P=0.012), mtDNA copy number (P=0.005), and mitochondrial membrane potential (P=0.009) in the aged group, while ROS content was increased (P=0.003). Additionally, the levels of SIRT3 and SOD2 were significantly decreased (P<0.001 and P=0.002, respectively). These differences were statistically significant. Following *in vitro* melatonin culture, improvements were observed in the mitochondrial ultrastructure, as well as increases in ATP levels (P<0.001), mtDNA copy number (P=0.038), and mitochondrial membrane potential (P=0.002). Correspondingly, SIRT3 and SOD2 levels increased (P=0.011 and P=0.031, respectively), while ROS content decreased (P<0.001). These changes were statistically significant. After siRNA transfection, the expression of SIRT3 in the granulosa cells was significantly down-regulated (P<0.001). After melatonin treatment, the ATP levels (P<0.001), the mtDNA copy number (P=0.001), and the mitochondrial membrane potential (P<0.001) were all lower than those in the negative control group without SIRT3 downregulation, and the ROS content was higher than that in the negative control group (P<0.001), with statistical differences. Similarly, the effects of melatonin on reducing ROS were also significantly diminished. **Conclusion** *In vitro* melatonin culture has the potential to enhance mitochondrial function and alleviate oxidative stress in granulosa cells from aged women with ovarian insufficiency. Furthermore, in addition to its direct antioxidative properties, melatonin may regulate the levels of SIRT3 and SOD2 to reduce ROS.

【Key words】 Melatonin; Granulosa cells; Aging; Mitochondria; Oxidative stress; Reactive oxygen species

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·实验研究·

玻璃化冷冻卵巢原位移植技术介导胰岛素/IGF-1 信号通路易感糖代谢紊乱风险的实验研究

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【摘要】 目的　初探玻璃化冷冻后卵巢原位移植技术对其子代小鼠糖代谢水平的影响和机制。方法　建立卵巢玻璃化冷冻后原位移植出生子代小鼠模型，实验分为新鲜卵巢原位移植出生子代（新鲜组）和玻璃化冷冻卵巢原位移植出生子代（玻璃化冷冻组），另设自然交配出生子代为对照组，每组 16 只小鼠，检测子代小鼠出生到 6 月龄时各阶段体质量及 6 月龄成年子代鼠的空腹血糖、空腹胰岛素、糖耐量水平；取材 6 月龄子代小鼠肝脏组织，qRT-PCR 检测生长因子受体结合蛋白 10（growth factor receptor-bound protein 10，Grb10） mRNA 的表达；Western blotting 检测 Grb10、磷酸化蛋白激酶 B（phosphate-protein kinase B，p-AKT）和磷酸化丝裂原活化蛋白激酶（phosphate-mitogen-activated protein kinase，p-MAPK）蛋白的表达。结果　玻璃化冷冻组 2 周龄和 3 周龄子代小鼠的体质量均低于对照组（P=0.007，P<0.001），差异均具有统计学意义；新鲜组 4 月、5 月龄子代小鼠的体质量均低于对照组（P=0.023，P=0.013），差异均具有统计学意义。6 月龄子代鼠新鲜组和玻璃化冷冻组小鼠空腹血糖均较对照组升高（P<0.001，P=0.002），差异均具有统计学意义；玻璃化冷冻组小鼠空腹胰岛素水平较对照组升高，差异具有统计学意义（P=0.017），但玻璃化冷冻组与新鲜组之间差异均无统计学意义（均 P>0.05）。葡萄糖注射后 30 min 时，新鲜组子代小鼠血糖水平显著高于玻璃化冷冻组（P<0.001），120 min 时，新鲜组和

玻璃化冷冻组子代小鼠血糖水平显著高于对照组（*P*=0.034，*P*=0.018），差异均具有统计学意义。新鲜组和玻璃化冷冻组子代肝脏内 *Grb*10 mRNA 和蛋白的表达显著高于对照组（均 *P*<0.001），差异均具有统计学意义；玻璃化冷冻组和新鲜组子代肝脏内 p-AKT（均 *P*=0.024）和 p-MAPK（*P*=0.019，*P*=0.002）蛋白的表达较对照组显著性降低，差异均具有统计学意义，玻璃化冷冻组与新鲜组之间差异均无统计学意义（均 *P*>0.05）。结论　卵巢玻璃化冷冻后原位移植技术影响子代小鼠生长和糖代谢，通过子代成年小鼠肝脏内印记基因 *Grb*10 过表达，抑制肝脏内胰岛素/胰岛素样生长因子-1 信号通路，降低细胞利用葡萄糖水平，使成年子代小鼠出现糖代谢紊乱的现象。

【关键词】　玻璃化冷冻；　卵巢组织；　生长因子受体结合蛋白 10；　胰岛素/IGF-1 信号通路

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Experimental study on the risk of glucose metabolism disorders in vitrified-frozen ovarian orthotopic transplantation technique mediated insulin/IGF-1 signaling pathway

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【Abstract】　Objective　To explore the effect and mechanism of vitrified ovarian transplantation *in situ* on the glucose metabolism level of its offspring mice. **Methods**　To establish mouse model of vitrified ovarian orthotopic transplantation, the mice were divided into three groups: fresh ovarian orthotopic transplantation offsprings group (fresh group), vitrified ovarian orthotopic transplantation offsprings group (vitrification group), natural mating birth offsprings group (control group), 16 mice per group. The growth weight from birth to 6 months, fasting blood glucose level, glucose tolerance and serum insulin level in 6-month mice were detected in the three groups. The liver tissues of 6-month mice were obtained. The mRNA expression of growth factor receptor-bound protein 10 (Grb10) was detected by qRT-PCR. The protein expressional levels of Grb10, phosphate-protein kinase B (p-AKT) and phosphate-mitogen-activated protein kinase (p-MAPK) were detected by Western blotting. **Results**　The body weight of the mice was lower in the vitrification group than in control group at 2 and 3 weeks after birth (*P*=0.007, *P*<0.001), the differences were statistically significant. The body weight of the mice was lower in the fresh group than in control group at 4 and 5 months after birth (*P*=0.023, *P*=0.013), the differences were statistically significant. The fasting plasma glucose level of 6-month-old mice in the fresh group and the vitrification group was significantly higher than that in control group (*P*<0.001, *P*=0.002), the differences were statistically significant; the fasting insulin level of the mice in the vitrification

group was higher than that in control group (*P*=0.017), the difference was statistically significant; however, no significant differences were found between the fresh and vitrification groups (all *P*>0.05). Thirty minutes after glucose injection, the fasting serum glucose level in fresh group was significantly higher than that in vitrification group (*P*<0.001), 120 min after glucose injection, the fasting serum glucose level in fresh group and vitrification group were significantly higher than that in control group (*P*=0.034, *P*=0.018), the difference was statistically significant. Compared with control group, the protein and mRNA expressional levels of Grb10 increased significantly in vitrification group and fresh group (all *P*<0.001), the difference was statistically significant. The protein expressional levels of p-AKT (all *P*=0.024) and p-MAPK (*P*=0.019, *P*=0.002) decreased significantly in vitrification group and fresh group compared with control group, the differences were statistically significant, there were no significant differences between vitrification group and fresh group (all *P*>0.05). **Conclusion** Vitrified ovarian orthotopic transplantation can affect the growth of the offspring of the mice, overexpression of the mRNA and protein of the imprinted gene *Grb*10 in the adult mouse liver, glucose metabolism disorder in adult offspring mice, reduced the cellular glucose levels by inhibiting the insulin/insulin-like growth factors-1 signaling pathway in offspring.

【Key words】 Vitrification; Ovarian tissue; Growth factor receptor-binding protein 10; Insulin/IGF-1 signaling pathway

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·现场调查·

膳食模式与育龄人群性功能的关联研究

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【摘要】 目的 分析膳食模式与育龄人群性功能的关联。方法 本研究为横断面研究，纳入 2020 年 12 月至 2022 年 3 月期间在安徽省马鞍山市妇幼保健院生殖中心、中国人民解放军联勤保障部队第 901 医院生殖中心和安徽皖北煤电集团总医院生殖中心就诊的所有女性和男性作为研究对象，通过女性性功能指数（Female Sexual Function Index，FSFI）和国际勃起功能指数-15（International Index of Erectile Function-15，IIEF-15）问卷评估性功能，采用因子分析建立膳食模式，采用多因素 logistic 回归分析膳食模式与性功能的相关性。结果 研究共纳入 1 290 例女性、1 331 例男性，其中女性性功能障碍者 1 031 例，男性性功能障碍者 899 例，均衡型膳食模式为主的女性 289 例、男性 272 例，传统型膳食模式为主的女性 473 例、男性 395 例，加工型膳食模式为主的女性 272 例、男性 324 例，饮料型膳食模式为主的女性 256 例、男性 340 例。调整居住地、年龄等混杂因素后发现，均衡型膳食模式与女性性欲障碍（*OR*=0.904，95% *CI*：0.820~0.995，*P*=0.039）、性唤起障碍（*OR*=0.840，95% *CI*：0.759~0.929，*P*=0.001）、阴道润滑障碍（*OR*=0.833，95% *CI*：0.710~0.979，*P*=0.026）、性高潮障碍（*OR*=0.764，95% *CI*：0.680~0.858，*P*<0.001）、性满意度低（*OR*=0.887，95% *CI*：0.796~0.987，*P*=0.028）、性功能障碍（*OR*=0.805，95% *CI*：0.714~0.907，*P*<0.001）和男性性高潮障碍（*OR*=0.859，95% *CI*：0.763~0.967，*P*=0.012）呈负相关；传统型膳食模式与女性性欲障碍（*OR*=0.879，95% *CI*：0.786~0.983，*P*=0.024）、性唤起障碍（*OR*=0.884，95% *CI*：0.784~0.995，*P*=0.042）和男性勃起功能障碍（*OR*=0.736，95% *CI*：0.634~0.855，*P*<0.001）、性欲障碍（*OR*=0.753，95% *CI*：0.648~0.876，*P*<0.001）、性功能障碍（*OR*=0.769，95% *CI*：0.653~0.907，*P*=0.020）呈负相关；加工型膳食模式与男性勃起功能障碍（*OR*=1.162，95% *CI*：1.049~1.287，*P*=0.004）、性高潮障碍（*OR*=1.207，95% *CI*：1.091~1.337，*P*<0.001）、性欲障碍（*OR*=1.199，95% *CI*：1.081~1.330，*P*=0.001）、性功能障碍（*OR*=1.134，95% *CI*：1.020~1.261，*P*=0.002）呈正相关；饮料型膳食模式与男女性功能障碍无关（均 *P*>0.05）。结论 均衡型、传统型膳食模式与育龄女性和男性性功能障碍的风险降低相关，加工型膳食模式与育龄男性性功障碍的风险增加相关。

【关键词】 膳食模式； 性功能； 男性； 女性

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Association between dietary patterns and sexual function in people of childbearing age

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【**Abstract**】 **Objective** To explore the relationship between dietary pattern and sexual function in people of childbearing age. **Methods** This study adopted a cross-sectional method and included all women and men who visited Reproduction Center of Maanshan Maternal and Child Health Hospital, Reproductive Medicine Center of the 901th Hospital of the Joint Logistics Support Force of People's Liberation Army and Reproduction Center of Anhui Wanbei Coal Power Group General Hospital from December 2020 to March 2022. The Female Sexual Function Index (FSFI) and International Index of Erectile Function-15 (IIEF-15) were used to assess sexual function. Factor analysis was used to establish dietary patterns, and multivariate logistic regression was used to analyze the association between dietary patterns and sexual function. **Results** A total of 1 290 females and 1 331 males were included in the study, including 1 031 females and 899 males with sexual dysfunction. There were 289 women and 272 men with balanced dietary pattern, 473 women and 395 men with traditional dietary pattern, 272 women and 324 men with processed dietary pattern, and 256 women and 340 men with beverage dietary pattern. After adjusting for confounding factors such as residence and age, it was found that balanced dietary pattern was negatively correated with female sexual desire disorder (*OR*=0.904, 95% *CI*: 0.820–0.995, *P*=0.039), sexual arousal disorder (*OR*=0.840, 95% *CI*: 0.759–0.929, *P*=0.001), vaginal lubrication disorder (*OR*=0.833, 95% *CI*: 0.710–0.979, *P*=0.026), orgasmic disorder (*OR*=0.764, 95% *CI*: 0.680–0.858, *P*<0.001), low sexual satisfaction (*OR*=0.887, 95% *CI*: 0.796–0.987, *P*=0.028), sexual dysfunction (*OR*=0.805, 95% *CI*: 0.714–0.907, *P*<0.001), and male orgasmic disorder (*OR*=0.859, 95% *CI*: 0.763–0.967, *P*=0.012). The traditional dietary pattern was negatively correlated with female sexual desire disorder (*OR*=0.879, 95% *CI*: 0.786–0.983, *P*=0.024), sexual arousal disorder (*OR*=0.884, 95% *CI*: 0.784–0.995, *P*=0.042), male erectile disorder (*OR*=0.736, 95% *CI*: 0.634–0.855, *P*<0.001), sexual desire disorder (*OR*=0.753, 95% *CI*: 0.648–0.876, *P*<0.001), and sexual dysfunction (*OR*=0.769, 95% *CI*: 0.653–0.907, *P*=0.020). The processed dietary pattern was positively correlated with erectile disorder (*OR*=1.162, 95% *CI*: 1.049–1.287, *P*=0.004), orgasmic dysfunction (*OR*=1.207, 95% *CI*: 1.091–1.337, *P*<0.001), sexual desire disorder (*OR*=1.199, 95% *CI*: 1.081–1.330, *P*=0.001) and sexual dysfunction (*OR*=1.134, 95% *CI*: 1.020–1.261, *P*=0.002). Beverage dietary pattern was not associated with sexual dysfunction in men and women (all *P*>0.05). **Conclusion** Balanced, traditional dietary patterns were related to the reduce risk of sexual dysfunction in both women and men of childbearing age, while processed dietary patterns were related to the increased risk of sexual dysfunction in men of childbearing age.

【**Key words**】 Dietary patterns; Sexual function; Men; Women

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·个案报道·

46,XY,t(1;18;9)(p34.1;q12.2;q32)复杂性染色体重排携带者的胚胎植入前遗传学检测

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【摘要】 目的 探讨胚胎植入前遗传学检测（preimplantation genetic testing， PGT）在复杂性染色体重排携带者助孕中的应用。方法 应用控制性超促排卵、卵胞质内单精子注射、囊胚活检、二代测序（next generation sequencing，NGS）等方法对1例复杂性染色体重排（complex chromosome rearrangements，CCRs）携带者行PGT助孕。结果 该夫妇行1个PGT周期，获卵27枚，共活检囊胚7枚，经NGS示：在检测范围内有3枚正常/平衡囊胚和4枚异常囊胚，解冻移植1枚囊胚后成功妊娠，足月产1男婴，胎儿染色体检查示：46,XY；未携带易位染色体。结论 CCRs携带者有高异常配子率、高流产风险。PGT能够筛查胚胎、降低其自然流产风险，是辅助治疗CCRs携带者生育问题的一种策略。

【关键词】 复杂性染色体重排； 复发性流产； 胚胎植入前遗传学检测
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Preimplantation genetic testing of 46,XY,t(1;18;9)(p34.1;q12.2;q32) with complex chromosome rearrangement carrier

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【**Abstract**】 **Objective** To detect the availability of the preimplantation genetic testing (PGT) in carriers of complex chromosome rearrangements (CCRs) for

assisting reproduction. **Methods** A couple with CCRs was treated by controlled hyperstimulation, intracytoplasmic sperm injection, blastocyst biopsy and next generation sequencing (NGS) for PGT assisting reproduction. **Results** The couple underwent 1 PGT cycle, 27 oocytes were obtained and 7 blastocysts were suitable for biopsy. NGS showed that there were 3 normal/balanced blastocysts and 4 abnormal blastocysts in the detection range. One normal/balanced blastocyst was used in frozen-thawed embryo transfer. Then the pregnancy was successful, and a male child was born at term. The fetal chromosome examination showed 46,XY with normal karyotype. **Conclusion** CCRs carriers have a high abnormal gamete rate and a high risk of miscarriage. PGT can screen embryos and reduce the risk of spontaneous miscarriage, which is a strategy to assist the treatment of fertility problems in CCRs carriers.

【 **Key words** 】 Complex chromosome rearrangements; Recurrent miscarriage; Preimplantation genetic testing

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·个案报道·

*NDP*基因变异携带合并未分化结缔组织病及血栓患者通过 PGT-M 成功助孕 1 例

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【摘要】 目的 总结 Norrie 病家系合并女方为未分化结缔组织病及血栓患者通过胚胎植入前单基因遗传学检测（preimplantation genetic testing for monogenic，PGT-M）助孕临床诊疗经验。方法 报道通过生殖遗传、生殖医学、眼科、风湿内科及产科多学科诊疗，对 1 例 *NDP*基因第 2 外显子杂合缺失合并未分化结缔组织病及血栓病的患者进行家系构建、促排取卵、胚胎检测、冻融胚胎移

植、羊膜腔穿刺、孕期及围产期监测的临床经过。结果　该患者成功妊娠并足月分娩 1 名健康女婴。结论　通过对该夫妇进行多学科诊疗管理，1 个周期的 PGT-M 助孕使患者顺利获得健康的后代，减轻患者的心理和生理负担。

【关键词】 Norrie 病；　血栓；　未分化结缔组织病；　胚胎植入前遗传学检测

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A case of assisted pregnancy by PGT-M in a patient carrying *NDP* gene mutation combined with undifferentiated connective tissue disease and thrombosis

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【Abstract】 **Objective** To summarize the experience of assisted pregnancy through preimplantation genetic testing for monogenic diseases (PGT-M) in a Norrie disease family where the female has undifferentiated connective tissue disease and thrombosis. **Methods** This article mainly reported the clinical process for a patient with a heterozygous deletion in exon 2 of the *NDP* gene combined with undifferentiated connective tissue disease and thrombosis, which was conducted through a multidisciplinary diagnostic and therapeutic process involving reproductive genetics, reproductive medicine, ophthalmology, rheumatology, and obstetrics. The stages of treatment included family pedigree construction, controlled ovarian hyperstimulation, embryo testing, frozen-thawed embryo transfer, amniocentesis, as well as antenatal and perinatal monitoring. **Results** The patient successfully conceived and gave birth to a healthy baby girl at full term. **Conclusion** Through multidisciplinary management, we successfully helped the couple achieve a healthy offspring with one PGT-M cycle, thus relieved their psychological and physiological burden.

【Key words】 Norrie disease; Thrombosis; Undifferentiated connective tissue diseases; Preimplantation genetic testing

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·综述·

DNA 甲基化在辅助生殖技术胚胎及胎儿发育中的研究进展

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【摘要】 辅助生殖技术（assisted reproductive technology， ART）被认为是帮助不孕女性妊娠的重要手段。随着技术进展，ART 的安全性越来越被广泛关注，而借助 ART 受孕相比自然受孕的妊娠结局较差。ART 的相关操作可能通过表观遗传机制进而影响后代发育和健康。DNA 甲基化则是研究最多的表观遗传调控机制。本文将对 DNA 甲基化在 ART 胚胎及胎儿发育中的研究进展进行简要综述，旨在为临床治疗提供新的思路。

【关键词】 DNA 甲基化； 胚胎发育； 生殖技术，辅助； 控制性卵巢刺激

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Research progress of DNA methylation in embryo and fetal development of assisted reproductive technology

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【Abstract】 Assisted reproductive technology (ART) is considered to be an important means to help infertile women get pregnant. With the development of technology, the safety of ART has been paid more and more attention. However, the neonatal pregnancy outcome of ART is worse than that of natural conception. The operation of ART may affect the development and health of offspring through epigenetic mechanisms. DNA methylation is the most studied epigenetic regulatory mechanism. This article briefly reviewed the research progress of DNA methylation in ART embryo and fetal development, aiming to provide a new idea for clinical treatment.

【**Key words**】 DNA methylation; Embryonic development; Reproductive technology,assisted; Controlled ovarian stimulation

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·综述·

圆形精子注射技术应用研究进展

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【摘要】 圆形精子是成熟精子的前体细胞，具有单倍体的遗传特性，通过卵胞质内圆形精子注射（round spermatid injection， ROSI）技术可以使卵母细胞受精并发育成胎儿。1996 年，第一例通过 ROSI 技术出生的婴儿诞生，但临床应用一直在成功与失败中反复交替。至今，ROSI 技术尚未广泛应用于临床，主要原因在于 ROSI 技术出生效率低，且出生婴儿的安全性未得到充分验证。ROSI 技术在解决部分非梗阻性无精子症患者生育生物学后代的问题上展现出广阔的应用前景。本文对 ROSI 技术的应用研究进展进行综述，以期更全面系统地认识 ROSI 技术，推动其在临床更高效、更安全地应用。

【关键词】 圆形精子注射； 生殖技术，辅助； 不育，男性； 胚胎发育

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Research progress in the application of round spermatid injection technology

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【**Abstract**】 Round spermatid is the precursor cell of mature spermatozoon with haploid genetic composition. The round sperm injection (ROSI) technology can

fertilize oocytes and develop into fetuses. In 1996 the first human baby was born through ROSI technology, but the subsequent clinical practice alternates between success and failure. Until today, ROSI technology has not been widely applied in clinical practice due to its low efficiency and insufficient research on the safety of the fetus born through ROSI technology. ROSI technology has shown broad application prospects in addressing some non-obstructive azoospermia patients' reproductive biology offspring issues. This article aims to provide a review of the application research progress of ROSI technology to gain a more comprehensive and systematic understanding of ROSI technology and promote its more efficient and safe clinical application.

【Key words】 Round spermatid injection; Reproductive technology, assisted; Infertility, male; Embryonic development

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·综述·

精浆在女性生殖调控中的作用

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【摘要】 精浆的功能包括作为精子的运输媒介，以及作为男性向女性生殖组织传递信息的交流手段。它是刺激女性的生殖道向受孕状态转变的重要因素。雌性的生殖道接触到精浆时会发生剧烈的炎症样反应，继而女性多个生殖器官的功能受到调节。在交配过程中可以观察到女性宫颈和子宫腔内对病原体和碎片的清除能力增强。精浆还能够影响子宫内膜上皮细胞和间质细胞的活动，调节子宫的容受性，并通过对免疫细胞系统的调节来建立母体对半异体胚胎的耐受性，为胚胎的有效着床和妊娠提供理想的条件。对于不孕症的治疗，辅助生殖技术已被广泛应用。应用精浆作为一种辅助治疗方法，可能在辅助生殖治疗周期中改善子宫内膜的接受性并调节母体免疫耐受，从而提高胚胎着床及继续发育的潜能。本文对精浆的组成及其对女性生殖道各部分的生理作用进行了综述，并对精浆目前在辅助生殖领域的应用进展进行综述。

【关键词】 精浆； 女性生殖系统； 炎症反应； 免疫耐受

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Role of seminal plasma in female reproductive regulation

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【Abstract】 The function of seminal plasma includes as a transport medium for sperm and as a means of communication for males to convey information to female reproductive tissues. It is an important factor in stimulating the female reproductive tract to become fertile. When the female reproductive tract exposed to seminal plasma, it occurs a violent inflammatory response, and the function of multiple female reproductive organs is changed. Increased pathogen and debris removal in the cervix and uterus can be observed during mating. Seminal plasma can also influence the activity of endometrial epithelial cells and stromal cells, thus promote the receptivity of the uterus, and establish maternal tolerance to semi-allogeneic embryos through immune cell system, providing ideal conditions for effective implantation and pregnancy of embryos. For the treatment of infertility, assisted reproductive technology has been widely used. It is possible to use seminal plasma as an adjuvant therapy to promote endometrial receptivity and regulate maternal immune tolerance, thereby improving the potential of embryo implantation and continued development during assisted reproductive therapy cycle. In this paper, the composition of seminal plasma and its physiological effects on various parts of female reproductive tract are reviewed. Meanwhile, the current clinical application of seminal plasma is reviewed as well.

【Key words】 Seminal plasma; Female reproductive system; Inflammatory response; Immune tolerance

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·综述·

Klinefelter 综合征的研究进展

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【摘要】 Klinefelter 综合征（Klinefelter syndrome， KS）是 X 染色体数目异常性疾病，可导致精子生成障碍、生殖细胞丢失，引起男性不育和生长发育异常。KS 患者多余染色体造成的基因表达异常和睾丸微环境异常与生精障碍、生殖细胞丢失密切相关，其发病机制尚未阐明。精子冷冻、显微取精术、卵胞质内单精子注射等技术为 KS 患者生育力保存和生育提供了技术手段，尤其是人造配子技术可能成为 KS 不育的新疗法，但该技术尚未完全成熟，仍存在安全性和伦理问题。本文对 KS 的研究进展作一综述，为其诊治提供新的思路。

【关键词】 Klinefelter 综合征； 染色体异常； 生育力保存； 生殖细胞丢失； 睾丸微环境异常

Research progress on Klinefelter syndrome

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【Abstract】 Klinefelter syndrome (KS) is a sex chromosome abnormal disease that can lead to spermatogenesis disorders, germ cell loss, male infertility and growth and developmental abnormalities. The abnormal gene expression and testicular microenvironment caused by the extra chromosome in KS patients are closely related to spermatogenesis disorders and germ cell loss, and the pathogenesis has not yet been elucidated. There are several technologies available that can provide technical means for fertility preservation and reproduction in KS patients, including sperm cryopreservation, microdissection testicular sperm extraction, and intracytoplasmic sperm injection, among which artificial gamete technology shows promise as a potential new treatment for KS infertility. Nevertheless, this technology is not yet fully mature and there are still safety and ethical issues. This article provides a comprehensive review of the research progress on KS, offering new insights for its diagnosis and treatment.

【Key words】 Klinefelter syndrome; Chromosome disorders; Fertility preservation; Germ cell loss; Abnormal testicular microenvironment

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·综述·

饮用水中消毒副产物对成人生殖功能影响的研究进展

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【摘要】 消毒副产物（disinfection by-products，DBPs）是饮用水消毒过程中消毒剂与水中的化学物质发生化学反应生成的化合物。目前已经鉴定的 DBPs 有 700 多种，其中含量最高的是三卤甲烷和卤代乙酸。DBPs 的安全性问题已经引起了人们的广泛关注，目前研究已证实其具有细胞毒性、遗传毒性、致癌性、发育毒性。近年来 DBPs 对生殖功能的损害也逐渐引起人们的重视。本文从毒理学和流行病学两方面综述 DBPs 暴露对成人生殖功能影响的研究进展，并对其今后的研究方向进行相关讨论和展望。

【关键词】 饮用水； 水污染，化学性； 生殖； 毒理学； 流行病学

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Research progress in the influence of disinfection by-products in drinking water on adult reproductive function

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【Abstract】 Disinfection by-products (DBPs) are compounds generated by chemical reactions between disinfectants and chemical substances in the water during the process of drinking water treatment. More than 700 kinds of DBPs have been identified, the most abundant components are trihalomethanes and haloacetic acids. The safety of DBPs has attracted widespread attention. At present, studies have confirmed that DBPs have cytotoxicity, genotoxicity, carcinogenicity and developmental toxicity. In recent years, the damage of DBPs to reproductive function has been an increasing concern. This article reviewed the research progress on the effects of DBPs exposure on adult reproductive function based on toxicological and epidemiological studies, and discussed the future research direction.

【Key words】 Drinking water; Water pollution, chemical; Reproduction; Toxicology; Epidemiology

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·综述·

体力活动对不孕女性生殖健康影响的研究进展

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【摘要】 全球范围内成年居民体力活动不足率高达27.5%。体力活动与不孕女性的月经失调、排卵障碍、生殖系统器质性疾病、生殖治疗结局等密切相关，合理、适当的体力活动对女性不孕的预防和治疗具有重要意义。本文通过查阅并分析相关文献，总结了近年来体力活动对不孕女性生殖健康影响的研究，并就可能的生物学机制进行探讨，为提高不孕女性的生殖健康水平提供科学依据。

【关键词】 生殖健康；　女性；　体力活动；　不孕症

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Research progress in the effects of physical activity on reproductive health of infertile women

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【Abstract】 Globally, the prevalence of physical inactivity in the adult population is as high as 27.5%. Physical activity is closely associated with menstrual disorders, ovulation disorders, organic diseases of the reproductive system, and outcomes of reproductive treatment in infertile women, and reasonable and appropriate physical activity is important for preventing and treating female infertility. This paper summarized the studies on the effects of physical activity on

the reproductive health of infertile women in recent years by reviewing and analyzing the relevant literature and exploring the possible biological mechanisms to provide a scientific basis for improving the reproductive health of infertile women.

【Key words】 Reproductive health; Female; Physical activity; Infertility

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