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# 冻融胚胎移植前 CD38、CD138 联合筛查慢性子宫内膜炎对妊娠结局的影响

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**【摘要】** 目的 探索既往胚胎移植未孕患者宫腔镜子宫内膜活检和 CD38、CD138 联合筛查慢性子宫内膜炎 (chronic endometritis, CE), 治疗后再次胚胎移植的妊娠结局。方法 采用回顾性队列研究, 收集 2015 年 1 月 1 日至 2018 年 12 月 31 日期间, 在北京大学第三医院妇产科生殖医学中心有胚胎移植未孕史、在下次冻融胚胎助孕前行宫腔镜子宫内膜活检的共 2073 例患者临床资料。依据子宫内膜病理结果将患者分为 CE 组 (CD38 和 CD138 同时阳性)、非 CE 组 (CD38 和 CD138 同时阴性)、可疑组 (CD38 和 CD138 其一阳性)、未查组 (HE 染色未提示 CE, 也未行免疫组织化学筛查), 以活产率为主要终点指标, 分析比较各组冻融胚胎移植妊娠结局, 并对相关因素进行分析。结果 患者组间一般情况, 包括年龄、体质指数、不孕年限、既往移植未孕次数、基础卵泡刺激素、窦卵泡计数等差异均无统计学意义 (均  $P>0.05$ ), 未查组宫腔镜手术至胚胎移植间隔较短 [4 (3, 6) 个月、4 (2, 6) 个月、4 (3, 6) 个月和 3 (2, 6) 个月,  $P<0.001$ ], 每周移植胚胎数较少 [2 (1, 2) 枚、2 (1, 2) 枚、2 (1, 2) 枚和 1 (1, 2) 枚,  $P=0.037$ ], 差异有统计学意义, 各组临床妊娠率、持续妊娠率、早期流产率、活产率差异均无统计学意义 (均  $P>0.05$ ), 但非 CE 组临床妊娠率、持续妊娠率、活产率较高。多因素回归分析显示, 药物治疗后 CE 不影响活产结局 ( $OR=0.789$ , 95%  $CI=0.579\sim1.075$ ,  $P=0.133$ )。结论 CD38、CD138 联合确诊 CE 患者建议在胚胎移植前进行必要的药物治疗, 药物治疗后患者妊娠结局与非 CE 患者相当, 其一指标阳性即 CD38 或 CD138 阳性不予药物治疗, 对妊娠结局无明显影响。

【关键词】 慢性子宫内膜炎； CD38； CD138； 着床失败； 受精，体外； 冻融胚胎移植

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## Effect on pregnancy outcome of women screening chronic endometritis by CD38 and CD138 before frozen-thawed embryo transfer

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**【Abstract】 Objective** To explore the pregnancy outcome of women with previous unpregnant embryo transfer (ET) cycles and screening chronic endometritis (CE) by hysteroscopic endometrial biopsy, CD38 and CD138 before the next frozen-thawed embryo transfer (FET). **Methods** A retrospective cohort study was conducted in Reproductive Center of Peking University Third Hospital from January 1st, 2015 to December 31st, 2018, including 2073 patients with previous unpregnant ET cycles and receiving hysteroscopic endometrial biopsy before FET. According to the pathological results of endometrium, the patients were divided into CE group (both CD38 and CD138 were positive), non-CE group (both CD38 and CD138 were negative), suspected group (one of CD38 or CD138 was positive), and unexamined group (no sign of CE in H&E stains or in the immunohistochemistry screening). The pregnancy outcomes after FET were compared among groups and logistic regression analysis was performed for live birth. **Results** There were no statistical differences in age, body mass index, duration of infertility, number of previous embryo transfer failures, basic follicle-stimulating hormone, number of antral follicles and endometrial thickness on the day of transfer among the four groups (all  $P>0.05$ ). Unexamined group had the shortest interval between hysteroscopy and embryo transfer and less transferred embryos per cycle, and the differences were statistically significant [4(3,6) months, 4(2,6) months, 4(3,6) months and 3(2,6) months,  $P<0.001$ ; 2(1,2), 2(1,2), 2(1,2) and 1(1,2),  $P=0.037$ ]. The pregnancy outcome of FET cycle was similar among the four groups including clinical pregnancy rate, ongoing pregnancy rate, early miscarriage rate and live birth rate (all  $P>0.05$ ). Clinical pregnancy rate, ongoing pregnancy rate and live birth rate were higher in non-CE group without statistical difference ( $P>0.05$ ). Multivariate regression analysis showed that treated CE did not affect live birth ( $OR=0.789$ , 95%  $CI=0.579-1.075$ ,  $P=0.133$ ). **Conclusion** Antibiotic treatment is recommended for patients with CE diagnosed by both CD38 and CD138 positive results, and the FET outcome of those patients is similar to patients without CE after treatment. Patients with either CD38 or CD138 positive have no adverse effects on pregnancy outcomes without treatment.

**【Key words】** Chronic endometritis; CD38; CD138; Implantation failure; Fertilization, *in vitro*; Frozen-thawed embryo transfer

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·临床研究·

# 新鲜胚胎移植术后并发重度卵巢过度刺激综合征患者的母婴结局分析

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**【摘要】** 目的 探讨新鲜胚胎移植术后并发重度卵巢过度刺激综合征(ovarian hyperstimulation syndrome, OHSS)对患者母婴结局的影响。方法 采用回顾性队列研究, 选择2018年1月至2018年12月期间在重庆市妇幼保健院妇产科就诊并行新鲜胚胎移植后并发重度OHSS的155例患者(OHSS组)以及同期行新鲜胚胎移植后未发生OHSS的366例临床妊娠患者作为对照(非OHSS组)。根据Mathur的OHSS时间分型标准, 将OHSS患者分为早发型亚组: 发生在取卵后9d(包括9d)以内; 晚发型亚组: 发生在取卵后10d或10d以上; 按照临床妊娠个数分为单胎亚组与双胎亚组。分析比较各组间的母婴结局差异(主要指标)及临床指标差异(次要指标)。结果 OHSS组中早发型亚组34例, 晚发型亚组121例; 单胎亚组80例, 双胎亚组75例。非OHSS组中单胎亚组194例, 双胎亚组172例。与非OHSS组相比, OHSS组患者的年龄更低[(29.99±4.02)岁比(31.85±3.62)岁,  $P<0.001$ ], 而获卵数更多[(11.62±4.17)个比(9.48±4.39)个,  $P<0.001$ ]。在OHSS患者中, 早发型亚组患者的卵巢大小[(7.95±1.46)cm]、胸水最大深度[(5.83±4.57)cm]、红细胞比积(hematocrit, HCT)[(44.59±4.85)%]、D-二聚体最高值[(2.87±1.84)mg/L FEU]、腹腔穿刺者占比[23.53% (8/34)]及住院时间[(12.91±6.64)d]均较晚发型亚组高[(7.26±1.41)cm,  $P=0.013$ ; (3.69±4.20)cm,  $P=0.012$ ; (42.03±4.53)%,  $P=0.005$ ; (2.01±1.09)mg/L FEU,  $P<0.001$ ; 9.09% (11/121),  $P=0.023$ ; (10.12±6.18)d,  $P=0.024$ ], 而获卵数、血清白蛋白(serum albumin, ALB)最低值、肝功能损害程度及胸腔穿刺

者占比两组差异均无统计学意义 (均  $P>0.05$ ) ; OHSS 组中单胎亚组与双胎亚组间的住院相关临床资料差异均无统计学意义 (均  $P>0.05$ ) 。OHSS 患者中早发型亚组与晚发型亚组的双胎率、活产率、产科并发症、剖宫产率、产后出血率及新生儿结局方面差异均无统计学意义 (均  $P>0.05$ ) 。OHSS 组与非 OHSS 组比较, 两组间的双胎率、流产率、异位妊娠率、活产率差异均无统计学意义 (均  $P>0.05$ ) ; 不论是单胎妊娠还是双胎妊娠, OHSS 组与非 OHSS 组间的产科并发症、早产率、产后出血率及新生儿结局方面差异均无统计学意义 (均  $P>0.05$ ) 。不论是 OHSS 还是非 OHSS 患者, 双胎亚组较单胎亚组有更高的早产率 [54.46% (116/213) 比 11.60% (29/250),  $P<0.001$ ] 、剖宫产率 [96.71% (206/213) 比 74.00% (185/250),  $P<0.001$ ] 及低出生体质量儿率 [59.39% (253/426) 比 5.20% (13/250),  $P<0.001$ ] 。

**结论** 新鲜胚胎移植后是否并发重度 OHSS 以及 OHSS 发生早晚对患者的远期妊娠并发症及母婴结局无明显影响; 但重度 OHSS 发病越早, 对母体造成的早期并发症更重, 增添患者的经济负担及妊娠风险。多胎妊娠明显增加新生儿不良结局。

**【关键词】** 卵巢过度刺激综合征; 胚胎移植, 新鲜周期; 妊娠结局; 母婴结局

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## Maternal-fetal outcomes in patients with severe ovarian hyperstimulation syndrome after fresh embryo transfer

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**【 Abstract 】 Objective** To explore the impact of severe ovarian hyperstimulation syndrome (OHSS) after fresh embryo transfer on the maternal and neonatal outcomes of patients. **Methods** A respective cohort study was performed. Totally 155 patients with severe OHSS (OHSS group) treated in the Department of Obstetrics and Gynecology of Chongqing Health Center for Women and Children and received fresh embryo transfer in the Reproductive Center from January 2018 to December 2018 were selected, and 366 clinical pregnant patients without OHSS after transplantation served as control group (non-OHSS group). According to Mathur's OHSS time classification standard, OHSS patients were divided into early-onset subgroup, occurring within 9 d (including 9 d) after oocytes retrieved, and late-onset subgroup, occurring within 10 d or more after oocytes retrieved; according to the number of pregnancies, patients were divided into singleton subgroup and twin subgroup. The differences in maternal and neonatal outcomes (primary indicators) and clinical indicators (secondary indicators) were compared between the two groups. **Results** In OHSS group, 34 early-onset and 121 late-onset, 80 singletons and 75 twins were included and in non-OHSS group 194 singletons and 172 twins were included. Compared with non-OHSS group, patients in OHSS group had lower maternal age [(29.99±4.02) years vs. (31.85±3.62) years,  $P<0.001$ ] and bigger number of oocytes retrieved (11.62±4.17 vs. 9.48±4.39,  $P<0.001$ ). For OHSS patients,



compared with late-onset group, the ovarian size  $[(7.95\pm1.46)\text{ cm vs. } (7.26\pm1.41)\text{ cm}]$ , depth of chest water  $[(5.83\pm4.57)\text{ cm vs. } (3.69\pm4.20)\text{ cm}]$ , hematocrit (HCT)  $[(44.59\pm4.85)\% \text{ vs. } (42.03\pm4.53)\%]$ , D-dimer  $[(2.87\pm1.84)\text{ mg/L FEU vs. } (2.01\pm1.09)\text{ mg/L FEU}]$ , percentage of patients undergoing abdominal puncture and hospitalization days  $[(12.91\pm6.64)\text{ d vs. } (10.12\pm6.18)\text{ d}]$  were higher in early-onset group ( $P=0.013, P=0.012, P=0.005, P<0.001, P=0.023, P=0.024$ ), while the number of oocytes retrieved, serum albumin (ALB), level of liver enzyme and percentage of patients undergoing pleural puncture were not significantly different between the two groups (all  $P>0.05$ ). The clinical data had no significant differences between singleton subgroup and twin subgroup (all  $P>0.05$ ). The twins rate, the miscarriage rate, the ectopic pregnancy rate and the live birth rate were not significantly different between OHSS group and non-OHSS group (all  $P>0.05$ ). There were no statistically significant differences in twin rate, live birth rate, obstetric complications, cesarean section rate, postpartum hemorrhage rate or neonatal outcomes between the early and late OHSS patients (all  $P>0.05$ ). Whether in singleton pregnancy or twin pregnancy, the obstetric complications, preterm birth rate, postpartum bleeding rate and neonatal outcome were not significantly different between OHSS group and non-OHSS group (all  $P>0.05$ ). Whether in OHSS or non-OHSS patients, the preterm birth rate  $[54.46\% (116/213)]$ , the cesarean section rate  $[96.71\% (206/213)]$  and the low birth weight rate  $[59.39\% (253/426)]$  were higher in twin subgroup than in singleton subgroup  $[11.60\% (29/250), P<0.001; 74.00\% (185/250), P<0.001; 5.20\% (13/250), P<0.001]$ . **Conclusion** The presentation and onset time of severe OHSS after fresh embryo transplantation had no adverse effect on the long-term pregnancy complications and pregnancy outcomes. Early-onset severe OHSS increased adverse effects on maternal in early pregnancy. Multiple pregnancies significantly increase the neonatal adverse outcomes.

**【Key words】** Ovarian hyperstimulation syndrome; Embryo transfer, fresh; Pregnancy outcome; Maternal and neonatal outcome

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·临床研究·

## 控制性超促排卵技术对亚临床甲状腺功能减退患者甲状腺功能的影响

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**【摘要】** 目的 探讨控制性超促排卵(controlled ovarian hyperstimulation, COH)对左旋甲状腺素(levothyroxine, LT4)替代治疗的亚临床甲状腺功能减退症(subclinical hypothyroidism, SCH)不孕妇女甲状腺功能的影响。方法 回顾性队列研究分析于2015年1月至2017年3月期间在云南省第一人民医院生殖医学中心行体外受精/卵胞质内单精子注射-胚胎移植(*in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer, IVF/ICSI-ET)助孕治疗的SCH不孕妇女(已接受LT4替代治疗)。最终纳入124例患者COH治疗前后的配对甲状腺功能数据进入统计分析。根据基线时血清促甲状腺素(thyroid stimulating hormone, TSH)控制水平,分为 $0.2\text{ mU/L} \leq \text{TSH} \leq 2.5\text{ mU/L}$ 组( $n=88$ )和 $2.5\text{ mU/L} < \text{TSH} \leq 4.2\text{ mU/L}$ 组( $n=36$ );根据首次IVF是否获得临床妊娠,分为临床妊娠组( $n=72$ )及未妊娠组( $n=52$ );根据基线时甲状腺过氧化物酶抗体和(或)甲状腺球蛋白抗体是否为阳性,分为甲状腺自身抗体(thyroid autoantibody, ATA)阳性组( $n=76$ )及ATA阴性组( $n=48$ )。入组者接受本中心常规进行的COH方案,于卵泡刺激前、人绒毛膜促性腺激素(human chorionic gonadotrophin, hCG)注射日以及胚胎移植后14 d行TSH、甲状腺激素及ATA检测(电化学发光法),分析IVF临床结局。结果 COH对接受LT4替代治疗的SCH不孕妇女的甲状腺功能有显著影响,基线时、hCG注射日、胚胎移植后14 d的TSH分别为 $1.75(0.43, 2.57)\text{ mU/L}$ 、 $1.03(0.37, 2.35)\text{ mU/L}$ 、 $4.27(1.13, 6.88)\text{ mU/L}$ ,组间比较差异均有统计学意义(均 $P < 0.001$ )。胚胎移植后14 d,基线时 $0.2\text{ mU/L} \leq \text{TSH} \leq 2.5\text{ mU/L}$ 组40.9%(36/88)的患者 $\text{TSH} > 4.2\text{ mU/L}$ , $2.5\text{ mU/L} < \text{TSH} \leq 4.2\text{ mU/L}$ 组COH后77.8%(28/36)的患者 $\text{TSH} > 4.2\text{ mU/L}$ 。IVF/ICSI-ET后14 d时,临床妊娠组的TSH水平显著高于未妊娠组 $[6.09(2.18, 9.09)\text{ mU/L}]$ 比 $1.84(0.62, 4.45)\text{ mU/L}$ ,  $P=0.002$ 。与ATA阴性组相比,ATA阳性组COH后TSH水平升高幅度更显著( $P=0.013$ )。结论 COH可导致已接受LT4替代治疗的SCH不孕妇女TSH水平升高,变化幅度与基线时TSH水平、ATA状态及是否妊娠有关。

**【关键词】** 控制性超促排卵; 亚临床甲状腺功能减退; 甲状腺功能

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**Effects of controlled ovarian hyperstimulation on thyroid function in infertile subclinical hypothyroidism women**

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**【Abstract】 Objective** To investigate the impact of controlled ovarian hyperstimulation(COH) on thyroid function in infertile subclinical hypothyroidism (SCH) women treated with levothyroxine (LT4). **Methods** A cohort study included LT4 treated infertile SCH patients undergoing *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) from January 2015 to March 2017 in the Reproductive Center of the First People's Hospital of Yunnan Province were retrospectively analyzed. Finally, the paired thyroid hormone data of 124 patients before and after COH were included for statistical analysis. According to baseline thyroid stimulating hormone (TSH) level, women were divided into 0.2 mU/L≤TSH≤2.5 mU/L group (*n*=88) and 2.5 mU/L<TSH≤4.2 mU/L group (*n*=36). Patients were divided into clinical pregnancy group (*n*=72) and non-pregnancy group (*n*=52) according to their first IVF outcomes. According to basal line thyroid peroxidase antibody and/or thyroglobulin antibody (ATA) levels, patients were classified into ATA positive group (*n*=76) and ATA negative group (*n*=48). The patients received COH routinely performed by our center, and TSH, thyroid hormone and ATA tests (electrochemiluminescence) were performed before follicular stimulation, on the day of human chorionic gonadotrophin (hCG) injection and 14 d after ET. IVF outcomes were analyzed. **Results** COH had a significant effect on thyroid function in LT4 treated SCH patients undergoing IVF. Serum levels of TSH before COH, the time of hCG injection and the 14th day after ET were 1.75(0.43, 2.57) mU/L, 1.03(0.37, 2.35) mU/L and 4.27(1.13, 6.88) mU/L (all *P*<0.001), respectively. At the 14th day after ET, compared with lower baseline TSH group (0.2 mU/L≤TSH≤2.5 mU/L), the higher baseline TSH group (2.5 mU/L<TSH≤4.2 mU/L) had a significant rise in TSH [proportion of TSH>4.2 mU/L, 77.8% (28/36) vs. 40.9% (36/88), *P*<0.001]. At the 14th day after ET, the TSH level in the clinical pregnancy group was significantly higher than that in the non-pregnancy group [6.09(2.18, 9.09) mU/L vs. 1.84(0.62, 4.45) mU/L, *P*=0.002]. The increment of TSH level was more significant in ATA positive group compared with ATA negative group after COH (*P*=0.013). **Conclusion** COH had a significant effect on serum TSH in LT4 treated infertile SCH women. The possible influence factors may include the baseline TSH level, status of ATA and pregnancy.

**【 Key words 】** Controlled ovarian hyperstimulation; Subclinical hypothyroidism; Thyroid function

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·临床研究·

# 不同授精方式对不明原因不孕患者妊娠结局的影响

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**【摘要】** 目的 比较体外受精 (*in vitro* fertilization, IVF) 和卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI) 两种不同授精方式对不明原因不孕患者妊娠结局的影响。方法 回顾性队列研究分析天津市中心妇产科医院生殖中心 2014 年 7 月至 2019 年 7 月期间采用 IVF 或 ICSI 治疗的不明原因不孕患者的临床资料, 按授精方式分为 IVF 组 (299 例) 和 ICSI 组 (234 例), 比较两组患者一般情况、受精情况、胚胎发育情况及妊娠结局。结果 ICSI 组和 IVF 组双原核 (two pronuclei, 2PN) 受精率、2PN 卵裂率、优质胚胎率间差异均无统计学意义 (均  $P>0.05$ )。ICSI 组原发性不孕患者比例较 IVF 组高 [79.5% (186/234) 比 39.8% (119/299),  $P<0.001$ ]。按原发性不孕和继发性不孕分层分析后, 原发性不孕患者中, ICSI 组 2PN 卵裂率 [91.2% (1339/1468)] 高于 IVF 组 [87.8% (1646/1844),  $P=0.062$ ], 两组患者 2PN 受精率、优质胚胎率差异均无统计学意义 (均  $P>0.05$ ), ICSI 组临床妊娠率 [39.8% (74/186)] 及活产率 [33.3% (62/186)] 均略高于 IVF 组 [37.8% (45/119), 31.1% (37/119)], 但差异均无统计学意义 (均  $P>0.05$ )。继发性不孕患者中, 两组间 2PN 受精率、2PN 卵裂率、优质胚胎率差异均无统计学意义 (均  $P>0.05$ ), ICSI 组临床妊娠率显著低于 IVF 组 [20.8% (10/48) 比 49.4% (89/180),  $P<0.001$ ], 活产率也显著低于 IVF 组 [18.8% (9/48) 比 40.0% (72/180),  $P=0.006$ ]。logistics 回归显示, 校正女方年龄、不孕年限、体质量指数、基础卵泡刺激素及获卵数等可能影响活产的指标后, 原发性不孕患者中不同授精方式有相似的活产率 ( $OR=1.178$ , 95%  $CI=0.686\sim2.202$ ), 继发性不孕患者中 ICSI 组活产率显著低于 IVF 组 ( $OR=0.408$ , 95%  $CI=0.180\sim0.924$ )。结论 在不明原因不孕患者中, ICSI 并不能显著改善受精情况、胚胎质量及妊娠结局, 尤其在继发性不孕患者中, IVF 患者妊娠结局显著优于 ICSI 患者, 此类患者行辅助生殖治疗时应首选常规 IVF 授精。

**【关键词】** 受精, 体外; 单精子注射, 细胞质内; 不孕; 妊娠率

## Effect of different fertilization methods on pregnancy outcome of unexplained infertility patients

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**【Abstract】 Objective** To compare the clinical pregnancy outcomes of conventional *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) fertilization in patients with unexplained infertility. **Methods** A retrospective cohort study was conducted to analyze the clinical data of patients with unexplained infertility from July 2014 to July 2019 in the Assisted Reproductive Center of Tianjin Central Hospital of Gynecology Obstetrics. The patients were divided into IVF group ( $n=299$ ) and ICSI group ( $n=234$ ) according to the fertilization methods. The general information, fertilization condition, embryo development and pregnancy outcomes were compared between the two groups. **Results** There were no statistically significant differences between ICSI group and IVF group in two pronuclei (2PN) fertilization rate, 2PN cleavage rate, and high-quality embryo rate (all  $P>0.05$ ). Infertility type had a statistically difference between the two groups ( $P<0.001$ ). Stratified analysis was conducted according to the primary and secondary infertility. Among patients with primary infertility, 2PN cleavage rate in ICSI group [91.2% (1339/1468)] was higher than that in IVF group [87.8% (1646/1844),  $P=0.062$ ]. There were no statistically significant differences in 2PN fertilization rate and high-quality embryo rate between the two groups (all  $P>0.05$ ). The clinical pregnancy rate and the live birth rate in ICSI group [39.8% (74/186), 33.3% (62/186)] were higher than those in IVF group [37.8% (45/119), 31.1% (37/119)] without significant differences (all  $P>0.05$ ). In the patients with secondary infertility, there were no statistically significant differences in 2PN fertilization rate, 2PN cleavage rate and high-quality embryo rate between the two groups (all  $P>0.05$ ). The clinical pregnancy rate [20.8% (10/48)] and the live birth rate [18.8% (9/48)] of ICSI group were significantly lower than those of IVF group [49.4% (89/180),  $P<0.001$ ; 40.0% (72/180),  $P=0.006$ ]. After adjusting female age, infertility duration, body mass index, basal follicle-stimulating hormone and the number of oocyte retrieved, logistics regression showed that different fertilization methods had similar live birth rate ( $OR=1.178$ , 95%  $CI=0.686-2.202$ ) in primary infertility patients, and the live birth rate of ICSI group was significantly lower than that of IVF group ( $OR=0.408$ , 95%  $CI=0.180-0.924$ ) in secondary infertility patients. **Conclusion** In patients with unexplained infertility, ICSI could not significantly improve fertilization rate, embryo quality and pregnancy outcome. Especially in patients with secondary infertility, IVF patients had significantly better pregnancy outcome than ICSI patients, and routine IVF fertilization should be preferred.

**【Key words】** Fertilization, *in vitro*; Sperm injection, intracytoplasmic; Infertility; Pregnancy rate

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·临床研究·

# 卵巢低反应患者新鲜周期妊娠结局的列线图预测模型的构建和评价

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**【摘要】** 目的 探究卵巢低反应(poor ovarian response, POR)患者新鲜周期妊娠结局的影响因素, 构建和验证列线图模型预估 POR 患者最终活产概率。方法 回顾性队列研究分析 2015 年 2 月 1 日至 2019 年 2 月 28 日期间在商丘市第一人民医院生殖医学中心及新疆医科大学第一附属医院生殖医学中心行助孕治疗的 2667 例预期 POR 患者, 采用单因素和多因素逻辑回归分析筛选出 POR 患者妊娠结局的独立影响因素, 根据因素变量的回归系数绘制相应的列线图预测模型, 内部验证按完全随机化分组及对照原则分为建模组和验证组, 通过受试者工作特征(receiver operating characteristic, ROC)曲线下面积(area under the curve, AUC)验证列线图模型的预测准确度。结果 通过多因素逻辑回归分析, 女性年龄( $OR=0.876$ , 95%  $CI=0.849\sim0.902$ ,  $P<0.001$ )、窦卵泡计数( $OR=1.283$ , 95%  $CI=1.133\sim1.463$ ,  $P<0.001$ )、促性腺激素使用总量( $OR=1.002$ , 95%  $CI=1.001\sim1.004$ ,  $P<0.001$ )、促性腺激素使用时间( $OR=0.786$ , 95%  $CI=0.636\sim0.963$ ,  $P=0.018$ )、 $M_{II}$  卵数( $OR=0.842$ , 95%  $CI=0.712\sim0.985$ ,  $P=0.033$ )和可移植胚胎数( $OR=2.052$ , 95%  $CI=1.762\sim2.403$ ,  $P<0.001$ )是最终活产率的独立影响因子, 根据上述独立影响因子构建 POR 患者妊娠结局的预测模型, 建模组的 AUC 为 0.894 (95%  $CI=0.878\sim0.909$ ), 验证组的 AUC 为 0.902 (95%  $CI=0.896\sim0.912$ ), 提示模型符合度良好。结论 女性年龄、窦卵泡计数、促性腺激素使用总量及时间、 $M_{II}$  卵数、可移植胚胎数是接受人类辅助生殖技术治疗的 POR 患者新鲜周期妊娠结局的独立影响因素, 列线图模型的成功构建能够有效、简便和直观地预测 POR 患者最终活产概率。

**【关键词】** 卵巢低反应; 逻辑回归; 列线图模型; 妊娠结局; 影响因素

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## **Establishment and evaluation of a nomogram prediction model for predicting pregnancy outcomes of poor ovarian response patients in fresh cycles**

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**【Abstract】 Objective** To explore the predictive factors associated with the pregnancy outcome for poor ovarian response (POR) patients, and to establish Nomogram prediction model to evaluate the probability of the live birth of POR patients. **Methods** The clinical data of 2667 patients who underwent *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment in the Center of Reproductive Medicine, the First People's Hospital of Shangqiu and the First Affiliated Hospital of Xinjiang Medical University from February 1, 2015 to February 28, 2019 were retrospectively analyzed by a cohort study. Logistic regression was used to screen out the independent predictive factors on the pregnancy outcome of IVF/ICSI in poor ovarian reserve patients, which was the model enrollment variable, and the Nomogram model was established according to the regression coefficient of the relevant variables. The prediction accuracy of the pregnancy outcome nomogram model was evaluated by calculating the receiver operating characteristic (ROC) curve and the area under the curve (AUC). **Results** Multivariate logistic regression analysis showed that female age ( $OR=0.876$ , 95%  $CI=0.849-0.902$ ,  $P<0.001$ ), antral follicle count (AFC) ( $OR=1.283$ , 95%  $CI=1.133-1.463$ ,  $P<0.001$ ), total dosage of gonadotropin (Gn) used ( $OR=1.002$ , 95%  $CI=1.001-1.004$ ,  $P<0.001$ ), duration of Gn used ( $OR=0.786$ , 95%  $CI=0.636-0.963$ ,  $P=0.018$ ), No. of MII oocytes ( $OR=0.842$ , 95%  $CI=0.712-0.985$ ,  $P=0.033$ ) and No. of transferable embryos ( $OR=2.052$ , 95%  $CI=1.762-2.403$ ,  $P<0.001$ ) were independent predictive factors of live birth. According to the independent predictive factors, the prediction model of pregnancy outcome of POR patients was established, and the AUC of the modeling group was 0.894(95%  $CI=0.879-0.909$ ), the AUC of the validation group was 0.902(95%  $CI=0.896-0.912$ ), indicating good model compliance. **Conclusion** Age, AFC, total dosage of Gn used, duration of Gn used, No. of MII oocytes and No. of transferable embryos are independent predictive factors of the pregnancy outcome for poor ovarian reserve patients, the successful establishment of nomogram model can effectively predict the live birth for POR patients.

**【Key words】** Poor ovarian response; Logistic analysis; Nomogram model; Pregnancy outcomes; Influence factor

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·临床研究·

# 禁欲时间对少精子症和弱精子症精液参数的影响

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**【摘要】** 目的 研究禁欲时间对少精子症和弱精子症患者精液参数的影响。  
方法 采用回顾性队列研究, 收集 2018 年 1 月至 2019 年 12 月期间就诊于四川大学华西第二医院生殖男科的正常育前检查、少精子症和弱精子症人群的临床资料。比较不同禁欲时间(分别为禁欲 2 d、3 d、4 d、5 d、6 d、7 d)对少精子症( $n=5127$ )、弱精子症( $n=4003$ )和正常对照男性( $n=4529$ )精液参数的影响, 观察不同组别男性的精子浓度、前向精子百分比、活动精子总数(total motile sperm count, TMSC)等参数随禁欲时间的变化。结果 正常育前检查组随禁欲时间延长, 精液体积从  $(3.3\pm 1.2)$  mL 升至  $(4.1\pm 1.3)$  mL ( $r=0.167$ ,  $P<0.001$ ), 精子浓度从  $(89.0\pm 60.9)\times 10^6$ /mL 升至  $(125.2\pm 82.3)\times 10^6$ /mL ( $r=0.181$ ,  $P<0.001$ ), 精子总数从  $(273.2\pm 169.8)\times 10^6$ /次升至  $(473.5\pm 193.7)\times 10^6$ /次 ( $r=0.310$ ,  $P<0.001$ ), 前向精子百分比从  $62.1\%\pm 13.0\%$  降至  $59.5\%\pm 13.3\%$  ( $r=-0.057$ ,  $P<0.001$ ), 存活率从  $80.6\%\pm 8.5\%$  降至  $79.0\%\pm 9.1\%$  ( $r=-0.048$ ,  $P<0.001$ )。少精子症组随禁欲时间延长, 精液体积从  $(3.1\pm 1.4)$  mL 升至  $(3.9\pm 1.6)$  mL ( $r=0.171$ ,  $P<0.001$ ), 精子浓度从  $(10.3\pm 5.5)\times 10^6$ /mL 降至  $(8.7\pm 4.3)\times 10^6$ /mL ( $r=-0.043$ ,  $P<0.001$ ), 精子总数从  $(29.0\pm 17.1)\times 10^6$ /次升至  $(38.6\pm 19.8)\times 10^6$ /次 ( $r=0.285$ ,  $P<0.001$ ), 前向精子百分比从  $41.1\%\pm 17.0\%$  降至  $35.1\%\pm 17.3\%$  ( $r=-0.141$ ,  $P<0.001$ ), 存活率从  $71.1\%\pm 12.3\%$  降至  $63.1\%\pm 16.6\%$  ( $r=-0.225$ ,  $P<0.001$ ), 禁欲 2 d 时精子浓度和前向精子百分比达峰值。弱精子症组随禁欲时间延长, 精液体积从  $(3.1\pm 1.4)$  mL 升至  $(3.8\pm 1.9)$  mL ( $r=0.197$ ,  $P<0.001$ ), 精子浓度从  $(35.1\pm 30.5)\times 10^6$ /mL 升至  $(49.7\pm 31.9)\times 10^6$ /mL ( $r=0.071$ ,  $P<0.001$ ), 精子总数从  $(109.1\pm 82.3)\times 10^6$ /次升至  $(170.1\pm 99.3)\times 10^6$ /



次 ( $r=0.394$ ,  $P<0.001$ ), 存活率从  $59.6\%\pm 16.4\%$  降至  $54.0\%\pm 16.4\%$  ( $r=-0.081$ ,  $P<0.001$ ), 前向精子百分比、圆细胞浓度与禁欲时间均无相关性 (均  $P>0.05$ ), TMSC ( $r=0.119$ ,  $P<0.001$ ) 随禁欲时间延长而增高。结论 延长禁欲时间可不同程度地增加少精子症患者、弱精子症和正常生育男性的精液体积和精子总数, 并使精子存活率降低。少精子症患者缩短禁欲时间可得到精子浓度、前向精子百分比、存活率、正常形态精子百分比比较高的精子, 但 TMSC 并未显著增加; 弱精子症患者通过延长禁欲时间能得到浓度、TMSC 较高的精子, 但前向精子百分比并未显著改善。

【关键词】 禁欲时间; 精液分析; 弱精子症; 少精子症; 精液参数  
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## Effect of sexual abstinence on semen analysis parameters in oligospermia and asthenozoospermia

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**【Abstract】 Objective** To investigate the impact of sexual abstinence (SA) on semen parameters in oligospermia and asthenozoospermia. **Methods** This retrospective cohort study was conducted for the clinical data from oligospermia ( $n=5127$ ), asthenozoospermia ( $n=4003$ ) and normozoospermia ( $n=4529$ ) with different SAs (2 d, 3 d, 4 d, 5 d, 6 d, 7 d) who were treated in Andrology Department of West China Second University Hospital during January 2018 to December 2019. The correlation between semen parameters (sperm concentration, motility, total motile sperm count etc.) and SA were observed. **Results** In normozoospermia, as the SA was getting longer, the semen volume was increased from  $(3.3\pm 1.2)$  mL to  $(4.1\pm 1.3)$  mL ( $r=0.167$ ,  $P<0.001$ ), the sperm concentration was increased from  $(89.0\pm 60.9)\times 10^6/\text{mL}$  to  $(125.2\pm 82.3)\times 10^6/\text{mL}$  ( $r=0.181$ ,  $P<0.001$ ), the total sperm count was increased from  $(273.2\pm 169.8)\times 10^6/\text{ejaculate}$  to  $(473.5\pm 193.7)\times 10^6/\text{ejaculate}$  ( $r=0.310$ ,  $P<0.001$ ). The progressive motility was decreased from  $62.1\%\pm 13.0\%$  to  $59.5\%\pm 13.3\%$  ( $r=-0.057$ ,  $P<0.001$ ). The viability was decreased from  $80.6\%\pm 8.5\%$  to  $79.0\%\pm 9.1\%$  ( $r=-0.048$ ,  $P<0.001$ ). In oligospermia, the semen volume was increased from  $(3.1\pm 1.4)$  mL to  $(3.9\pm 1.6)$  mL ( $r=0.171$ ,  $P<0.001$ ) and the sperm concentration was decreased from  $(10.3\pm 5.5)\times 10^6/\text{mL}$  to  $(8.7\pm 4.3)\times 10^6/\text{mL}$  ( $r=-0.043$ ,  $P<0.001$ ), the total sperm count was increased from  $(29.0\pm 17.1)\times 10^6/\text{ejaculate}$  to  $(38.6\pm 19.8)\times 10^6/\text{ejaculate}$  ( $r=0.285$ ,  $P<0.001$ ). The progressive motility was decreased from  $41.1\%\pm 17.0\%$  to  $35.1\%\pm 17.3\%$  ( $r=-0.141$ ,  $P<0.001$ ). The viability was decreased from  $71.1\%\pm 12.3\%$  to  $63.1\%\pm 16.6\%$  ( $r=-0.225$ ,  $P<0.001$ ). The peak value of sperm concentration and motility were observed on day 2. In asthenozoospermia, the semen volume was increased from  $(3.1\pm 1.4)$  mL to  $(3.8\pm 1.9)$  mL ( $r=0.197$ ,  $P<0.001$ ) and the sperm concentration was increased from  $(35.1\pm 30.5)\times 10^6/\text{mL}$  to  $(49.7\pm 31.9)\times 10^6/\text{mL}$  ( $r=0.071$ ,  $P<0.001$ ), the total sperm count was increased from

(109.1±82.3)×10<sup>6</sup>/ejaculate to (170.1±99.3)×10<sup>6</sup>/ejaculate ( $r=0.394$ ,  $P<0.001$ ). The viability was decreased from 59.6%±16.4% to 54.0%±16.4% ( $r=-0.081$ ,  $P<0.001$ ). The SA was not related to motility and round cells ( $P>0.05$ ). TMSC was slightly increased with extending EAT ( $r=0.119$ ,  $P<0.001$ ). **Conclusion** The longer SA has positive influence on semen volume and total sperm count on different levels in males with normozoospermia, oligospermia and asthenozoospermia. The viability was decreased by extended SA. Shortening the SA was likely to help oligospermic patients conduct sperm with higher concentration, motility, viability and normal morphology. TMSC was not significantly increased by extended SA. Asthenozoospermia can conduct sperm with higher concentration and TMSC when applying longer SA. The progressive motility was not significantly influenced by SA.

**【 Key words 】** Sexual abstinence; Semen analysis; Oligospermia; Asthenozoospermia; Semen parameters

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·临床研究·

## 基于 GEO 数据库芯片对反复种植失败者子宫内膜生物信息学分析

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**【摘要】** 目的 利用生物信息学分析方法挖掘反复胚胎种植失败患者相关关键基因及通路, 探讨其对子宫内膜容受性的影响。方法 从 GEO 数据库中下载 GSE26787 数据集及 GSE111974 数据集为研究样本, 以重复植入失败的患者及既往正常妊娠的女性的子宫内膜组织数据为研究对象, 使用 R 语言将原始数据经过质量分析、归一化、探针和基因名转换, 构建表达矩阵后, 利用 limma 包进行差异基因的筛选, 进而利用 DAVID 数据库进行 GO 及 KEGG 分析, 再使用 String 数据库及 Cytoscape 软件筛选关键基因。结果 得到两数据集共同关键基因 *PTGS2*、*PLCB1*、

*MGP*、*CYP3A5*、*LPAR3*、*VCAM1*、*ALPL*、*SLC1A1*、*SLC4A7*、*SULT1E1* 及关键通路 hsa01100。结论 本研究所得的关键基因及通路可通过调控子宫内膜氧化还原及代谢状态进而影响子宫内膜容受性，可作为研究其相关作用的靶点。

【关键词】 胚胎移植； 子宫内膜容受性； 氧化还原； 代谢途径

## Analysis of endometrial bioinformatics based on GEO database chip for repeated implanted losers

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**【Abstract】 Objective** To explore key genes and pathways in women with repeated implant failure, and to explore the influence of those genes on endometrial receptivity. **Methods** Firstly, data sets GSE26787 and SE111974 were downloaded from GEO database as research samples, and endometrial tissue data of patients with repeated implantation failure and women with previous normal pregnancy were used as research objects. Secondly, the expression matrix was constructed after using R language for quality analysis, normalization, transformation of probe and gene name. Then, limma package was used to screen differentially expressed genes, and DAVID database was used for GO and KEGG analysis. Finally, String database and Cytoscape software were used to screen key genes. **Results** The key genes are *PTGS2*, *PLCB1*, *MGP*, *CYP3A5*, *LPAR3*, *VCAM1*, *ALPL*, *SLC1A1*, *SLC4A7* and *SULT1E1*, and the key pathways is hsa01100. **Conclusion** The key genes and pathways obtained in this study can affect the endometrial receptivity by regulating the endometrial redox and metabolic status.

**【Key words】** Embryo transfer; Endometrial receptivity; Oxidation-reduction; Metabolic pathways

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·实验研究·

## 环孢素 A 改善滋养细胞轻度受损小鼠囊胚的着床

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**【摘要】** 目的 探讨环孢素 A (cyclosporin A, CsA) 是否可以改善滋养细胞轻度受损的小鼠胚胎的着床。方法 ①将 30 只 ICR 小鼠腹腔注射 CsA 5 mg/kg, 采用化学发光法检测注射后 1 h、3 h、4 h、6 h、8 h、10 h、13 h、14 h、16 h、20 h 鼠体内 CsA 血药浓度变化情况; ②将 36 只小鼠随机分为对照组和实验组, 实验组腹腔注射 CsA 5 mg/kg, 对照组相同体质量下注射同等剂量橄榄油, 根据 Gardner 评分结合实验需要将移植胚胎分为 A、B、C 三类, 分类后胚胎分别移植至两组小鼠子宫, 于交配后 (days postcoitum, dpc) 5.5 d 时采用实时荧光定量 PCR 技术检测小鼠胚胎着床率及着床部位白血病抑制因子 (leukemia inhibitory factor, LIF) mRNA 的表达情况。结果 ①小鼠体内 CsA 血药浓度在给药后 6~10 h 达到高峰; ②B 类胚胎在实验组小鼠中着床率 [73.9% (34/46)] 高于对照组 [50.0% (23/46)],  $P=0.018$ ; ③两组小鼠着床部位 LIF mRNA 的表达差异无统计学意义 ( $P>0.05$ )。结论 CsA 给药剂量为 5 mg/kg 时, CsA 可以改善滋养细胞形态上存在轻度受损的小鼠胚胎的着床; CsA 可能成为提高 IVF 成功率的潜在药物。

**【关键词】** 环孢素 A; 胚胎着床; 滋养细胞

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### Cyclosporine A improves mouse blastocyst implantation with mild impaired trophoblast cells

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**【Abstract】 Objective** To investigate whether the cyclosporin A (CsA) can improve the blastocyst implantation with mild impaired of trophoblast cells of mice.

**Methods** 1) Totally 30 ICR mice were intraperitoneally injected with 5 mg/kg CsA, then the blood concentrations of CsA in mice were detected at 1 h, 3 h, 4 h, 6 h, 8 h, 10 h, 13 h, 14 h, 16 h and 20 h after administration using chemiluminescence method. 2) A total of 36 mice were randomly divided into control group and experimental group (CsA group); the experimental group was intraperitoneally injected with 5 mg/kg CsA and control group was injected with the equivalent dose olive oil of the same body weight. Embryos were classified into A, B, C types according to the

guidelines of Gardner and experimental needs. Embryos were transferred to the uterus in the two groups. The embryo implantation rate was calculated and the leukemia inhibitory factor (LIF) mRNA level was measured by real time fluorescence quantitative PCR in 5.5 d postcoitum (dpc). **Results** 1) The blood concentration of CsA in mice reached a peak at 6–10 h after administration. 2) The embryo implantation rate of B type [73.9% (34/46)] had significantly improved in experimental group [50.0% (23/46),  $P=0.018$ ]. 3) The expression of *LIF* mRNA level was not significantly different between the two groups ( $P>0.05$ ). **Conclusion** When CsA was administered at a dose of 5 mg/kg, CsA can improve the embryo implantation rate with mild impaired trophoblast cells. CsA might become a potential drug to increase the success rates of the *in vitro* fertilization.

**【Key words】** Cyclosporine A; Embryo implantation; Trophoblast

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·循证医学·

# 左旋甲状腺素片对甲状腺功能正常伴 TPO-Ab 阳性孕妇的流产率及早产率 影响的 meta 分析

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**【摘要】** 目的 系统评价口服左旋甲状腺素片对甲状腺功能正常伴甲状腺过氧化物酶抗体 (antithyroid peroxidase-antibody, TPO-Ab) 阳性 [即自身免疫性甲状腺炎 (thyroid autoimmunity, TAI)] 孕妇流产率及早产率的影响。方法 计算机检索 Pubmed、Cochrane、中国生物医学文献数据库、CNKI、维普、万方等中英文数据库, 系统性搜索口服左旋甲状腺素片治疗 TAI 孕妇的相关研究, 检索时限为建库至 2020 年 8 月。由 2 名研究者独立筛选文献、提取资料 and 评价纳入研究的偏倚风险, 采用 Revman5.3 软件进行 meta 分析。结果 ①本研究最终纳入 6 篇文献, 均为随机对照试验 (randomized controlled trial, RCT) 研究, 共计 1427 例患者; ②与对照组相比, 口服左旋甲状腺素片不能降低 TAI 孕妇的早产率和流产率; ③进一步按照受孕方式将数据进行亚组分析后显示, 自然妊娠的 TAI 孕妇口服左旋甲状腺素片可有效降低早产率 ( $RR=0.54$ ,  $95\% CI=0.31\sim0.95$ ,  $P=0.03$ ), 但不能降低孕妇流产率 ( $RR=0.86$ ,  $95\% CI=0.69\sim1.06$ ,  $P=0.15$ )。辅助生殖受孕的 TAI 孕妇口服左旋甲状腺素片不能降低流产率 ( $RR=0.80$ ,  $95\% CI=0.47\sim1.36$ ,  $P=0.41$ )。结论 口服左旋甲状腺素片不能降低 TAI 孕妇的流产率, 但可以降低自然受孕的 TAI 孕妇早产的风险, 无法评价是否能降低辅助生殖受孕的 TAI 孕妇早产率。因此自然受孕的 TAI 妇女孕期可以起始予  $25\sim50\mu g/d$  的左旋甲状腺素片治疗, 而辅助生殖受孕的 TAI 妇女口服左旋甲状腺素片不能获益。建议临床上将两组患者分开管理, 并告知患者治疗的局限性, 避免过高的期望值。

**【关键词】** 碘化物过氧化物酶; 自身抗体; 流产; 早产

# Effect of levothyroxine on abortion rate and preterm birth rate in pregnant women with thyroid autoimmunity and normal thyroid function: a systematic review and meta-analysis

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**【Abstract】 Objective** To evaluate the efficacy of oral levothyroxine on abortion rate and preterm birth rate in pregnant women with thyroid autoimmunity (TAI) and normal thyroid function. **Methods** The relevant studies of oral levothyroxine tablets in the treatment of TAI pregnant women were systematically searched in Pubmed, Cochrane, CBM, CNKI, VIP and Wanfang databases. The retrieval period was established until August 2020. Two researchers independently screened the literatures, extracted the data and evaluated the risk of bias in the included study. Meta-analysis was performed using Revman5.3 software. **Results** 1) Totally six eligible studies were all randomized controlled studies, involving 1427 patients. 2) Compared with control group, the meta-analysis suggests oral levothyroxine tablets cannot effectively reduce the preterm delivery rate and the abortion rate. 3) Further subgroup analysis of the data according to the natural pregnancy group and assisted reproduction group found that oral levothyroxine tablets in natural pregnancy women with TAI can effectively reduce the preterm delivery rate ( $RR=0.54$ ,  $95\% CI=0.31\sim0.95$ ,  $P=0.03$ ), but not reduce the abortion rate

( $RR=0.86$ , 95%  $CI=0.69-1.06$ ,  $P=0.15$ ). However, oral levothyroxine tablets cannot reduce the abortion rate for TAI women conceived by reproductive technology ( $RR=0.80$ , 95%  $CI=0.47-1.36$ ,  $P=0.41$ ). **Conclusion** Oral levothyroxine tablets can effectively reduce the premature delivery rate of TAI women who are naturally pregnant, but it is not beneficial to reduce the abortion rate. There is only one study on TAI women who are pregnant with reproductive technology, so it is impossible to evaluate whether this population can benefit from taking levothyroxine tablets. In view of the above results, it is recommended that the two groups of patients be managed separately.

**【Key words】** Thyroid peroxidase; Autoantibody; Miscarriage; Premature delivery

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·临床报道·

## 中、重度卵巢过度刺激综合征患者取卵与解冻移植间隔时间对妊娠结局的影响

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**【摘要】** 目的 探讨中、重度卵巢过度刺激综合征患者取卵术后最佳解冻移植时间。方法 回顾性队列研究分析 2017 年 1 月至 2019 年 12 月期间在西北妇女儿童医院生殖中心第一次行取卵术且术后因中、重度卵巢过度刺激综合征行全胚冷冻患者的临床资料。按取卵术与解冻移植间隔时间分为 3 组, A 组: 间隔 1 个月; B 组: 间隔 2 个月; C 组: 间隔 $\geq 3$  个月。主要观察指标为活产率, 次要观察指标为生化妊娠率、临床妊娠率、胚胎种植率、异位妊娠率、流产率、早产率及出生缺陷率。采用卡方检验比较各项指标组间差异。结果 B 组活产率为 70.27% (26/37), 高于 A 组 [58.62% (17/29)] 和 C 组 [52.27% (23/44)], 但三组间比较差异无统计学意义 ( $P=0.667$ ); A 组流产率 [0% (0/18)] 显著低于 C 组 [25.81% (8/31)],

$P=0.017$ ]; 三组间生化妊娠率、临床妊娠率、胚胎种植率、异位妊娠率、早产率及出生缺陷率组间比较差异均无统计学意义 (均  $P>0.05$ )。结论 中、重度卵巢过度刺激综合征患者取卵术后解冻移植间隔时间对妊娠结局无影响。

【关键词】 受精, 体外; 胚胎移植; 卵巢过度刺激综合征; 解冻移植; 妊娠结局

## Effect of different intervals between oocyte retrieval and frozen-thawed embryo transfer in pregnancy outcome in patients with moderate and severe ovarian hyperstimulation syndrome

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**【Abstract】 Objective** To investigate the pregnancy outcomes of different intervals between oocyte retrieval and frozen-thawed embryo transfer (FET) in moderate and severe ovarian hyperstimulation syndrome (OHSS) patients. **Methods** Clinical data of infertile patients who underwent their first *in vitro* fertilization-embryo transfer (IVF-ET) and froze all their embryos for moderate or severe OHSS from January 2017 to December 2018 in the ART Center, Northwest Women's & Children's Hospital were analyzed retrospectively. All patients were divided into three groups according to the interval between oocyte retrieval and FET. Group A: one month interval; group B: two months interval; group C: the interval was three months or above. Main outcome was live birth rate; secondary outcomes included biochemical pregnancy rate, clinical pregnancy rate, implantation rate, ectopic pregnancy rate, miscarriage rate, preterm birth rate and birth defect rate. Chi square test was performed to compare the differences of the outcomes among the three groups. **Results** The live birth rate of group B [70.27% (26/37)] was higher than that of group A [58.62% (17/29)] and group C [52.27% (23/44)], but the difference was not statistically significant ( $P=0.667$ ). The miscarriage rate of group A [0% (0/18)] was significantly lower than that of group C [25.81% (8/31),  $P=0.017$ ]. There were no significant differences among the three groups in biochemical pregnancy rate, implantation rate, ectopic pregnancy rate, preterm birth rate and birth defect rate (all  $P>0.05$ ). **Conclusion** The interval between oocyte retrieval and FET in moderate and severe OHSS patients does not impact pregnancy outcome.

**【 Key words 】** Fertilization *in vitro*; Embryo transfer; Ovarian hyperstimulation syndrome; Frozen-thawed embryo transfer; Pregnancy outcome

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## 蜡样透明带卵母细胞患者临床助孕结局分析

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**【摘要】** 目的 探讨蜡样透明带卵母细胞与正常形态卵母细胞临床助孕结局的差异。方法 回顾性队列研究分析 2015 年 1 月至 2019 年 12 月期间在南京医科大学第一附属医院生殖医学中心行辅助生殖助孕的 93 个卵胞质内单精子注射 (intracytoplasmic sperm injection, ICSI) 周期, 根据卵母细胞的形态和授精方式分为三组: 正常形态卵母细胞组 (A 组,  $n=52$ ), 蜡样透明带卵母细胞常规 ICSI 组 (B 组,  $n=30$ ); 蜡样透明带卵母细胞补救 ICSI 组 (C 组,  $n=11$ )。比较三组间的实验室和临床结局。结果 三组的获卵率、正常受精率、临床妊娠率、种植率差异均没有统计学意义 (均  $P>0.05$ )。A、B 组的优质胚胎率 [62.50% (250/400), 59.07% (114/193)] 均高于 C 组 [40.85% (29/71)], 差异有统计学意义 ( $P=0.001$ ,  $P=0.006$ )。A 组的囊胚形成率 [64.78% (160/247)] 高于 C 组 [37.14% (13/35)], 差异有统计学意义 ( $P=0.002$ )。另外, A 组的流产率 [2.44% (1/41)] 低于 B 组和 C 组 [21.05% (4/19),  $P=0.031$ ; 44.44% (4/9),  $P=0.002$ ], 累积妊娠率 [82.69% (43/52)] 高于 B 组和 C 组 [56.67% (17/30),  $P=0.009$ ; 45.45% (5/11),  $P=0.014$ ], 差异有统计学意义。结论 蜡样透明带样的卵母细胞采用常规 ICSI 授精可获得与正常形态卵母细胞相当的优质胚胎率和囊胚形成率, 但总体的临床结局仍低于正常形态卵母细胞。建议蜡样透明带的异常卵母细胞直接采用 ICSI 授精方式, 可以获得较为理想的临床结局。

**【关键词】** 精子注射, 细胞质内; 胚胎发育; 蜡样透明带卵母细胞; 累积妊娠率

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### Clinical outcome analysis of patients with indented zona pellucida oocytes

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**【Abstract】 Objective** To explore the difference of embryological and clinical outcomes between the oocytes with indented zona pellucida and normal morphology. **Methods** A retrospective cohort study was conducted on 93 cycles

treated with intracytoplasmic sperm injection (ICSI) in the Clinical Reproductive Medicine Center of the First Affiliated Hospital of Nanjing Medical University from January 2015 to December 2019. According to the morphology of oocytes and the methods of fertilization, the cycles were divided into three groups, normal oocytes with traditional ICSI group (group A,  $n=52$ ), indented zona pellucida oocytes with traditional ICSI group (group B,  $n=30$ ), and indented zona pellucida oocytes with rescue ICSI group (group C,  $n=11$ ). Laboratory and clinical results were compared among the three groups. **Results** There were no differences in oocytes retrieved rate, normal fertility rate, clinical pregnancy rate and implantation rate among the three groups (all  $P>0.05$ ). The good-quality embryo rate in groups A [62.50% (250/400)] and B [59.07% (114/193)] was significantly higher than that in group C [40.85% (29/71);  $P=0.001$ ,  $P=0.006$ ] and blastocyst formation rate in group A [64.78% (160/247)] was significantly higher than that in group C [37.14% (13/35),  $P=0.002$ ]. Otherwise, the abortion rate in group A [2.44% (1/41)] was significantly lower than that in groups B and C [21.05% (4/19),  $P=0.031$ ; 44.44% (4/9),  $P=0.002$ ] and the cumulative pregnancy rate in group A [82.69% (43/52)] was comparatively higher than that in groups B and C [56.67% (17/30),  $P=0.009$ ; 45.45% (5/11),  $P=0.014$ ]. **Conclusion** Traditional ICSI insemination of the indented pellucida oocytes showed the similar results of good-quality embryo rate and blastocyst formation rate with that of normal oocytes, but the overall clinical outcome was lower than that of normal oocytes. Abnormal oocytes of zona pellucida should be inseminated by ICSI directly, which can obtain better clinical outcome.

**【Key words】** Sperm injections, intracytoplasmic; Embryonic development; Indented zona pellucida oocytes; Cumulative pregnancy rate

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·现场调查·

## 不孕女性心理弹性的潜在类别分析

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**【摘要】** 目的 探讨不孕女性心理弹性的分类特点，并分析各类别在文化程度、不孕类型等人口学和疾病相关变量上的分布差异。方法 通过方便抽样的方法，采用横断面调查法于2019年9月至2020年12月期间对苏州大学附属第一医院生殖医学中心400例不孕女性采用心理弹性量表（CD-RISC-10）进行评估，对其心理弹性进行潜在类别分析，并采用多元logistic回归分析不同类别的人口学和疾病相关特征。结果 不孕女性的心理弹性可以分为“低弹性组”（记为C1组），“高弹性组”（记为C2组）和“中等弹性-低力量组”（记为C3组）三个类别，人数分别占总人数的21.8%（87/400）、37.5%（150/400）和40.7%（163/400）。多元logistic回归分析显示，C1组与C2组在结婚年限、不孕类型和有无恐惧或无助感的差异上均有统计学意义（“<3.0年”比“≥7.0年”， $P=0.019$ ； $P=0.045$ ； $P=0.015$ ）；C1组与C3组在结婚年限上差异有显著统计学意义（“<3.0年”比“≥7.0年”， $P=0.039$ ；“3.0~4.9年”比“≥7.0年”， $P=0.024$ ）；C2组与C3组在文化程度上差异有统计学意义（“高中或中专”比“本科及以上”， $P=0.003$ ；“大专”比“本科及以上”， $P=0.030$ ）。结论 不孕女性的心理弹性状况具有明显的亚类特征，不同弹性类别的不孕女性在文化程度、结婚年限、不孕类型和有无恐惧或无助的分布上存在差异。应及时关注文化程度低、结婚时间较短、原发性不孕、经历过强烈恐惧或无助感的不孕女性，采用合理干预以提高其心理弹性。

**【关键词】** 不孕症； 心理弹性； 潜在类别

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## Resilience status of infertile women: a latent class analysis

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**【Abstract】 Objective** To explore the classification characteristics of the resilience of infertile women, and to analyze the distribution differences of each category in demographic and disease-related variables such as education level and type of infertility. **Methods** Using convenient sampling method and cross-sectional survey, 400 infertile women in the Reproductive Medicine Center of the First Affiliated Hospital of Soochow University were assessed with the scale CD-RISC-10

from September 2019 to December 2020. The potential categories of resilience were analyzed, and then multivariate logistic regression was used to analyze the demographic and disease-related characteristics of different categories. **Results** The resilience of infertile women can be divided into 3 potential categories: "low tenacity class" (group C1), "high tenacity class" (group C2) and "general resilience but low strength class" (group C3), accounting for 21.8% (87/400), 37.5% (150/400) and 41.8% (163/400) of the total respectively. Multivariate logistic regression analysis showed that there were significant differences in marriage duration type of infertility and the sense of fear or helplessness between group C1 and group C2 (<3.0 years vs. ≥7.0 years,  $P=0.019$ ;  $P=0.045$ ;  $P=0.015$ ); there was a significant difference in marriage duration between group C1 and group C3 (<3.0 years vs. ≥7.0 years,  $P=0.039$ ; 3.0–4.9 years vs. ≥7.0 years,  $P=0.024$ ); there was a significant difference in education level between group C2 and group C3 (Junior high school or technical secondary school vs. Bachelor degree or above,  $P=0.003$ ; Junior college vs. Bachelor degree or above,  $P=0.030$ ). **Conclusion** The resilience of infertile women has obvious sub category characteristics. There are differences in the distribution of education level, marriage duration type of infertility and the sense of fear or helplessness among different groups of infertile women. We should pay attention to the infertile women with low education level, short marriage time, primary infertility, strong sense of fear or helplessness, and adopt reasonable intervention to improve their resilience.

**【Key words】** Infertility; Resilience; Latent class analysis

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·综述·

## 子宫内膜异位症对子宫内膜容受性的影响新进展

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**【摘要】** 胚胎植入失败是目前辅助生殖技术面临的难题, 而子宫内膜容受性又是影响胚胎成功着床的关键因素。尽管目前对子宫内膜在健康和疾病方面的研究

取得了很大的进展,子宫内膜容受性的调控机制仍不完全清楚。许多临床证据表明子宫内膜异位症是育龄女性不孕的主要原因之一,然而子宫内膜异位症通过影响子宫内膜容受性并导致不孕的机理仍有待进一步阐述。本文将对国内外有关妊娠早期子宫内膜异位症对子宫内膜容受性影响的最新进展作一简要概述。

【关键词】 子宫内膜; 子宫内膜异位症; 基因表达; 胚胎着床

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## New progress in the influence of endometriosis on endometrial receptivity

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【Abstract】 Failure in embryo implantation is a common issue in assisted reproduction technology, and establishment of endometrial receptivity plays a critical role in the process of embryo implantation. Although it was extensively studied in the endometrial physiology, the molecular mechanism underlying regulation of endometrial receptivity remains elusive. Ample clinical evidence suggests that endometriosis is closely associated with female infertility in reproductive age, it is still unclear how endometriosis adversely affects endometrial receptivity that leads to failure in embryo implantation. This literature review is mainly focusing on recent progress on adverse effect of the endometriosis on endometrial receptivity during early pregnancy.

【Key words】 Endometrium; Endometriosis; Gene expression; Embryo implantation

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·综述·

## 宫腔液细胞外囊泡在子宫内膜容受性中的研究进展

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【摘要】 子宫内膜容受性是指子宫内膜允许囊胚定位、黏附、穿透、植入从而促进胚胎着床、发育的能力。种植期子宫内膜的特征以及子宫内膜容受性标志物一直以来都是研究热点，尽管已经取得了较大进展，但仍缺乏公认的预测临床妊娠的标志物。已有研究显示，抽吸宫腔液对胚胎种植过程没有负面影响，宫腔液检查可作为无创检测的一种手段；同时宫腔液中含有细胞外囊泡，细胞外囊泡中 miRNA、蛋白质、DNA 及脂质在卵泡发育成熟、胚胎发育及着床等生殖过程中起重要作用，将来有望成为子宫内膜容受性标志物并作为治疗靶点。本文将对宫腔液细胞外囊泡在子宫内膜容受性中的研究进展进行综述。

【关键词】 子宫内膜容受性； 宫腔液； 细胞外囊泡； 胚胎着床

## Research progress of uterine fluid extracellular vesicles in endometrial receptivity

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【Abstract】 Endometrial receptivity refers to the ability of the endometrium to allow blastocyst location, adhesion, penetration, implantation, and to promote embryo implantation and development. The study of endometrial characteristics during implantation to find markers of endometrial receptivity has long been a hot topic of research. Although progress has been made, there is still a lack of recognized markers for predicting clinical pregnancy. Recent studies have shown that aspiration of uterine fluid has no negative effect on embryo implantation and can be studied as a non-invasive test. At the same time, it was found that there were extracellular vesicles in uterine fluid, in which miRNA, protein, DNA and lipid play an important role in the reproductive process of follicle development and maturation, embryo development and implantation, etc., and it is expected to be used as endometrial receptivity markers and therapeutic targets in the future. In this article, we will review the research progress of uterine fluid extracellular vesicles in the evaluation of endometrial receptivity.

【Key words】 Endometrial receptivity; Uterine fluid; Extracellular vesicles; Embryo implantation

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·综述·

## 单纯男方 HIV 阳性夫妇的自然备孕与辅助生殖技术助孕

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**【摘要】** 随着长期有效的抗逆转录病毒治疗 (highly active antiretroviral therapy, HAART) 不但显著地改善了人类免疫缺陷病毒 (human immunodeficiency virus, HIV) 感染男性的生存预期, 而且明显降低了性接触传染的风险性。暴露前预防 (pre-exposure prophylaxis, PrEP) 和易孕期定时精准合房, 明显提高了 HIV 非感染女性伴侣对性传播感染的预防效果, 已经证明是单纯男方 HIV 阳性夫妇自然受孕的有效方式。利用 HIV 感染男性的处理后的精子进行辅助生殖助孕, 目前并没有发现女方或子代的感染, 是单纯男方 HIV 阳性夫妇在生殖能力下降时的首选治疗手段。HIV 感染者的生活质量与生育愿望不能被忽视。

**【关键词】** 人类免疫缺陷病毒; 暴露前预防; 生殖技术, 辅助; 自然妊娠; 定时合房; 性接触传染

# **Natural conception and conception with assisted reproductive technique for male only HIV positive couples**

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**【Abstract】** With the implement of long-term effective highly active antiretroviral therapy (HAART), it not only significantly improves the survival expectation of HIV-infected men, but also significantly reduces the risk of sexually transmitted infections. The combination of pre-exposure prophylaxis (PrEP) and precisely timed intercourse during easy pregnancy period significantly improves the prevention of HIV non-infected female partners from sexually transmitted infection, and has proved to be an effective way for male only HIV positive couples to conceive naturally. Using processed semen of HIV-infected men for assisted reproduction treatment, no female partner or children infection is found, which is the preferred treatment for male only HIV positive couples with decreased fertility. The quality of life and fertility desires of HIV infected people cannot be ignored.

**【Key words】** Human immunodeficiency virus; Pre-exposure prophylaxis; Reproductive technique, assisted; Natural conception; Timed intercourse; Sexually transmitted infections

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# 雄激素不敏感综合征研究进展

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**【摘要】** 雄激素不敏感综合征 (androgen insensitivity syndrome, AIS) 是一种先天性生殖器发育畸形的特殊疾病, 由染色体 Xq11-12 上的雄激素受体发生功能异常导致。近年来对雄激素受体新突变报道中显示, 同一位点突变可导致不同的疾病表型, 除去外显子突变外, 内含子剪切位点突变对受体功能亦可产生影响。治疗上, 性腺切除时机存在争议, 对于希望保留性腺的患者, 建议进行定期筛查。由于样本案例少及其特殊临床表现与治疗方式, 本疾病需要引起人们的关注。本文从发病机制、临床表现、治疗及预后几个方面对此疾病进行总结, 促进对 AIS 的诊疗。

**【关键词】** 雄激素不敏感综合征; 性发育障碍; 雄激素受体; 基因突变

## Research progress of androgen insensitivity syndrome

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**【Abstract】** Androgen insensitivity syndrome (AIS) is a special disease of congenital malformations of genital development. It is caused by the abnormal function of the androgen receptor on chromosome Xq11-12. In recent years, reports of new mutations in the androgen receptor have found that mutations at the same site can lead to different disease phenotypes. In addition to exon mutations, mutations at intron splicing sites can also affect receptor function. In terms of treatment, the timing of gonadal resection is controversial. For patients who wish to preserve their gonads, regular screening is recommended. Due to the small number of sample cases and its special clinical manifestations and treatment methods, this disease needs to arouse people's attention. This article summarizes the disease from several aspects of pathogenesis, clinical manifestations, treatment and prognosis, and promotes the diagnosis and treatment of AIS.

**【Key words】** Androgen insensitivity syndrome; Disorder of sex development; Androgen receptor; Gene mutation

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·综述·

## 卵巢储备功能下降小鼠模型研究进展

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**【摘要】** 卵巢储备功能下降(decreased ovarian reserve, DOR)损害女性身心健康。因伦理原因, 难以对人体卵巢组织进行研究, 构建DOR动物模型是解决这一难题的办法。构造DOR动物模型有助于研究其病理生理及探索治疗措施。目前构建小鼠DOR模型的方法主要有: 使用药物(化疗药物、干扰代谢类药物、免疫调节剂等)、射线照射、基因工程、环境毒物损伤等, 这些造模方法各具特点, 其中注射化疗药物环磷酰胺是建立DOR小鼠模型的一种较好的方法, 具有操作简单、经济、周期快、效果确切、易重复、卵巢损伤程度可控的优点。本文对DOR小鼠常用建模方法的原理及特点进行综述。

**【关键词】** 卵巢储备功能下降; 模型; 动物; 小鼠; 环磷酰胺

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### Research progress on the model of decreased ovarian reserve in mice

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**【Abstract】** Decreased ovarian reserve (DOR) impairs the physical and mental health of women. It is difficult to obtain the ovary of human for research due to ethical reason. Construction of animal model of DOR may handle the problem. Research on animal model of DOR is useful to explore the pathophysiology and

treatment of DOR. There are several mouse models of DOR with its individual characteristics, including drug model (chemotherapeutic drugs, metabolic drugs, immunomodulators), radiation exposure model, genetic engineering model and environmental toxicant exposure model. The better mouse model of DOR is conducted by injection of cyclophosphamide, with the following advantages: simple, economic, efficient, effective, repeatable and controllable. In this paper, the principles and characteristics of commonly used mouse model of DOR were reviewed.

**【 Key words 】** Decreased ovarian reserve; Models; Animal; Mice; Cyclophosphamide

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