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霍莹 覃清圆 卢翠玲 宋雪凌 郑晓英 于洋 闫丽盈 廉颖 刘平 李蓉 严杰 乔杰
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【摘要】 目的 探索玻璃化冷冻保存技术对体外成熟（*in vitro* maturation，IVM）卵母细胞发育潜能和转录组的影响。**方法** 选择 2014 年 9 月—2016 年 3 月期间在北京大学第三医院生殖医学中心接受腹腔镜手术联合经阴道穿刺取卵行卵母细胞 IVM 治疗的不孕症患者为研究对象进行前瞻性队列研究，将研究对象分为 IVM 组（A 组，*n*=13）和 IVM- 冻卵组（B 组，*n*=24）。分析卵母细胞的早期胚胎发育状况和单细胞水平的转录组学情况。**结果** IVM 后玻璃化冷冻 - 解冻对存活卵母细胞的早期胚胎发育没有明显影响，受精率、卵裂率、优质胚胎率和可移植胚胎率组间差异均无统计学意义。但 IVM 后行玻璃化冷冻 - 解冻对转录组存在一定影响，与 A 组相比，B 组共有 1 913 个基因呈现差异表达，其中 570 个基因表达量升高，主要富集到 59 个生物学过程；1 343 个基因表达量降低，主要富集到 140 个生物学过程，而且一些差异基因参与了卵母细胞质量、受精和胚胎发育潜能的调控。**结论** IVM 后行玻璃化冷冻 - 解冻对早期胚胎发育没有明显影响，但对转录组具有一定影响，且发生表达量变化的基因与卵母细胞质量、受精和胚胎发育潜能有关，提示玻璃化冷冻 - 解冻有可能影响子代安全性。

【关键词】 体外成熟（IVM）；卵母细胞；玻璃化冷冻；早期胚胎发育；转录组

基金项目： 国家重点研发计划（2017YFC1002002）；国家自然科学基金（81571386，31230047，31429004）；中华医学会临床医学科研专项基金（16020280644）

·生育力保存·

Effects of vitrification on the development potential and transcriptome of human oocyte matured *in vitro*

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【**Abstract**】 **Objective** To investigate the effect of vitrification on the development potential and transcriptome of *in vitro* matured human oocytes. **Methods** This is a prospective cohort study. The infertility patients treated by laparoscopic surgery combined with *in vitro* maturation (IVM) treatment were analyzed in Center for Reproductive Medicine of Peking University Third Hospital, between September 2014 and March 2016. The research subjects were divided into two groups: IVM group (group A, *n*=13) and IVM-vitrification group (group B, *n*=24). The early embryonic development and transcriptome at the single cell level of the oocytes from two groups were compared and analyzed. **Results** The process of oocytes vitrification-thawing after IVM had no significant effect on the early embryonic development. There was no significant difference in survival oocyte fertilization rate, cleavage rate, advanced embryo rate and transferable embryo rate between the two groups. However, vitrification-thawing after IVM had a certain effect on transcriptome. Compared with group A, 1 913 genes in group B showed differential expression, of which 570 genes were upregulated and mainly enriched to 59 biological processes while 1 343 genes were downregulated and mainly enriched to 140 biological processes. Furthermore, some differentially expressed genes and their related biological processes were involved in the regulation of oocyte quality, fertilization and embryonic development potential. **Conclusion** The process of oocyte vitrification-thawing after IVM had no significant effect on early embryonic development, but had some effects on transcriptome. These changed genes were related to oocyte quality, fertilization and embryo development potential, suggesting that vitrification-thawing may affect the offspring safety.

【**Key words**】 *In vitro* maturation (IVM); Oocyte; Vitrification; Early embryonic development; Transcriptome

Fund program: National Key Technology R&D Program of China (2017YFC1002002); National Natural Science Foundation of China (81571386, 31230047, 31429004); Special Fund for Clinical Research of Chinese Medical Association (16020280644)

·生育力保存·

卵子玻璃化冷冻在辅助生殖技术治疗中的临床应用

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【摘要】目的　探讨卵子冷冻以及冻卵冻胚 (卵裂胚及囊胚) 双次冷冻在辅助生殖技术 (ART) 中临床应用的安全性和可行性。**方法**　回顾性分析 2014 年 1 月—2017 年 12 月期间行卵子玻璃化冷冻，随后解冻并后续培养移植共 164 个周期，其中新鲜胚胎移植组解冻卵 88 个周期，冻融胚胎移植卵裂胚组冻卵冻胚 40 个周期，冻融胚胎移植囊胚组冻卵冻囊胚 36 个周期，并分别以同期未行卵子冷冻的新鲜胚胎 (*n*=1 480)、解冻胚胎 (*n*=246)、解冻囊胚 (*n*=304) 移植作为对照，比较卵子受精率、卵裂率及可利用胚胎率，以及各组的复苏率、后续的着床率、临床妊娠率、早期流产率、活产率等指标。**结果**　解冻卵复苏存活率为 [94.00%(999/1 063)]。解冻卵受精率 [84.00%(838/999)] 优于新鲜卵子受精率 [72.67%(10 703/14 729)]，组间差异有统计学意义 (*P*=0.00)，第 3 日可利用胚胎率、冻融后存活率、着床率、临床妊娠率、早期流产率、活产率差异均无统计学意义 (*P*>0.05)。**结论**　卵子冷冻不会降低卵子的发育潜能，冷冻后可获得比较满意的复苏效果，行卵胞质内单精子显微注射 (ICSI) 仍可获得较好的妊娠和活产结局，对于需要保存生育力的女性来说卵子冷冻是一种较为安全有效的方法。

【关键词】卵子冷冻；体外受精 (IVF) 结局；生育力保存

基金项目：生殖医学国家重点实验室创新基金项目 (SKLRM-GC201804)

·生育力保存·

Clinical application of egg vitrification on assisted reproductive technology therapy

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【**Abstract**】 **Objective** To investigate the safety and feasibility of egg vitrification and refrozen embryo in assisted reproductive technology (ART). **Methods** Patients with intracytoplasmic sperm injection (ICSI) treatment in our hospital from January 2014 to December 2017 were retrospectively analyzed. The thawing egg cycles (n=164, including 88 cycles with frozen eggs, 40 cycles with refrozen embryos, 36 cycles with refrozen blastocyst) were compared with fresh egg cycles in the same period, to get the index of survival rate, fertilization rate, available embryo rate, and subsequent implantation and pregnancy outcomes. **Results** Survival rate of thawing eggs was 94.00%. The fertilization rate of thawing eggs (84.00%) was significantly higher than that of fresh eggs (72.67%) (P=0.00). And there were no statistical differences in available embryo rate of day 3, embryo survival rate, implantation rate, clinical pregnancy rate, early abortion rate and live birth rate (P>0.05). **Conclusion** Egg vitrification does not reduce the development potential of the embryo. Frozen eggs can achieve a satisfactory recovery results, with good pregnancy outcomes. In conclusion, for women who need to preserve fertility, egg vitrification is a relatively safe and effective method.

·生育力保存·

女性霍奇金淋巴瘤患者分别应用卵巢组织冷冻和体外成熟卵子进行卵子冷冻——1 例报告

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【摘要】 目的　探讨女性血液肿瘤患者生育力保存的方法。**方法**　分析 1 例未婚霍奇金淋巴瘤患者通过卵巢组织冷冻并在体外获得成熟卵母细胞后行卵子冷冻的病例并进行文献复习。**结果**　未婚霍奇金淋巴瘤患者可通过卵母细胞体外成熟 (IVM) 技术行卵母细胞冷冻，同时结合卵巢组织冷冻技术来尽快完成生育力保存。**结论**　对于急切需要接受抗肿瘤治疗的肿瘤患者，可通过卵母细胞 IVM 技术在最短的时间内进行卵母细胞或胚胎冷冻，同时结合卵巢组织冷冻技术在最大程度上达到生育力保存的目的。

【关键词】霍奇金淋巴瘤；生育力保存；卵巢组织冷冻；体外成熟 (IVM)

基金项目：国家自然科学基金 (81200476，81601347，81503156)；广东省自然基金面上项目 (2014A030313039)；广东省科技项目 (2016A020218006)

·生育力保存·

Combination of ovarian tissue cryopreservation and oocytes maturated *in vitro* for fertility preservation used in female patients with Hodgkin lymphoma: 1 case analysis

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【**Abstract**】 **Objective** To investigate the fertility preservation strategy choice of female patients with hematologic malignancies. **Methods** A case about a single female with Hodgkin lymphoma (HL) received fertility preservation by ovarian tissue frozen and oocyte maturated *in vitro* which aspirated just before ovarian tissue cryopreservation was reported and the literatures were reviewed. **Results** Combined ovarian tissue cryopreservation with retrieval of immature oocytes followed by *in vitro* maturation (IVM) was recommended for patients with HL who required urgent treatment for fertility preservation. **Conclusion** The fertility preservation strategy choice of combining ovarian tissue cryopreservation with retrieval of immature oocytes followed by IVM is recommended for patients with HL who require urgent anticancer therapy, which can ensure the patient achieve the cryopreservation of matured oocytes and embryo in a short time, to the greatest extent.

【**Key words**】 Hodgkin lymphoma (HL); Fertility preservation; Ovarian tissue cryopreservation; *In vitro* maturation (IVM)

Fund program: National Natural Science Foundation of China (81200476, 81601347, 81503156); Natural Science Foundation of Guangdong Province (2014A030313039); Science Foundation of Guangdong Province (2016A020218006)

·生育力保存·

人类卵母细胞冷冻保存技术的安全性及其临床应用

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【摘要】 随着冷冻技术的发展，特别是玻璃化冷冻技术的应用，卵母细胞冷冻技术越来越成熟，目前已成为辅助生殖技术重要的组成部分。本文从人卵母细胞冷冻方法、影响冷冻安全性因素、临床应用及临床安全性方面对人卵母细胞冷冻技术进行阐述与总结，以期指导其在临床的应用。

【关键词】卵母细胞；冷冻；生育力保存；安全性

·生育力保存·

Safety and clinical application of human oocytes cryopreservation

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【Abstract】 With the development of cryotechnology, especially the application of vitrification, oocyte cryopreservation has been a mature technology and plays an important role in assisted reproductive technology. To be better used in clinic, in this review, we elaborate on the following contents about oocytes cryopreservation: freezing methods, factors that influence freezing effects, clinic applications and clinical safety.

【Key words】 Oocytes; Cryopreservation; Fertility preservation; Safety

·生育力保存·

卵巢组织冷冻技术在女性生育力保存中的应用

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【摘要】 卵巢是雌性动物的重要生殖器官，富含许多不同发育阶段的卵泡，是一种天然的卵泡池。原始卵泡对冷冻保护剂的耐受性要高于生长卵泡，而卵巢皮质是原始卵泡的聚集地，因此卵巢皮质组织冷冻保存是一种更安全、有效、极具开发潜能的女性生育力保存方式。卵巢组织冷冻可以一次性保存大量的配子。然而，目前卵巢组织冷冻技术还是一个试验性的技术，临床应用面临很多困难和阻碍。本文将从卵巢组织冷冻技术、移植、临床应用及发展方向作一综述。

【关键词】卵巢组织；冷冻；生育力保存

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·生育力保存·

Progress in ovarian tissue cryopreservation in female fertility preservation

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【**Abstract**】 Ovary is an important reproductive organ of the female. It is a natural follicle pool which rich in many follicles at different developmental stages. Primitive follicles, which are concentrated in the ovarian cortex, are more tolerant to cryopreservation agent than growth follicles, so the cryopreservation of ovarian cortex tissue is a safer, effective and highly potential method for preserving female fertility. Ovarian tissue cryopreservation can preserve a large number of oocytes at one time. However, ovarian tissue cryopreservation is an experimental technology, and its clinical application is faced with many difficulties and obstacles. This article will focus on the technology and graft of ovarian tissue cryopreservation and its application and direction in female fertility preservation.

【**Key words**】 Ovarian tissue; Cryopreservation; Fertility preservation

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·生育力保存·

卵巢组织体外培养及冻融技术的研究进展

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【摘要】 癌症患者治疗前行卵巢组织冷冻保存、待其病情稳定后，重新进行卵巢组织移植，可使其保持女性的正常生殖内分泌功能，并能够进行正常生育。目前常用的冷冻方案包括慢速程序化冷冻和玻璃化冷冻，其中慢速程序化冷冻是卵巢组织冷冻的标准方法，但近年来玻璃化冷冻由于其方便、高效，越来越受到关注。卵巢组织冷冻保存作为癌症患者保留生育能力的一种选择具有广泛的应用前景。虽然卵巢组织移植已用于临床，并有成功分娩的报道，但卵巢组织体外培养技术尚处于研究阶段，仍不够成熟。本文旨在对卵巢组织体外培养及冻融技术的方法改进以及现阶段的研究情况作一综述。

【关键词】卵巢组织；冷冻保存；体外培养

·生育力保存·

Research progress of *in vitro* culture and freeze-thaw technology for ovarian tissue

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【**Abstract**】 Cryopreserving ovarian tissue before the cancer treatment and ovarian tissue retransplantation can maintain the normal reproductive endocrine function and fertility. At present, frequently used freezing programs include slow programmed freezing and vitrification freezing. Slow programmed freezing is the standard protocol, while vitrification has attracted more and more attention due to its convenience and efficiency in recent years. Ovarian tissue transplantation has been used clinically, and there are reports of successful delivery. Cryopreservation of ovarian tissue has a broad application prospect in clinic as a choice of fertility preservation for cancer patients. But the *in vitro* culture technology of ovarian tissue is immature, and it is still in the research stage. This article aims to review the improvement of the methods of *in vitro* culture for ovarian tissue and the freeze-thaw technology, as well as the current research.

【**Key words**】 Ovarian tissue; Cryopreservation; *In vitro* culture

·临床研究·

不同卵巢储备患者促性腺激素受体表达及影响因素分析

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【摘要】 目的 探讨不同卵巢储备女性颗粒细胞促卵泡激素受体 (FSHR)、促黄体生成素受体 (LHR) mRNA 相对表达水平与获卵情况的关系，以及与其他促排卵治疗过程中相关指标的影响。**方法** 收集 850 例患者卵泡液及颗粒细胞。纳入患者分为卵巢功能正常组 (*n*=419)、预期低反应组 (*n*=255)、多囊卵巢综合征 (PCOS) 组 (*n*=176)。采用反转录 - 实时定量 PCR(qRT-PCR) 法测定 *FSHR*、*LHR*、抗苗勒管激素 (AMH) 及 AMH Ⅱ型受体 (AMHR Ⅱ) mRNA 的表达，分析以上指标在不同卵巢储备患者中表达差异及影响因素。**结果** ① 3 组患者在年龄、体质量指数 (BMI)、窦卵泡数 (AFC)、基础激素水平、用药情况、*FSHR* mRNA 及获卵数等方面差异均有统计学意义 (*P*<0.05)。② PCOS 组促排卵后卵巢高反应患者 *FSHR* mRNA 表达量低于正常反应患者 (*P*<0.05)。③ 对卵巢功能正常组患者 *FSHR* mRNA 主要与 *AMH* mRNA(*r*=0.404，*P*<0.001)、*LHR* mRNA(*r*=0.388，*P*<0.001) 呈正相关，预期低反应组患者 *FSHR* mRNA 主要与 LHR(*r*=0.415，*P*<0.001) 呈正相关，PCOS 患者 *FSHR* mRNA 主要与 *AMHR* Ⅱ mRNA(*r*=0.311，*P*<0.001) 呈正相关。**结论** 不同卵巢储备患者促性腺激素 (Gn) 受体表达量存在差异，且 Gn 受体与 *AMH* mRNA 表达具有显著相关性，可能与卵巢储备异常发病机制相关，临床 Gn 用药可参考 Gn 受体表达情况进行选择。

【关键词】 卵巢储备；促卵泡激素受体 (FSHR)；促黄体生成素受体 (LHR)；抗苗勒管激素 (AMH)；卵巢反应性

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·临床研究·

Expression of gonadotrophin receptor and influencing factors among different ovarian reserve patients

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【**Abstract**】 **Objective** To compare the relationship between the relative expression level of follicle stimulating hormone receptor (FSHR), luteinizing hormone receptor (LHR) mRNA and oocyte retrieve outcomes, and to explore influencing factors in female granulosa cells with different ovarian reserves. **Methods** Follicular fluid and granulosa cells of 850 women were collected, including normal ovarian function group (419 cases), expected low ovarian response group (255 cases) and polycystic ovary syndrome (PCOS) group (176 cases). The expression of *FSHR*, *LHR*, anti-Müllerian hormone (AMH) and AMH receptor (AMHR) Ⅱ mRNA were measured by quantitative Real-time polymerase chain reaction (qRT-PCR) and compared among different ovarian reserve patients. Influencing factors of these differentially expressed gonadotrophin (Gn) receptors were analyzed. **Results** 1) There were significant differences in age, body mass index (BMI), antral follicle count (AFC), basal hormone level, medication, *FSHR* mRNA and number of oocytes retrieved among the three groups (P<0.05). 2) The expression of *FSHR* mRNA in high ovarian response PCOS patients was lower than that in normal response PCOS patients (P<0.05). 3) In the normal ovarian function group, *FSHR* mRNA mainly positively correlated with the expression of *AMH* mRNA (r=0.404, P<0.001) and *LHR* mRNA (r=0.388, P<0.001). In expected low ovarian response group, *FSHR* mRNA mainly positively correlated with the expression of *LHR* mRNA (r=0.415, P<0.001). In PCOS group, *FSHR* mRNA mainly positively correlated with the expression of *AMHR* Ⅱ mRNA (r=0.311, P<0.001). **Conclusion** The different expression of Gn receptor in patients with different ovarian reserve was observed, and the expression of Gn receptor had a significant correlation with *AMH* mRNA. This result could be related to the pathogenesis of abnormal ovarian reserve, and provided reference for the clinical Gn medication according to the expression of Gn receptors.

【**Key words**】 Ovarian reserve; Follicle stimulating hormone receptor (FSHR); Luteinizing hormone receptor (LHR); Anti-Müllerian hormone (AMH); Ovarian response

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·临床研究·

减少胚胎移植数量对高龄妇女体外受精 - 胚胎移植临床结局的影响

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【摘要】 目的　探讨减少移植胚胎数量对于年龄≥ 35 岁妇女体外受精 - 胚胎移植 (*in vitro* fertilization and embryo transfer，IVF-ET) 临床结局的影响。**方法**　回顾性分析 2009 年 1 月—2015 年 12 月期间在本中心接受新鲜周期胚胎移植且年龄≥ 35 岁患者的临床资料，每名患者只纳入第一个取卵周期。取卵后第 3 日 (D3) 可移植胚胎数均 >3 个但选择移植 2 个胚胎者为研究组，共 2 361 个周期；按照 1 ∶ 1 对年龄、体质量指数 (BMI)、基础卵泡刺激素 (FSH) 水平等进行配比选择移植 3 个胚胎者为对照组，共计 2 361 个周期。比较研究组和对照组患者的基线数据和临床结局。根据女方年龄将研究组和对照组再分为 35~37 岁组、38~40 岁组和 >40 岁组，比较不同年龄亚组减少胚胎移植数量对临床结局的影响。**结果**　患者年龄、不孕年限、BMI、基础 FSH 水平、促性腺激素 (Gn) 用量、使用时间等组间差异均无统计学意义 (P>0.05)；研究组与对照组相比，临床妊娠率、活产率、流产率，差异均无统计学意义 (P>0.05)；研究组着床率 (13.55%) 显著高于对照组 (10.36%，P<0.001)；研究组多胎妊娠率 (19.18%)、异位妊娠率 (6.15%)、早产率 (13.62%) 均显著低于对照组 (24.56%、10.8%、24.7%；P=0.03、P=0.006、P=0.001)。研究组新生儿的胎龄 [(37.9±2.0) 周] 及平均出生体质量 [(3 110.9±653.9) g] 均显著大于对照组 [(37.3±2.4) 周，(2 957.7±656.1) g]，差异有统计学意义 (P=0.002，P=0.004)。在 35~37 岁组、38~40 岁组、>40 岁组中，研究组与对照组的临床妊娠率、活产率、流产率差异均无统计学意义 (P>0.05)，>40 岁研究组多胎妊娠率 (6.41%) 显著低于对照组 (18.18%，P=0.035)。**结论**　对于年龄≥ 35 岁妇女减少移植胚胎数量并不降低临床妊娠率和活产率，同时显著降低多胎妊娠率，改善妊娠结局。

【关键词】 体外受精 - 胚胎移植 (IVF-ET)；高龄；临床妊娠率；多胎妊娠率；活产率

·临床研究·

Influence of decreasing the number of embryos transferred on pregnancy outcomes in advanced age women undergoing *in vitro* fertilization-embryo transfer

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【**Abstract**】**Objective** To study the effect of decreasing the number of embryos transferred on pregnancy outcomes in women aged ≥ 35 years. **Methods** A retrospective study was performed in infertile women aged ≥ 35 years undergoing fresh transfer cycles, who were treated in our center between January 2009 and December 2015. After egg retrieval on day 3, the patients with more than 3 embryos who were transferred 2 embryos were defined as study group, which contained 2 361 cycles. Each IVF cycles were matched to the control cycles by age, body mass index (BMI) and basal follicle stimulating hormone (FSH) level. Control group which were transferred 3 embryos had a total of 2 361 cycles. The clinical outcomes in the two groups were analyzed and compared. The study and control groups were divided into three age groups, respectively, namely 35–37 years group, 38–40 years group, and >40 years group. The effect of decreasing the number of embryo transferred on pregnancy outcomes were compared between different age groups. **Results** There were no significantly differences in terms of patients age, duration of infertility, BMI, basal FSH level, total gonadotrophin (Gn) used dosage and Gn stimulation days (P>0.05). Between study group and control group, there were no major difference in the prevalence of clinical pregnancy rate, abortion rate and live birth rate (P>0.05). The incidence of implantation rate (13.55%) in study group was significantly higher than that in control group (10.36%, P<0.001). The prevalence of multiple pregnancy rate (19.18%), ectopic pregnancy rate (6.15%) and premature delivery rate (13.62%) in study group were evidently lower than those in control group (24.56%, 10.8%, 24.7%; P=0.03, P=0.006, P=0.001). The analysis of live born children's basic characteristic showed that the mean gestational age [(37.9±2.0) weeks] in study group was significantly longer than that in control group [(37.3±2.4) weeks, P=0.002]. The mean neonatal weight in study group [(3 110.9±653.9) g] was significantly heavier than that in control group [(2 957.7±656.1) g, P=0.004]. In patients aged 35–37 years, 38–40 years and >40 years, there were no significantly differences in clinical pregnancy rate, abortion rate and live birth rate between study group and control group (P>0.05). The prevalence of multiple pregnancy rate (6.41%) in study group was evidently lower than control group (18.18%, P=0.035). **Conclusion** For women ≥ 35 years old reducing the number of embryos transferred does not effect clinical pregnancy rate and live birth rate, but can reduce the occurrence of multiple pregnancy rate and improve the clinical outcome of the patients.

【**Key words**】 *In vitro* fertilization and embryo transfer (IVF-ET); Advanced age; Clinical pregnancy rate; Multiple pregnancy rate; Live birth rate

·临床研究·

人绒毛膜促性腺激素改善反复种植失败患者冻融周期子宫内膜厚度及血流的研究

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【摘要】 目的 探讨人绒毛膜促性腺激素 (hCG) 改善反复种植失败 (RIF) 患者冻融胚胎解冻移植周期 (FET) 子宫内膜容受性的作用效果。**方法** 对激素替代人工周期方案准备子宫内膜拟行 FET 的 RIF 患者进行前瞻性研究，随机分为 hCG 组 (*n*=275)，自月经周期第 7 日起肌内注射 hCG 150 IU/d 直至胚胎移植后第 6 日；对照组 (*n*=237)，自月经周期第 7 日起肌内注射等体积 0.9% 生理盐水直至胚胎移植后第 6 日。监测移植日子宫内膜厚度、子宫内膜血流分支、放射状动脉血流搏动指数 (PI) 与血流阻力指数 (RI)、基底区螺旋动脉 PI 与 RI，以及胚胎种植率和临床妊娠率。**结果** 移植日 hCG 组子宫内膜厚度 [(9.72±0.20) mm]、子宫内膜血流分支 [(5.1±1.6) 支] 高于对照组 [(9.35±0.18) mm，*P*=0.033；(4.8±1.3) 支，*P*=0.013]；放射状动脉 PI、放射状动脉 RI 组间差异无统计学意义 (*P*>0.05)；hCG 组基底区螺旋动脉 PI(1.03±0.17)、基底区螺旋动脉 RI(0.57±0.06) 均小于对照组 (1.15±0.20，*P*=0.000；0.62±0.07，*P*=0.000)，差异有统计学意义；hCG 组胚胎种植率 (38.66%) 和临床妊娠率 (61.40%) 均显著高于对照组 (30.48%，*P*=0.005；51.49%，*P*=0.025)。**结论** 对于 RIF 患者，在 FET 周期添加小剂量 hCG 是有益的。hCG 通过促进血管生成丰富子宫内膜的血流供应，从而增加子宫内膜厚度，提高胚胎种植率及临床妊娠率。

【关键词】 人绒毛膜促性腺激素 (hCG)；反复种植失败 (RIF)；冻融胚胎移植 (FET)；内膜厚度；内膜血流

·临床研究·

Study of human chorionic gonadotrophin in improving endometrial thickness and blood flow in recurrent implantation failure patients during frozen-thawed embryo transfer cycles

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【**Abstract**】 **Objective** To investigate the effect of human chorionic gonadotrophin (hCG) on improving endometrial receptivity in recurrent implantation failure (RIF) patients during frozen-thawed embryo transfer (FET). **Methods** A prospective study was carried out for RIF patients with hormone replacement manual cycle program during FET. The RIF patients were randomly divided into hCG group (n=275), in which hCG 150 IU/d was intramuscular injected from day 7 of menstrual cycle until day 6 after embryo transfer, and control group (n=237), in which intramuscular injection of an equal volume of 0.9% saline from day 7 of menstrual cycle until day 6 after embryo transfer. Endometrial thickness, endometrial blood flow branch, radial artery blood flow pulsatility index (PI) and blood flow resistance index (RI), basal area spiral artery blood flow PI and RI on day of embryo transfer, as well as embryo implantation rate and clinical pregnancy rate were compared between the two groups. **Results** Endometrial thickness [(9.72±0.20) mm] and endometrial blood flow branch (5.1±1.6) in hCG group were higher than those in control group [(9.35±0.18) mm, P=0.033; 4.8±1.3, P=0.013]. The radial artery blood flow PI and blood flow RI between the two groups was not statistically different (P>0.05). The basal area spiral artery blood flow PI (1.03±0.17) and RI (0.57±0.06) of hCG group were lower than that of control group (1.15±0.20, P=0.000; 0.62±0.07, P=0.000). The embryo implantation rate (38.66%) and clinical pregnancy rate (61.40%) in hCG group were significantly higher than those in control group (30.48%, P=0.005; 51.49%, P=0.025). **Conclusion** For RIF patients, small dosages of hCG addition during their FET was benifit. hCG enriches endometrial blood flow by promoting angiogenesis, and finally increase endometrial thickness, embryo implantation rate and clinical pregnancy rate.

【**Key words**】 Human chorionic gonadotrophin (hCG); Recurrent implantation failure (RIF); Frozen-thawed embryo transfer (FET); Endometrial thickness; Endometrial blood flow

·临床研究·

高通量测序技术检测自然流产绒毛样本的染色体拷贝数变异情况

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【摘要】 目的　探讨高通量测序 (NGS) 技术在检测自然流产绒毛样本的遗传学分析准确性和异常结果检出率中的应用价值。**方法**　选取早期自然流产患者的绒毛组织作为研究对象，采用 NGS 方法对流产绒毛组织的染色体拷贝数变异情况进行检测。同时，我们采用比较基因组杂交芯片 (a-CGH) 法进行验证，以确保 NGS 检测结果的准确性。**结果**　本研究共纳入 256 例绒毛样本，检测成功率 100%。染色体异常共计 145 例 (56.64%)，染色体未见明显异常共计 111 例 (43.36%)。染色体微缺失 / 微重复共 34 例 (13.28%)。在染色体异常结果中，非整倍体 128 例 (50%)，其中三体共计 94 例 (36.72%)，主要涉及 22 号和 16 号染色体，占三体总例数的 50%；单体共 24 例 (9.37%)，Turner 综合征为 22 例 (91.7%)；四体共 10 例 (3.91%)。染色体结构异常共 17 例 (6.64%)。随机选取的 5 例样本同时采用 a-CGH 芯片检测，结果与高通量测序结果一致。**结论**　NGS 技术是一项敏感、高效的遗传学检测手段，可有助于明确自然流产的遗传学因素，以期指导下次妊娠。

【关键词】 高通量测序 (NGS) 技术；自然流产；染色体拷贝数变异 (CNV)

·临床研究·

Using the high-throughput sequencing to detect the chromosomal copy number variants of chorionic villi

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【**Abstract**】 **Objective** To investigate the clinical application of high-throughput sequencing in detecting the accuracy of genetic analysis and the detect rate of abnormal results of chorionic villi from spontaneous abortion. **Methods** Chorionic villus samples were collected from early spontaneous abortion to be detected the chromosomal copy number variants (CNVs) of chorionic villi using the high-throughput sequencing. Meanwhile, we adopted array-based comparative genomic hybridization (a-CGH) to confirm the selected results of high-throughput sequencing to ensure its accuracy. **Results** A total of 256 chorionic villus samples were collected in this study. The success rate of the detection was 100%. The total of chromosomal abnormalities were 145 cases (56.64%) and the normal chromosomal samples were 111 cases (43.36%). There were 34 cases (13.28%) of the chromosomal segment deletion or duplication. In these chromosomal abnormalities, aneuploidy was identified in 128 cases (50%), including 94 cases (36.72%) of trisomy, 24 cases (9.37%) of monomer and 10 cases (3.91%) of tetrasome. The results of trimosy involved the 22 and the 16 chromosomal, which contributed the half number of the trimosy. Turner syndrome were detected in 22 cases (91.7%) in monomer. There were 17 cases (6.64%) involved the abnormality of the chromosomal structure. The results of the high-throughput sequencing and a-CGH of the 5 samples selected were consistent. **Conclusion** The high-throughput sequencing is a susceptible and efficient technology. It may help to clarify the genetic causes of spontaneous abortion to guide the next pregnancy.

【**Key words**】 High-throughput sequencing technology; Spontaneous abortion (SA); Copy number variants (CNVs)

·临床研究·

抗苗勒管激素和内分泌代谢指标在多囊卵巢综合征诊断中的应用

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【摘要】 目的 建立用于检测多囊卵巢综合征 (PCOS) 患者的血清抗苗勒管激素 (AMH) 和其他激素代谢指标的临床截断值。**方法** 本研究共纳入 653 名 PCOS 患者，同时纳入 118 名健康妇女作为对照组。分析血清 AMH、卵泡刺激素 (FSH)、黄体生成素 (LH)、FSH/LH、催乳素 (PRL)、雌二醇 (E_2)、睾酮 (T)、硫酸脱氢表雄酮 (DHEA-S)、性激素结合球蛋白 (SHBG)、17α-OH 孕酮 (17α-OHP)、空腹胰岛素 (INS)、空腹血糖 (GLU)、胰岛素抵抗指数 (HOMA-IR) 的水平，通过受试者工作特征 (ROC) 曲线评估 AMH、LH/FSH、T 和 INS 诊断多囊卵巢的诊断效能。以 AMH、LH/FSH、T 和 INS 为自变量，建立 logistic 回归模型，并根据概率值拟合联合检测的 ROC 曲线。**结果** 与对照相比，PCOS 患者血清 FSH、LH、LH/FSH、AMH、游离雄激素指数 (FAI)、17α-OHP、空腹 INS、T、SHBG、DHEA-S 和 HOMA-IR 差异均有统计学意义 (P 均 <0.05)。针对 20~29 岁的女性，AMH 作为 PCOS 的诊断指标的临床截断值为 8.16 μg/L，ROC 曲线下面积为 0.846，针对 30~34 岁女性的截断值为 6.98 μg/L，ROC 曲线下面积为 0.845，针对 35~39 岁女性的截断值为 5.65 μg/L，ROC 曲线下面积为 0.832。AMH、LH/FSH、T 和 INS 联合检测 PCOS 的 ROC 曲线下面积为 0.951。 **结论** 20~29 岁 PCOS 患者的 AMH 的截断值为 8.16 μg/L，30~34 岁为 6.98 μg/L，35~39 岁为 5.65 μg/L。血清 AMH、LH/FSH、T 和 INS 可以作为 PCOS 诊断的有效检测指标，这些标志物的联合检测可以提高 PCOS 的诊断特异性和敏感性。

【关键词】 抗苗勒管激素 (AMH)；多囊卵巢综合征 (PCOS)；高雄激素血症；胰岛素抵抗 (IR)

·临床研究·

Application of anti-Müllerian hormone and hormone metabolic parameters in the diagnosis of polycystic ovary syndrome

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【**Abstract**】 **Objective** To establish the threshold of anti-Müllerian hormone (AMH) and other hormone metabolic parameters for detection of polycystic ovary syndrome (PCOS) in China. **Methods** A total of 653 PCOS patients and 118 healthy controls were enrolled in this study. The serum AMH, follicle stimulating hormone (FSH), luteinizing hormone(LH), FSH/LH, prolactin (PRL), estradiol (E_2), testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), sex hormone binding globulin (SHBG), 17α-OH progesterone (17α-OHP), fasting insulin (INS), fasting glucose (GLU) and HOMA-IR were analyzed and the diagnostic utility of AMH, LH/FSH, T and INS were established using receiver operator characteristic (ROC) curves. With AMH, LH/FSH, T and INS as independent variables, the logistic regression model was established, and the ROC curve of joint detection was fitted by the probability value in the model. **Results** The serum level of FSH, LH, LH/FSH, AMH, free androgenindex (FAI), 17α-OHP, fasting INS, T, SHBG, DHEA-S and HOMA-IR were changed in PCOS. The best compromise between sensitivity and specificity was found at an AMH cut-off level of 8.16 μg/L, 6.98 μg/L and 5.65 μg/L, and the area under the curve for AMH identifying polycystic ovaries were 0.846, 0.845 and 0.832 for 20−29, 30−34 and 35−39 years old women, respectively. The area under ROC curve of joint detection was 0.951. **Conclusion** The cut-off level of AMH was 8.16 μg/L for PCOS during 20−29 years old, 6.98 μg/L for PCOS during 30−34 and 5.65 μg/L for PCOS during 35−39 years old women in China. Serum AMH, LH/FSH, T and INS had the capacity to act as a diagnostic test for PCOS. Combined detection of these markers can improve the diagnostic specificity and sensitivity of PCOS.

【**Key words**】 Anti-Müllerian hormone (AMH); Polycystic ovary syndrome (PCOS); Hyperandrogenism; Insulin resistance

·临床研究·

精子过量残留胞质的特性研究

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【摘要】目的　观察精子过量残留胞质 (ERC) 结构在体外的稳定性，探讨 ERC 的适宜检测方法及其临床意义。**方法**　监测精子在干、湿片检测状态下精子 ERC 率与精液离体时间、精子活动力、活性氧类物质 (ROS) 以及精子成熟度指标的关系。**结果**　①精液射出体外 0~120 min 时间段内，无论精子处于干、湿状态，其 ERC 率均随精液标本离体时间延长而持续下降 (P<0.001)；各时间段内湿片活动精子 ERC 率均明显高于不活动精子 (P<0.001)，且 ERC 保有率明显高于干片 (P<0.001)。②精液标本经上泳分离后，上泳精子湿片 ERC 率显著高于底层精子 (P<0.001)，而干片 ERC 水平则明显低于底层精子 (P<0.001)，同层精子湿片法 ERC 率明显高于干片法 (P<0.001)。③湿片状态下精子 ERC 率与精子前向运动率、活动率无相关性 (P 均 >0.05)，但干片状态下呈显著负相关 (r=−0.472、r=−0.430，P=0.009、P=0.018)；④湿片状态下精子 ERC 率与 ROS、核蛋白不成熟度 (湿染法)、DNA 碎片率 (湿染法)、精子 - 透明质酸结合率 (HBA) 均无显著相关性 (P>0.05)；干片状态下精子 ERC 率与 ROS(r=0.784，P<0.001)、DNA 碎片 (干片法) (r=0.574，P=0.001)、HBA(r=−0.336，P=0.036) 显著相关，与核蛋白不成熟度 (干片法) 无显著相关性 (P>0.05)，但标本内部 ERC 精子较非 ERC 精子的核蛋白不成熟率更高 (P<0.001)。**结论**　精子 ERC 结构随精液离体时间延长呈进行性崩解趋势，精子在经历自然干燥后 (干片法) 其 ERC 保有率更具临床意义，干片法 ERC 水平与精子活动能力、ROS 水平及成熟度显著相关，ERC 结构是不良质量精子的标志物。

【关键词】精子；过量残留胞质 (ERC)；稳定性；成熟度；活性氧类物质 (ROS)

·临床研究·

A study on the characteristics of excess residual cytoplasm in human spermatozoa

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【**Abstract**】 **Objective** To observe the stability of human spermatozoa excess residual cytoplasm (ERC) *in vitro* and to explore the suitable detection method of ERC and its clinical significance. **Methods** The relationship between sperm ERC rate and time *in vitro* of semen, sperm motility, reactive oxygen species (ROS) and sperm maturation index levels were measured by dry and wet smear detection. **Results** 1) The ERC rate significantly decreased with the prolongation of spermatozoa *in vitro* for 0−120 min (P<0.001). The ERC rate of motile spermatozoa was significantly higher than that of immotile spermatozoa (P<0.001), and the ERC rate was significantly higher by wet-smear detection than by dry-smear detection (P<0.001). 2) After spermatozoa was selected by swim-up technique, the ERC rate of swim-up spermatozoa was significantly higher than that of underlying spermatozoa (P<0.001) for the wet-smear detection, while it was significantly lower than that of the underlying spermatozoa (P<0.001) for the dry-smear detection. Compared with the same layer spermatozoa, the ERC rate of wet-smear detection was higher than that of dry-smear detection (P<0.001). 3) There was no significant correlation between sperm ERC percentage and sperm progressive and total motility rate by wet-smear detection. But there was a significant negative correlation between sperm ERC rate and sperm progressive and total motility rate by dry-smear detection (r=−0.472, P=0.009; r=−0.430, P=0.018, respectively). 4) There was no significant correlation between the ERC rate and ROS, immature sperm nucleoprotein (wet staining), DNA fragmentation (wet staining) as well as the sperm-hyaluronic acid binding assay (HBA) score by wet-smear detection (P>0.05). However, underwent dry sperm, there were significant correlations between the ERC rate and ROS (r= 0.784, P<0.001), DNA fragment (dry staining) (r=0.574, P=0.001), HBA (r=−0.336, P=0.036), except for immature sperm nucleoprotein (dry staining). The immature sperm nucleoprotein rate of ERC spermatozoa was higher than that of non-ERC spermatozoa after drying process (P<0.001). **Conclusion** The ERC of spermatozoa has a tendency of progressive disintegration with the prolongation of semen *in vitro*. And compared with wet-smear method, the ERC retention rate of spermatozoa after natural drying (dry-smear method) has more clinical significance. The ERC level by dry-smear detection was significantly correlated with sperm motility, ROS levels and maturation. Moreover, the ERC might be a marker of poor sperm quality.

【**Key words**】Sperm; Excess residual cytoplasm (ERC); Stability; Maturation; Reactive oxygen species (ROS)

·临床报道·

认知行为疗法对肥胖型多囊卵巢综合征不孕妇女心理状态和辅助生殖结局的影响

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【摘要】 目的 探讨认知行为疗法对肥胖型多囊卵巢综合征 (PCOS) 不孕妇女心理状态和辅助生殖结局的影响。**方法** 本研究为前瞻性队列研究，将 2015 年 9 月—2018 年 6 月期间在我中心进行辅助生殖技术 (ART) 治疗的 84 例肥胖型 PCOS 不孕妇女分为对照组 (n=35)：接受常规护理和知识宣教；治疗组 (n=49)：在常规护理和知识宣教基础上，接受认知行为疗法。认知行为疗法包括认知、情感、行为 3 个层面内容，采用小组课程与微信群沟通相结合模式对入组成员进行指导。了解两组患者在进入 ART 周期前和胚胎移植后的心理状态和辅助生殖妊娠相关结局。**结果** 治疗组患者治疗后的焦虑状态评分 (28.5±7.6) 和抑郁状态评分 (13.8±7.0) 显著低于对照组 (43.2±8.6，P=0.008；17.2±6.3，P=0.021)。治疗组的生育生活质量的治疗环境评分 (79.7±18.0) 和治疗耐受性评分 (85.6±21.1) 显著高于对照组 (64.2±20.2，P=0.015；64.9±22.3，P=0.023)。两组患者的取卵数、流产率、异位妊娠率差异无统计学意义 (P>0.05)。治疗组的胚胎种植率和临床妊娠率略高于对照组，但差异无统计学意义 (P>0.05)。**结论** 认知行为疗法可以有效改善肥胖型 PCOS 不孕女性的焦虑、抑郁状态和提高生育生活质量，一定程度上有助于改善这类不孕女性 ART 治疗效果。

【关键词】 肥胖；多囊卵巢综合征 (PCOS)；不孕症；辅助生殖技术 (ART)；认知行为疗法

·临床报道·

Effect of cognitive-behavioral therapy on psychological status and assisted reproductive outcomes in infertile women with obese polycystic ovary syndrome

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【**Abstract**】 **Objective** To investigate the effect of cognitive-behavioral therapy on psychological status and assisted reproductive outcomes among infertile women with obese polycystic ovary syndrome (PCOS). **Methods** This was a prospective cohort study. Eighty-four obese PCOS women undergoing assisted reproductive technology (ART) treatment from September 2015 to June 2018 were divided into two groups: control group (n=35) received routine nursing care and healthy education, while treatment group (n=49) accepted cognitive-behavioral therapy which included recognition, emotional and behavioral interventions. The cognitive-behavioral therapy was performed through small group workshop and intercommunication via wechat. The psychological status before and after ART cycles and ART outcomes were compared between the two groups. **Results** The anxiety score (28.5±7.6) and depression score (13.8±7.0) were significantly lower among patients in treatment group than in control group (43.2±8.6, P=0.008; 17.2±6.3, P=0.021) . The score of treatment environment (79.7±18.0) and treatment tolerance of fertility-related quality of life (85.6±21.1) were significantly higher in the treatment group than in control group（64.2±20.2, P=0.015; 64.9±22.3, P=0.023). No significant differences were identified considering the number of retrieved oocytes, miscarriage rate and ectopic pregnancy rate between the two groups (P>0.05). The implantation rate and clinical pregnancy rate were slightly higher in treatment group than control group, but failed to reach significant differences (P>0.05). **Conclusion** Cognitive-behavioral therapy could effectively decrease the anxiety and depression status, improve treatment-related fertility quality of life, and might improve ART outcomes of obese PCOS infertile women.

【**Key words**】 Obesity; Polycystic ovary syndrome (PCOS)；Infertility; Assisted reproductive technology (ART); Cognitive-behavioral therapy

·综　述·

卵母细胞人工激活技术在卵胞质单精子注射受精失败后的应用

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【摘要】 卵胞质内单精子注射 (ICSI) 受精失败是辅助生殖治疗中面临的一项难题，近年来卵母细胞人工激活 (artificial oocyte activation，AOA) 技术的应用使人们看到了解决这一问题的希望。但由于对卵母细胞激活失败的机制还缺乏明确的研究，AOA 技术也并不能解决所有类型的 ICSI 受精失败，其临床应用指征和安全性仍然是人们关注的焦点。虽然目前的研究未显示出 AOA 技术会明显增加子代的出生缺陷，但该技术还是应该谨慎地用于有合适指征的病例。本综述从 ICSI 受精失败机理和类型，AOA 的临床应用及其安全性等方面将该技术目前的研究进展予以总结，以期为生殖医学工作者提供较为全面的参考。

【关键词】 卵胞质内单精子注射 (ICSI)；受精失败；卵母细胞人工激活 (AOA)
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·综　述·

Application of artifcial oocyte activation in fertilization failure of intracytoplasmic sperm injection

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【**Abstract**】 Fertilization failure is a serious challenge of assisted reproduction treatment especially for intracytoplasmic sperm injection (ICSI) cycles, in recent years, artificial oocyte activation (AOA) technology had shined a light on this problem. But the mechanism of oocyte activation failure is still a lack of clear research, as AOA cannot recover all types of fertilization failure, the clinical indications and safety of AOA is still the focus of attention. Although the current study did not show the AOA technology could significantly increase their offspring birth defects, this technology should be cautiously used for selected cases with appropriate indications. This article summarized recent progress of mechanisms and types of ICSI fertilization failure, also the application of AOA and its safety, hoping to give a general view of AOA technique for the ART clinicians and embryologists.

【**Key words**】 Intracytoplasmic sperm injection (ICSI); Fertilization failure; Artificial oocyte activation (AOA)

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·综　述·

Toll 样受体 4 通过调节性 T 细胞引起不明原因复发性流产的机制研究进展

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【摘要】 母 - 胎界面免疫耐受状态异常是致不明原因复发性流产 (URM) 的重要原因之一，但其机制目前尚不明确。调节性 T(regulatory T，Treg) 细胞在维持母 - 胎界面免疫耐受中发挥重要作用。最新研究发现 Toll 样受体可能是调节 Treg 细胞增殖、分化和功能的关键。母 - 胎界面 Toll 样受体 4(Toll like receptor 4，TLR4) 参与调控 Treg 细胞抑制活性，参与诱导滋养细胞凋亡和影响 Treg/Th17 平衡，可影响免疫耐受状态致不明原因复发性流产 (URM) 发生。本文就蜕膜 TLR4 调节 Treg 细胞对 URM 发生的作用机制作一综述。

【关键词】不明原因复发性流产 (URM)；Toll 样受体 4(TLR4)；母 - 胎界面；蜕膜；调节性 T(Treg) 细胞

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·综　述·

Role of Toll like receptor 4 in unexplained recurrent miscarriage induced by regulating T cells

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【**Abstract**】Abnormal state of the maternal-fetal interface tolerance is one of the important reasons of unexplained recurrent miscarriage (URM), but its mechanism is not clear yet. Regulatory T (Treg) cells play an important role in the maintenance of maternal-fetal interface tolerance. The latest research has found that Toll like receptors may be the key to regulate proliferation, differentiation and function of Treg cells. The maternal-fetal interface of Toll like receptor 4 (TLR4) participates in the regulation of Treg cell inhibitory activity and the induction of trophoblast apoptosis, influences the balance of Treg/Th17, and may disturb the balance the immune tolerance and then cause URM. In this review, the mechanism of TLR4 regulating Treg cells in the pathogenesis of the URM decidua surface is reviewed.

【**Key words**】 Unexplained recurrent miscarriage (URM); Toll like receptor 4 (TLR4); Maternal-fetal interface; Decidual; Regulatory T (Treg) cells

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