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·述评·

微生态与健康生育

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【摘要】 健康生育是社会之关切，微生物菌群可从各方面密切影响女性全生命周期的生殖健康。菌群失调可通过调控机体炎症、免疫及代谢等过程，导致或加重生殖内分泌疾病、不孕症、肿瘤、不良妊娠结局等，甚至影响子代健康。本文重点关注生殖道及肠道菌群对女性全生命周期的生殖健康影响，以期从菌群角度更好地了解女性健康。未来，深入解析菌群平衡和稳态对健康生育的预防和保护机制，对推动生殖障碍疾病的诊疗具有重要意义。通过菌群干预手段，建立生殖障碍疾病诊治新策略的临床转化体系，对提高生育全周期的健康水平具有深远影响。

【关键词】 生殖健康；　微生态；　生殖道菌群；　肠道菌群
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Microbiome and reproductive health

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【Abstract】 Reproductive health is a major concern of society. The microbial community can deeply affect the reproductive health of women throughout their entire life cycle from various aspects. The imbalance of microbial can lead to reproductive endocrine diseases, infertility, tumors, adverse pregnancy outcomes, and even affect the health of offspring by regulating the body's inflammation, immunity and metabolism. This article focused on the effects of reproductive tract and intestinal flora on female reproductive health during the whole life cycle in order to better understand female health from the perspective of microbial. In the future, in-depth analysis of the prevention and protection mechanism of microbial balance and homeostasis on reproductive health is of great significance to promote the diagnosis and treatment of reproductive disorders. The establishment of a clinical

transformation system of new strategies for the diagnosis and treatment of reproductive disorders by means of microbial intervention has a profound impact on improving the health level of the whole reproductive cycle.

【**Key words**】 Reproductive health; Microecology; Reproductive tract microbiota; Intestinal flora

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·微生态与生殖健康专栏·

女性生殖道菌群与细胞因子紊乱对反复着床失败的影响

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【摘要】 目的 探索反复着床失败（recurrent implantation failure， RIF）患者生殖道菌群的功能组成变化及其与免疫调控相关的细胞因子的关系。方法 采用病例对照研究，纳入了北京大学第三医院妇产科生殖医学中心 2020 年 8 月至 2021 年 1 月期间因不孕而就诊的患者，入组患者分为对照组（单纯男性因素不孕，*n*=20）和 RIF 组（*n*=15）。研究通过 16S rRNA 测序和 MSD 电化学发光检测入组患者阴道和宫腔灌洗液的菌群和细胞因子表达情况。使用 Spearman 相关分析观察菌群和差异细胞因子之间的相关性。结果 两组患者的年龄、体质量指数、月经周期或基础性激素水平差异均没有统计学意义（均 *P*>0.05）。与对照组相比，RIF 组阴道菌群和宫腔灌洗液菌群的 Shannon 指数差异均有统计学意义（*P*=0.032，*P*=0.015），宫腔灌洗液菌群的 β 多样性差异有统计学意义（*P*=0.020）。RIF 组单核细胞趋化蛋白（monocyte chemotactic protein，MCP）-4 的表达水平[（3.39±1.23）ng/L]明显高于对照组[（1.07±0.31）ng/L，*P*=0.044]，而白细胞介素（interleukin，IL）-17A 的表达水平[（1.12±0.29） ng/L]明显低于对照组[（2.70±0.52） ng/L，*P*=0.040]。宫腔灌洗液中 RIF 组的干扰素（interferon， IFN）-γ [（4.70±2.10） ng/L]、IL-10 [（0.20±0.10） ng/L]、肿瘤坏死因子-α [（0.84±0.13） ng/L]以及 IL-5 [（0.35±0.05） ng/L]的表达水平明显高于对照组[（0.97±0.30） ng/L，

P=0.049；（0.05±0.01）ng/L，*P*=0.009；（0.56±0.07）ng/L，*P*=0.045；（0.23±0.03）ng/L，*P*=0.029）。相关性分析显示，阴道菌群厌氧杆菌属（*Anoxybacillus*）与 MCP-4 的表达呈显著负相关（*r*=−0.42，*P*=0.025）；宫腔灌洗液菌群中 *Muribaculaceae* 菌属与 IL-5 呈显著正相关（*r*=0.51，*P*=0.017），而 *Vulcaniibacterium* 菌属、贪铜菌属（*Cupriavidus*）以及厌氧杆菌属（*Anoxybacillus*）与 IL-5 呈显著负相关（*r*=−0.55，*P*=0.010；*r*=−0.62，*P*=0.003；*r*=−0.45，*P*=0.041）；厌氧杆菌属（*Anoxybacillus*）、土芽孢杆菌属（*Geobacillus*）、嗜热菌属（*Thermus*）以及亚栖热菌属（*Meiothermus*）还与 IFN-γ 呈显著负相关（*r*=−0.43，*P*=0.015；*r*=−0.38，*P*=0.035；*r*=−0.39，*P*=0.029；*r*=−0.38，*P*=0.035）。结论 RIF 患者生殖道菌群和相应细胞因子发生紊乱，菌群与细胞因子之间存在相关性。

【关键词】 细胞因子； 反复着床失败； 阴道菌群； 宫腔灌洗液菌群；子宫内膜容受性

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Impact of female reproductive tract microbiota and cytokine disorders on recurrent implantation failure

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【 **Abstract** 】 **Objective** To explore the changes in the functional composition of genital tract microbiota in patients with recurrent implantation failure (RIF) and its relationship with cytokines related to immune regulation. **Methods** This was a case-control study. The study included patients from the Reproductive Medicine Center of Peking University Third Hospital, enrolled from August 2020 to January 2021. The enrolled patients were divided into control group (*n*=20) and the RIF group (*n*=15). The study examined the expression of flora and cytokines in vaginal and uterine lavage fluid by 16S rRNA sequencing and MSD electrochemiluminescence. Spearman analysis was used to observe the correlation between flora and differently expressional cytokines. **Results** Compared with control group, there were statistically significant differences in the Shannon index of vaginal microbiota and uterine lavage fluid microbiota in the RIF group (*P*=0.032, *P*=0.015). There was a statistically significant difference in β diversity of the bacterial community in uterine lavage fluid (*P*=0.020). The expression level of monocyte chemotactic protein-4 (MCP-4) in the RIF group [(3.39±1.23) ng/L] was significantly higher than that in control group [(1.07±0.31) ng/L, *P*=0.044], while the expression level of interleukin (IL)-17A [(1.12±0.29) ng/L] was significantly lower than that in control group [(2.70±0.52) ng/L, *P*=0.040]. The expression levels of interferon (IFN)-γ [(4.70±2.10) ng/L], IL-10 [(0.20±0.10) ng/L], tumor necrosis factor-α [(0.84±0.13) ng/L], and IL-5 [(0.35±0.05) ng/L] in the RIF group in the uterine lavage were

significantly higher than those in control group [(0.97±0.30) ng/L, *P*=0.049; (0.05±0.01) ng/L, *P*=0.009; (0.56±0.07) ng/L, *P*=0.045; (0.23±0.03) ng/L, *P*=0.029]. Correlation analysis revealed significant correlations between vaginal flora and MCP-4 (*r*=−0.42, *P*=0.025), and in the microbial community of uterine cavity lavage fluid, there was a significant positive correlation between the *Muribaculaceae* genus and IL-5 (*r*=0.51,*P*=0.017). Conversely, the *Vulcaniibacterium* genus, *Cupriavidus* genus, and *Anoxybacillus* genus exhibited a significantly negative correlation with IL-5 (*r*=−0.55,*P*=0.010; *r*=−0.62,*P*=0.003; *r*=−0.45,*P*=0.041). Additionally, the genera *Anoxybacillus*, *Geobacillus*, *Thermus*, and *Meiothermus* showed a significantly negative correlation with IFN-γ (*r*=−0.43, *P*=0.015; *r*=−0.38, *P*=0.035; *r*=−0.39, *P*=0.029; *r*=−0.38, *P*=0.035). **Conclusion** The reproductive tract microbiota and corresponding cytokines in RIF patients are disrupted, and there is a correlation between the microbiota and cytokines.

【Key words】 Cytokines; Repeated implantation failure; Vaginal microbiota; Uterine lavage microbiota; Endometrial receptivity

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·微生态与生殖健康专栏·

女性常见生殖内分泌疾病与微生物组关系的研究进展

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【摘要】 女性生殖内分泌相关疾病严重影响女性生殖健康及生活质量，其中多囊卵巢综合征和早发性卵巢功能不全是育龄期女性最常见的两种生殖内分泌疾病。而随着微生物组学技术的不断发展，人体共生微生物已被证实与多种内分泌代谢疾病相关。越来越多研究表明肠道及生殖道微生物组与女性生殖内分泌疾病密不可分，在疾病发生、发展过程中起着重要作用。本文拟就多囊卵巢综合征和早发性

卵巢功能不全和肠道、生殖道微生物组之间的关系进行综述，并探讨微生态制剂的应用，以期为女性生殖内分泌的临床诊治提供新的思路。

【关键词】 微生物组； 多囊卵巢综合征； 早发性卵巢功能不全； 女性生殖内分泌疾病

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Progress of research on the relationship between common female reproductive endocrine diseases and microbiome

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【Abstract】 Female reproductive endocrine diseases seriously affect female reproductive health and quality of life, among which polycystic ovary syndrome and premature ovarian insufficiency are the two most common reproductive endocrine diseases of women of childbearing age. With the continuous development of microbiology technology, human symbiotic microbiota have been proved to be related to various endocrine and metabolic diseases. More and more studies have shown that intestinal and reproductive tract microbiome are closely related to female reproductive endocrine diseases and play an important role in the occurrence and development of diseases. This article reviews the relationship between two kinds of female reproductive endocrine diseases and microbiome of intestinal tract and reproductive tract, and discusses the application of microecological preparation in order to provide new ideas for clinical diagnosis and treatment of female reproductive endocrine.

【Key words】 Microbiome; Polycystic ovary syndrome; Premature ovarian insufficiency; Female reproductive endocrine diseases

Fund program: National Key Rresearch and Development Program of China (2022YFA1303900); Shanghai Shen-kang Hospital Development Center Special Medical Enterprise Integration Innovation Achievements (SHDC2022CRD007); Shanghai Industrial Collaborative Innovation Project (XTCXKJ202233)

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肠道微生物群与早期自然流产病因相关性的研究进展

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【摘要】 肠道微生物在维持宿主体内代谢稳态及宿主代谢性疾病发生发展过程中发挥重要作用，其通过代谢物与宿主相互作用，对机体代谢和免疫调节等生理病理过程产生影响。早期流产是常见妊娠并发症之一，占所有临床妊娠的 10%~15%。既往研究表明，肠道微生物群在妊娠并发症的病理生理过程中发挥着重要的作用，有望成为早期自然流产临床预防和治疗的新候选者。早期自然流产与肠道微生物之间的相关性得到越来越多的关注，但肠道微生物群影响早期自然流产的机制需要进一步研究。本文综述了肠道微生物群与早期自然流产发病原因的相关性，显示其可能通过调节人体内分泌、免疫功能、子宫环境参与了早期自然流产的发生发展，希望能够为临床诊治及研究提供新的思路。

【关键词】 肠道微生物群；　肠道微生态紊乱；　免疫调节；　早期自然流产

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Interactions between gut microbiota and the etiology of early spontaneous abortion

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【Abstract】 Gut microbiota plays an important role in maintaining metabolic homeostasis as well as the occurrence and development of metabolic diseases in the host. Physiological and pathological processes such as body metabolism and immune regulation are impacted by the interaction of metabolites of gut microbiota with the host. Early spontaneous abortion is one of the most common pregnancy complications, accounting for 10%−15% of all clinical pregnancies. According to the previous studies, gut microbiota had an important effect in the pathophysiological process of pregnancy complications and was expected to be a new candidate for clinical prevention and treatment of early spontaneous abortion. While the correlation between early spontaneous abortion and gut microbiota has gained

attention, further investigation is needed to understand the mechanism by which the gut microbiota affects early abortion. In this review, we discussed the influence of gut microbiota on early spontaneous abortion. We found that gut microbiota may participate in the development of early spontaneous abortion by regulating human endocrine, immune functions and uterine environment, hoping to provide new ideas for clinical diagnosis and treatments.

【 **Key words** 】 Gut microflora dysbiosis; Gut microflora dysbiosis; Immunomodulation; Early spontaneous abortion

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·微生态与生殖健康专栏·

肠道菌群在妊娠期肝内胆汁淤积症发病中作用的研究进展

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【摘要】 妊娠期肝内胆汁淤积症（intrahepatic cholestasis of pregnancy，ICP）是特发于妊娠中晚期肝内胆汁淤积性疾病，以皮肤瘙痒、肝功能异常、胆汁酸水平升高、产后恢复正常为临床特点。研究显示，肠道菌群失调和内源性胆汁酸在胆汁淤积性肝病的发生发展中起着重要作用。孕期激素水平和能量代谢的剧烈变化可能引起了肠道菌群和胆汁酸构成的变化。肠道通透性的改变、胆汁酸的过度积累、胆汁酸转运体和核受体的异常表达都参与了胆汁淤积症的发病机制。本文就 ICP 中肠道菌群的变化及其在疾病发生发展中的作用机制进行综述，以及展望 ICP 的潜在治疗方法。

【关键词】 妊娠期肝内胆汁淤积症； 妊娠； 肠道菌群； 胆汁酸

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Research progress on the effect of gastrointestinal microbiota on intrahepatic cholestasis of pregnancy

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【Abstract】 Intrahepatic cholestasis of pregnancy (ICP), as an idiopathic disease, often occurs in the second and third trimester of pregnancy. It is characterized by maternal pruritus, abnormal liver function and raised serum bile acids which are resolved rapidly and spontaneously after delivery. It has been reported that abnormal intestinal microbiota and endogenous bile acids play important roles in the progression of cholestatic liver diseases. Dramatic changes in metabolic hormone levels and energy metabolism during pregnancy disrupt the microbiota composition and bile acid pool as well. Altered intestinal permeability, overaccumulation of bile acids, aberrant expression of bile acid transporters and nuclear receptors are all involved in the pathogenesis of cholestasis. This paper reviews the changes of intestinal flora and the mechanism of gastrointestinal microbiota in intrahepatic cholestasis of pregnancy, explore the potential treatments for ICP.

【Key words】 Intrahepatic pregnancy of cholestasis; Pregnancy; Gastrointestinal microbiota; Bile acid

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年轻女性抗苗勒管激素水平与IVF/ICSI-ET后早期自然流产的关系分析

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【摘要】 目的 探讨抗苗勒管激素（anti-Müllerian hormone，AMH）水平与年轻女性体外受精/卵胞质内单精子注射-胚胎移植（*in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer，IVF/ICSI-ET）术后早期自然流产的关系。方法 采用回顾性队列研究，分析2017年1月至2020年12月期间在北京大学第三医院生殖医学中心首次行IVF/ICSI-ET助孕获得妊娠的<35岁的患者资料（*n*=2 640）。按AMH水平，根据年龄进行1∶2匹配，患者分为2组：低AMH组（AMH<1.1 μg/L）880例和正常AMH组（1.1 μg/L≤AMH<4.0 μg/L）1760例，比较两组一般情况及早期自然流产率。采用二分类logistic回归控制混杂因素，分析AMH水平和早期自然流产的关系。结果 ①两组中女方年龄、男方年龄差异均无统计学意义（均*P*>0.05），低AMH组基础卵泡刺激素［follicle-stimulating hormone，FSH，7.1（6.1，9.2） U/L］高于正常AMH组［6.9（5.3，8.0） U/L，*P*<0.001］，而窦卵泡计数［6（3，8）］、人绒毛膜促性腺激素（human chorionic gonadotropin，hCG）注射日雌激素水平［4 446.5（2 999.5，6 264.1） pmol/L］、孕激素水平［1.9（1.4，2.6） nmol/L］均低于正常AMH组［9（6，12），*P*<0.001；6 264.0（4 609.5，8 913.5） pmol/L，*P*<0.001；2.0（1.4，2.7） nmol/L，*P*=0.001］。低AMH组获卵数［（7.4±3.9）枚］和优质胚胎数［3（2，5）枚］均低于正常AMH组［（10.8±3.9）枚，*P*<0.001；4（3，7）枚，*P*<0.001］，低AMH组单胚胎移植率［14.1%（124/880）］高于正常AMH组［8.6%（275/1 760），*P*<0.001］，两组间不孕因素构成差异有统计学意义（*P*<0.001）。②低AMH组早期自然流产率[12.2%（107/880）]高于正常AMH组[8.9%（156/1 760），*P*=0.008]。两组间晚期自然流产率差异无统计学意义（*P*=0.631）。③二分类logistic分析调整促排卵方案、hCG注射日雌激素、孕激素水平和移植胚胎数影响后，低AMH水平（<1.1 μg/L）是早期自然流产的因素之一（*OR*=1.343， 95% *CI*：1.019~1.769，*P*=0.036）。结论 在进行IVF/ICSI-ET助孕的<35岁女性中，低AMH患者有更高的早期流产率。AMH水平对于年轻女性助孕后的流产率具有一定的预测价值。

【关键词】 抗苗勒管激素； 生殖技术，辅助； 卵巢储备功能下降； 早期自然流产

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Analysis of the relevance between anti-Müllerian hormone and early spontaneous abortion after IVF/ICSI-ET in young women

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【**Abstract**】 **Objective** To explore the effect of anti-Müllerian hormone (AMH) level on early spontaneous abortion of young women with *in vitro* fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET). **Methods** A retrospective cohort study was performed to analyze the clinical data of the first cycle IVF/ICSI-ET women in Reproductive Medical Center, Peking University Third Hospital from January 2017 to December 2020. Totally 2 640 young women (less than 35 years old, matched according to age with 1∶2 of case-control) were included in this study. They were divided into two groups according to AMH level, 880 cases in low AMH group (AMH<1.1 μg/L) and 1 760 cases in normal AMH group (1.1 μg/L≤AMH<4.0 μg/L), the general characteristics and early spontaneous abortion rate between the two groups were compared. Binary logistic regression was used to control confounding factors and analyze the relationship between AMH level and early spontaneous abortion. **Results** 1) There was no significant difference in the age of women and men between the two groups (all P>0.05). The basal follicle-stimulating hormone [FSH, 7.1 (6.1,9.2) U/L] in low AMH group was significantly higher than that in normal AMH group [6.9 (5.3, 8.0) U/L, P<0.001], while the antral follicle count [6 (3,8)], the levels of estrogen [4 446.5 (2 999.5, 6 264.1) pmol/L] and progesterone [1.9 (1.4, 2.6) nmol/L] on human chorionic gonadotropin (hCG) injection day were lower than those in the normal AMH group [9 (6, 12), P<0.001; 6 264.0 (4 609.5, 8 913.5) pmol/L, P<0.001; 2.0 (1.4, 2.7) nmol/L, P=0.001]. The number of oocytes retrieved (7.4±3.9) and the number of high-quality embryos [3 (2, 5)] in low AMH group were significantly lower than those in normal AMH group [10.8±3.9, P<0.001; 4 (3, 7), P<0.001], and the single embryo transfer rate in low AMH group [14.1% (124/880)] was significantly higher than that in normal AMH group [8.6% (275/1 760), P<0.001]. There was a significant difference in infertility factors between the two groups (P<0.001). 2) The rate of early spontaneous abortion [12.2% (107/880)] in low AMH group was significantly higher than that in normal AMH group [8.9% (156/1 760), P=0.008]. There was no significant difference in the rate of late spontaneous abortion between the two groups (P=0.631). 3) Binary logistic analysis showed that low AMH level (<1.1 μg/L) was one of the factors of early spontaneous abortion after adjusting the influence of ovulation induction scheme, the level of estrogen and progesterone on hCG injection day and the number of embryos transferred (OR=1.343, 95% CI: 1.019−1.769, P=0.036). **Conclusion** Low AMH level can predict the early spontaneous abortion

rate of young women after IVF/ICSI-ET, and its mechanism needs to be further explored.

【**Key words**】 Anti-Müllerian hormone; Reproductive techniques, assisted; Diminished ovarian reserve; Early spontaneous abortion

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·临床研究·

剖宫产术后即刻放置固定式宫内节育器脱落率及其影响因素前瞻性队列研究

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【摘要】 目的 探讨剖宫产术后即刻放置固定式宫内节育器（postpartum intrauterine device， PPIUD）1 年内的脱落率及其影响因素。方法 采用前瞻性队列研究方法，2017 年 9 月至 2020 年 11 月期间在全国 4 个省市 14 家医疗机构招募自愿于剖宫产术后即刻（胎盘娩出后 10 min 内）放置固定式 PPIUD 的妇女为研究对象，通过问卷收集研究对象术前、术中和术后 24 h 相关信息，并于产后 42 d、3 个月、6 个月和 12 个月进行门诊随访，了解固定式 PPIUD 脱落和意外妊娠等信息。采用寿命表和 Cox 回归模型分析累积脱落率以及相关影响因素。结果 共招募 470 名研究对象，461 名（98%）为本文提供了合格数据，剖宫产术后 1 年内固定式 PPIUD 累积脱落率为 8.4%（95% *CI*：7.0%~9.8%）。多因素 Cox 回归分析显示，分娩年龄>35 岁放置固定式 PPIUD 后 1 年内脱落率显著低于年龄<25 岁女性（*HR*=0.16，95% *CI*：0.04~0.64），且均未显示剖宫产既往史和哺乳方式与固定式 PPIUD 脱落风险均显示有统计学关联（均 *P*>0.05）。但脱落率存在医院聚集性。分析显示，产后 1 年累积避孕失败比尔指数为 2.37（95% *CI*：1.09~4.50）/100 人年，避孕失败与产妇年龄、哺乳和剖宫产史均无统计学关联（均 *P*>0.05）。结论 剖宫产术后即刻放置固定式 PPIUD 1 年累积脱落率为 8.4%，低龄是其脱落的高危因素。建议加强该 PPIUD 使用者脱落风险识别的指导，一旦脱落，应及时更换或用其他高效避孕方法。建议加强服务提供者放置技术培训。

【关键词】 剖宫产术； 固定式产后放置宫内节育器； 脱落； 避孕失败

临床试验注册：中国临床试验注册中心，ChiCTR1900023828

Expulsion rate and influencing factors of GyneFix postpartum intrauterine device placed immediately after cesarean section: a prospective cohort study

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【**Abstract**】 **Objective** To investigate the expulsion rate of GyneFix postpartum intrauterine device (PPIUD) placed immediately after cesarean section within one year and its influencing factors. **Methods** A prospective cohort study was conducted. Women who volunteered to use a GyneFix PPIUD placed immediately after cesarean section (within 10 min after placenta delivery) for postpartum contraception were recruited from September 2017 to November 2020. The relevant information was collected through questionnaires before, during and 24 h after cesarean section. Outpatient follow-up was conducted at 42 d, 3 months, 6 months and 12 months after delivery to obtain information on expulsion of GyneFix PPIUD and unwanted pregnancy. Life table and Cox regression model were used to analyze the cumulative expulsion rate and related influencing factors. **Results** A total of 470 subjects were recruited and 461 (98%) subjects were eligible for this study. The cumulative expulsion rate of GyneFix PPIUD within one year after cesarean section was 8.4% (95% *CI*: 7.0%–9.8%). Multivariate Cox regression analysis showed that women aged >35 years had significantly lower risk of PPIUD expulsion than those aged <25 years (*HR*=0.16, 95% *CI:* 0.04–0.64). The risk of GyneFix PPIUD was not statistically significantly associated with cesarean section history and breastfeeding mode (all *P*>0.05). Nevertheless, this risk was statistically significant between hospitals. The Pearl index of contraceptive failure of the device was 2.37 (95% *CI*: 1.09–4.50) per 100 person-years. The rate of contraceptive failure was not associated with maternal age, breastfeeding mode, and history of cesarean delivery (all *P*>0.05). **Conclusion** The one-year cumulative expulsion rate of GyneFix PPIUD placed immediately after cesarean section is 8.4%. Young mothers were at a higher risk of expulsion than their older counterparts. The

device users should be counseled regarding the signs of expulsion. In case of expulsion, women should be offered reinsertion or other contraceptive methods. The training of service skills of GyneFix PPIUD should be strengthened in order to mitigate the risk of the device expulsion.

【Key words】 Cesarean section; GyneFix postpartum intrauterine device; Expulsion; Contraceptive failure

Trial Registration: Chinese Clinical Trial Registry, ChiCTR1900023828

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·实验研究·

miR-515-5p 靶向 ITLN2 对子宫内膜基质细胞增殖、迁移和侵袭的影响

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【摘要】 目的　探讨微小 RNA-515-5p（miR-515-5p）是否可靶向内凝集素 2（lectin 2， ITLN2）影响子宫内膜异位症（endometriosis， EMT）子宫内膜基质细胞（endometrial stromal cells， ESCs）的增殖、迁移和侵袭。方法　收集 2020 年 12 月至 2021 年 12 月期间在济宁医学院附属医院生殖医学科就诊治疗的 24 例 EMT 患者的在位内膜和异位内膜组织及 18 例行腹腔镜手术的非 EMT 患者的正常内膜组织。RT-qPCR 检测内膜组织 miR-515-5p、*ITLN2* mRNA 相对表达量；Western blotting 法检测内膜组织中 ITLN2 蛋白表达量。原代分离、培养 EMT 患者的 ESCs，利用 Lipofectamine 2000 试剂转染 ESCs，并将其分为空白组、miR-515-5p 抑制剂组、miR-515-5p 抑制剂阴性对照（negative control， NC）组，CCK-8 法检测细胞增殖情况；划痕愈合和 Transwell 实验分别评估细胞迁移、侵袭能力；双荧光素酶报告基因检测 miR-515-5p 和 ITLN2 的靶向关系；RT-qPCR 技术检测各组细胞 miR-515-5p、*ITLN2* mRNA 相对表达量；Western blotting 技术检测 ITLN2、白细胞介素（interleukin，IL）-1β、IL-6 及肿瘤坏死因子-α（tumor necrosis factor-α， TNF-α）蛋白相对表达量。结果　EMT 患者在位和异位子宫内膜组织 miR-515-5p 相对表达

量显著高于正常子宫内膜组织（均 *P*<0.001），*ITLN2* mRNA 相对表达量显著低于正常子宫内膜组织，异位子宫内膜组织 *ITLN2* mRNA 相对表达量显著低于在位子宫内膜组织（均 *P*<0.001），EMT 患者异位子宫内膜组织 ITLN2 蛋白质水平显著低于 EMT 在位和正常子宫内膜组织（均 *P*<0.001），EMT 患者在位子宫内膜组织 ITLN2 蛋白质水平显著低于正常子宫内膜组织（*P*<0.001）。miR-515-5p 抑制剂组细胞存活率[（54.71±2.78）%]、划痕愈合率[（38.31±3.78）%]及侵袭数[（286.67±25.15）个]、miR-515-5p 相对表达量、IL-1β、IL-6、TNF-α 蛋白相对表达量均显著低于空白组[（100.00±0.00）%，*P*<0.001；（84.08±5.14）%，*P*<0.001；（515.67±22.19）个，*P*<0.001；*P*<0.001；*P*=0.012；*P*=0.010；*P*<0.001]，*ITLN2* mRNA 和蛋白相对表达量均显著高于空白组（*P*<0.001；*P*<0.001）。经生物信息学分析和双荧光素酶报告基因检测，*ITLN2* 为 miR-515-5p 的潜在靶基因。结论　降低 miR-515-5p 水平可抑制 EMT 患者 ESCs 增殖、迁移和侵袭，这可能与靶向提高 ITLN2 表达进而降低炎症因子水平有关。

【关键词】　子宫内膜异位症；　微小 RNA-515-5p；　内凝集素 2；　子宫内膜基质细胞；　增殖；　迁移；　侵袭

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Effect of miR-515-5p targeting ITLN2 on proliferation, migration and invasion of endometrial stromal cells

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【Abstract】　Objective　To investigate whether microRNA-515-5p (miR-515-5p) can target the endogenous lectin 2 (ITLN2) to affect the proliferation, migration and invasion of endometrial stromal cells (ESCs) in endometriosis (EMT). **Methods**　Eutopic and ectopic endometrium tissues of 24 patients with EMT who attended Department of Reproductive Medicine, the Affiliated Hospital of Jining Medical College for treatment from December 2020 to December 2021, and normal endometrium tissues of 18 non-EMT patients who underwent laparoscopic surgery were selected. RT-qPCR was used to detect the relative expression of miR-515-5p and *ITLN2* mRNA, and Western blotting was used to detect ITLN2 protein expression in endometrium tissues. ESCs from EMT patients were isolated and cultured in primary culture. ESCs were transfected with Lipofectamine 2000 reagent, and were divided into blank group, miR-515-5p inhibitor group, miR-515-5p inhibitor negative control (NC) group. Cell proliferation was detected by CCK-8 method. The ability of cell migration and invasion was evaluated by scratch healing and Transwell test. The target relationship between miR-515-5p and ITLN2 was detected by double luciferase reporter gene. RT-qPCR was used to detect the relative expression of miR-515-5p and *ITLN2* mRNA in each group. Western blotting was used to detect the relative expression of ITLN2, interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) protein. **Results**　The relative expression of miR-515-5p in EMT eutopic

and ectopic endometrium was significantly higher than that in normal endometrium (both *P*<0.001). The *ITLN*2 mRNA level in EMT eutopic and ectopic endometrium was significantly lower than that in normal endometrium, and *ITLN*2 mRNA level in ectopic endometrium was significantly lower than that in eutopic endometrium (all *P*<0.001). The level of ITLN2 protein in EMT ectopic endometrium was significantly lower than that in EMT eutopic endometrium and normal endometrium (both *P*<0.001), and the protein level of ITLN2 in EMT eutopic endometrium was significantly lower than that in normal endometrium (*P*<0.001). In miR-515-5p inhibitor group, the cell survival rate [(54.71±2.78)%], the scratch healing rate [(38.31±3.78)%], invasion number (286.67±25.15), the relative expressions of miR-515-5p, IL-1β, IL-6 and TNF-α were significantly lower than those of the blank group [(100.00±0.00)%, *P*<0.001; (84.08±5.14)%, *P*<0.001; 515.67±22.19, *P*<0.001; *P*<0.001; *P*=0.012; *P*=0.010; *P*<0.001], the relative expression levels of *ITLN*2 mRNA and protein were significantly higher than those in the blank group (*P*<0.001; *P*<0.001). Through bioinformatics analysis and double luciferase reporter gene detection, ITLN2 was a potential target gene of miR-515-5p. **Conclusion** Lowering the level of miR-515-5p can inhibit the proliferation, migration and invasion of ESCs in EMT patients, which may be related to the targeted increase of ITLN2 expression, thereby reducing inflammatory factors level.

【Key words】 Endometriosis; MicroRNA-515-5p; Intelectins 2; Endometrial stromal cells; Proliferation; Migration; Invasion

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·流行病学研究·

不同暴露窗口空气污染对体外受精妊娠结局的影响

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【摘要】 目的 探讨不同窗口期空气污染物暴露水平与体外受精（*in vitro* fertilization，IVF）/卵胞质内单精子注射（intracytoplasmic sperm injection，ICSI）患者妊娠结局之间的关系，并探索对空气污染物暴露敏感的时间窗。方法 对 2014 年 1 月至 2021 年 12 月期间在哈尔滨医科大学附属第一医院生殖医学科接受首次新鲜卵裂期胚胎移植的 2 071 例 40 岁以下不孕症患者的资料进行回顾性队列研究。按促性腺激素（gonadotropin，Gn）启动日是否供暖将患者分为供暖季组和非供暖季组，比较两组的基线资料和妊娠结局。按 IVF/ICSI 治疗时间线划分为 4 个离散的暴露时间窗：暴露窗 1，即 Gn 启动前 75 d 到 Gn 启动日；暴露窗 2，即 Gn 启动日到取卵前一天；暴露窗 3，即取卵日到第 3 天胚胎移植日；暴露窗 4，即胚胎移植日到血清人绒毛膜促性腺激素检测日。分别计算每个患者在各个暴露窗口期 6 种空气污染物［细颗粒物（fine particulate matter，$PM_{2.5}$）、可吸入颗粒物（inhalable particulate matter，PM_{10}）、二氧化氮（nitrogen dioxide，NO_2）、二氧化硫（sulfur dioxide，SO_2）、一氧化碳（carbon monoxide，CO）和臭氧（ozone，O_3）］的日平均水平。主要结局指标是持续妊娠率。采用多因素逻辑回归模型研究不同暴露窗口期的空气污染物暴露水平与妊娠结局之间的关联，并针对重要的混杂因素进行调整。结果 供暖季组的生化妊娠率［51.7%（465/900）］、临床妊娠率［45.2%（407/900）］、持续妊娠率［38.2%（344/900）］和活产率［36.1%（325/900）］均显著低于非供暖季组［56.3%（659/1 171），*P*=0.037；51.2%（599/1 171），*P*=0.007；44.3%（519/1 171），*P*=0.005；41.3%（484/1 171），*P*=0.016］。在 4 个时间窗都可以观察到 SO_2 和 NO_2 暴露与持续妊娠呈显著负相关，SO_2 每增加一个四分位间距（interquartile range，IQR），对应 a*OR* 和 95% *CI* 分别为 0.92（0.85~0.99）、0.92（0.87~0.99）、0.93（0.87~0.99）和 0.93（0.87~0.99）。对于 NO_2，每个 IQR 增量的 a*OR* 和 95% *CI* 分别为 0.83（0.72~0.95）、0.87（0.77~0.97）、0.90（0.81~1.00）和 0.85 （0.77~0.95）。在暴露窗 1 和 4，PM_{10} 暴露与持续妊娠可能性降低显著相关（a*OR*=0.86，95% *CI*：0.75~0.98；a*OR*=0.89，95% *CI*：0.80~1.00）。在暴露窗 1，$PM_{2.5}$ 暴露与持续妊娠呈显著负关联（a*OR*=0.86，95% *CI*：0.75~0.99）。此外，在除暴露窗 3 之外的所有暴露窗口中都观察到 NO_2 暴露与临床妊娠失败显著相关（暴露窗 1：a*OR*=0.85，95% *CI*：0.74~0.97；暴露窗 2：a*OR*=0.88，95% *CI*：0.79~0.99；暴露窗 4：a*OR*=0.89，95% *CI*：0.81~0.99）。没有显示 CO 和 O_3 对妊娠结局的影响。结论 空气污染物暴露会降低 IVF/ICSI 鲜胚移植周期持续妊娠的可能性，并且在 IVF 助孕之前的窦前卵泡到窦卵泡阶段，这种影响同样存在。在几乎所有暴露窗口中都观察到，NO_2 暴露与临床妊娠和持续妊娠失败显著相关，提示 NO_2 可能是与 IVF 妊娠结局相关的主要空气污染物。

【关键词】 受精，体外； 空气污染； 二氧化氮； 持续妊娠

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Association between ambient air pollution and pregnancy outcomes in women undergoing *in vitro* fertilization

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【**Abstract**】 **Objective** To investigate the association between exposure to ambient air pollutants and pregnancy outcomes in patients undergoing *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI), and to clarify the susceptible windows of exposure. **Methods** A retrospective cohort study was conducted on 2 071 infertile women aged ≤40 years who underwent the first fresh cleavage stage embryo transfer in the Department of Reproductive Medicine of the First Affiliated Hospital of Harbin Medical University from January 2014 to December 2021. Patients were divided into heating season group and non-heating season group based on whether the start date of gonadotropin (Gn) was during the heating season or not, and baseline data and pregnancy outcomes were compared between the two groups. Daily average levels of six criteria air pollutants [fine particulate matter ($PM_{2.5}$), inhalable particulate matter (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), ozone (O_3) max-8 h] in four discrete periods were obtained. The four discrete periods included period 1, 75 d prior to Gn start to Gn start; period 2, Gn start to oocyte retrieval; period 3, oocyte retrieval to day 3 embryo transfer; period 4, embryo transfer to serum human chorionic gonadotropin test. The primary outcome was ongoing pregnancy. A multiple logistic regression model was used to investigate the association between air pollutant exposure and pregnancy outcomes, adjusted for important confounders. **Results** The biochemical pregnancy rate [51.7% (465/900)], the clinical pregnancy rate [45.2% (407/900)], the ongoing pregnancy rate [38.2% (344/900)], and the live birth rate [36.1% (325/900)] in the heating season group were significantly lower than those in the non-heating season group [56.3% (659/1 171), *P*=0.037; 51.2% (599/1 171), *P*=0.007; 44.3% (519/1 171), *P*=0.005; 41.3% (484/1 171), *P*=0.016]. A significant negative correlation was observed between SO_2 and NO_2 exposure and ongoing pregnancy in all four time windows. SO_2 increased by one interquartile range (IQR), corresponding to adjusted *OR* (a*OR*) and 95% *CI* were 0.92 (0.85–0.99), 0.92 (0.87–0.99), 0.93 (0.87–0.99) and 0.93 (0.87–0.99), respectively. An IQR increase in NO_2 was also significantly associated with decreased odds of ongoing pregnancy (a*OR*=0.83, 95% *CI*: 0.72–0.95; a*OR*=0.87, 95% *CI*: 0.77–0.97; a*OR*=0.90, 95% *CI*: 0.81–1.00; a*OR*=0.85, 95% *CI*: 0.77–0.95, respectively). During period 1 and period 4, we observed adverse effects of PM_{10} exposure on ongoing pregnancy (a*OR*=0.86, 95% *CI*: 0.75–0.98; a*OR*=0.89, 95% *CI*: 0.80–1.00, respectively). In Period 1, $PM_{2.5}$ exposure was significantly associated with reduced odds for ongoing pregnancy with a*OR*=0.86, 95% *CI*: 0.75–0.99. In addition, NO_2 exposure was associated with a decreased likelihood of achieving clinical pregnancy

across all exposure windows except for period 3. However, no associations were noted with CO and O_3. **Conclusion** Ambient air pollution has detrimental effects on pregnancy outcomes in patients undergoing fresh embryo transfer. Notably, the adverse impacts were also observed during preantral-antral follicle transition stage before IVF/ICSI treatment. A significant negative association between NO_2 exposure and pregnancy outcomes was observed in almost all exposure windows, indicating that NO_2 may be the main air pollutant associated with adverse pregnancy outcomes.

【Key words】 Fertilization *in vitro*; Ambient air pollution; NO_2; Ongoing pregnancy

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·临床报道·

人卵泡液中肾素-血管紧张素系统与年龄、卵巢功能及 IVF 实验室结局的相关性研究

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【摘要】 目的 探索人卵泡液（human follicular fluid，hFF）中肾素-血管紧张素系统（renin-angiotensin system，RAS）与年龄、卵巢功能及体外受精（*in vitro* fertilization，IVF）实验室结局的相关关系。方法 设计非干预的观察性研究，收集 2021 年 1 月至 2022 年 2 月期间在苏州大学附属第一医院生殖医学中心单纯因男方因素接受 IVF 女性患者的 hFF 及不包含个人身份的病历信息。采用酶联免疫吸附试验试剂盒检测 hFF 中的肾素、血管紧张素转换酶（angiotensin converting enzyme，ACE）、ACE2、血管紧张素（angiotensin， Ang）Ⅱ和 Ang 1-7 的水平。一元线性回归用于 RAS 组分与年龄的相关性分析，多元线性回归用于 RAS 组分与卵巢功能及 IVF 实验室结局的相关性分析。结果 ①共获 139 例可分析样本。②年龄与肾素（Pearson's r=−0.313 3， P<0.001）、ACE（Pearson's r=−0.183 6， P=0.031）、AngⅡ（Pearson's r=−0.218 6， P=0.010）、ACE/ACE2（Pearson's r=−0.319 2，

P<0.001）、AngⅡ/Ang1-7（Pearson's *r*=−0.224 3， *P*=0.008）存在线性负相关关系，而与 ACE2、Ang1-7 的线性关系不显著（均 *P*>0.05）。③基础卵泡刺激素与年龄（*β*=0.636， *P*<0.001）、ACE2（*β*=0.267， *P*=0.026）和 AngⅡ（*β*=0.268，*P*=0.001）呈正相关，与 ACE（*β*=−0.320，*P*<0.001）和 Ang1-7（*β*=−0.217，*P*=0.014）呈负相关；黄体生成素与 AngⅡ（*β*=0.330， *P*=0.003）呈正相关，与 Ang1-7（*β*=−0.395， *P*=0.002）呈负相关；窦卵泡计数与 Ang1-7（*β*=0.153， *P*=0.049）呈正相关，与年龄（*β*=−0.869， *P*<0.001）和 ACE2（*β*=−0.082， *P*=0.004）呈负相关；基础抗苗勒管激素仅与年龄（*β*=−0.349， *P*<0.001）呈负相关；基础雌二醇、孕酮、泌乳素、睾酮与年龄及 RAS 的相关关系不显著（均 *P*>0.05）。④获卵数与肾素（*β*=0.146，*P*=0.014）、AngⅡ（*β*=0.113，*P*=0.034）和 Ang1-7（*β*=0.185，*P*=0.002）呈正相关，与年龄（*β*=−0.717，*P*<0.001）呈负相关；MⅡ卵成熟率与 AngⅡ（*β*=0.207，*P*=0.019）和 Ang1-7（*β*=0.217， *P*=0.026）呈正相关，与年龄（*β*=−0.518，*P*<0.001）呈负相关；双原核胚胎率、可移植胚胎率、优质胚胎率仅与年龄呈负相关（均 *P*<0.05）。结论　卵泡局部 RAS 受到年龄影响，且与卵巢功能及 IVF 实验室结局存在一定关系。

【关键词】 受精，体外； 卵泡液； 肾素-血管紧张素系统； 年龄； 卵巢

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Association of the renin-angiotensin system components in human follicular fluid with age, ovarian function and IVF laboratory outcomes

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【**Abstract**】 **Objective** To investigate the association between the local renin-angiotensin system (RAS) in human follicular fluid (hFF) and age, ovarian function, *in vitro* fertilization (IVF) laboratory outcome. **Methods** A non-intervention observational study was designed. hFF and medical case history without personal identity of patients who received IVF simply because of male factor infertility in Reproductive Medicine Center, the First Affiliated Hospital of Soochow University during January 2021 and February 2022 were collected. The renin, angiotensin converting enzyme (ACE), ACE2, angiotensin (Ang)Ⅱ and Ang 1-7 levels were detected by enzyme-linked immunosorbent assay kit. The correlation between age and RAS in hFF was analyzed by simple linear regression, and multivariate linear regression was used to further analyze the correlation between the RAS and IVF laboratory outcome. **Results** 1) A total of 139 samples of analysable hFF were obtained. 2) There was a linear negative correlation between age and renin (Pearson's *r*=−0.313 3, *P*<0.001), angiotensin converting enzyme (ACE; Pearson's *r*=−0.183 6, *P*=0.031), angiotensinⅡ (AngⅡ; Pearson's *r*=−0.218 6, *P*=0.010),

ACE/ACE2 (Pearson's r=−0.319 2, P<0.001), AngⅡ/Ang1-7 (Pearson's r=−0.224 3, P=0.008), while the linear relationship with ACE2 and Ang1-7 was not significant (all P>0.05). 3) Basal follicle-stimulating hormone was positively correlated with age (β=0.636, P<0.001), ACE2 (β=0.267, P=0.026) and AngⅡ (β=0.268, P=0.001), while negatively correlated with ACE (β=−0.320, P<0.001) and Ang1-7 (β=−0.217, P=0.014). Basal luteinizing hormone was positively correlated with AngⅡ (β=0.330, P=0.003), while negative correlated with Ang1-7 (β=−0.395, P=0.002). Antral follicle count was positively correlated with Ang1-7 (β=0.153, P=0.049), while negatively correlated with age (β=−0.869, P<0.001) and ACE2 (β=−0.082, P=0.004). Basal anti-Müllerian hormone was only negatively correlated with age (β=−0.349, P<0.001). There was no correlation between RAS and basal estradiol, progesterone, prolactin, testosterone (all P>0.05). 4) Oocyte retrieval count was positively correlated with renin (β=0.146, P=0.014), AngⅡ (β=0.113, P=0.034) and Ang1-7 (β=0.185, P=0.002), while negatively correlated with age (β=−0.717, P<0.001); MⅡ oocyte maturation rate was positively correlated with AngⅡ (β=0.207, P=0.019) and Ang1-7 (β=0.217, P=0.026), while negatively correlated with age (β=−0.518, P<0.001). There was no correlation between RAS and the rates of two pronuclei embryos, transplantable embryos, high-quality embryos (all P>0.05). **Conclusion** The local RAS in ovarian follicles is affected by age and correlated with ovarian function and IVF laboratory outcome.

【Key words】 Fertilization *in vitro*; Follicular fluid; Renin-angiotensin system; Age; Ovary

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·病案报道·

完全型圆头精子症患者精子表型、致病基因及辅助生殖治疗结局分析

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【摘要】 目的 探讨完全型圆头精子症患者临床表型、精子形态特征及辅助生殖技术治疗的效率。方法 收集 2019 年 11 月至 2022 年 5 月期间在广西壮族自治区人民医院生殖医学与遗传中心就诊的完全型圆头精子症患者（完全型圆头精子症组），采集外周血进行遗传学检测，全外显子测序挖掘致病基因，并对精液常规、精子形态及超微结构进行分析；全部患者均接受了卵胞质内单精子注射（intracytoplasmic sperm injection，ICSI）联合人工卵子激活（artificial oocyte activation，AOA）治疗。选取同日取卵的行常规 ICSI 周期患者作为对照组，并采用时差动态监测系统监测发育全程动态参数，分析 2 组受精及胚胎发育效率、发育动力学参数及临床治疗结局。结果 完全型圆头精子症组 4 例，对照组 9 例。完全型圆头精子症患者均合并精子活力低下、精子 DNA 碎片率升高，精子形态及顶体荧光染色均显示头部呈小圆形伴顶体区缺失；透射电子显微镜下圆头精子头部顶体完全缺失且多见核质松散、空泡化等异常，颈部线粒体鞘数量减少且排列杂乱，鞭毛轴丝“9+2”结构多见异常。4 例患者中 1 例为 *DPY*19L2 基因纯合缺失，1 例为 *DPY*19L2 基因新发纯合移码变异。完全型圆头精子症组受精率、双原核受精率、第 3 天优质胚胎率、第 6 天囊胚形成率、第 6 天优质囊胚形成率与对照组差异均无统计学意义（均 $P>0.05$）；完全型圆头精子症组胚胎发育早期时间参数第二极体释放时间、原核消失时间，2 至 6-细胞各时期时间显著早于对照组且差异均有统计学意义（均 $P<0.05$），2 组胚胎分裂模式差异无统计学意义（$P>0.05$）。4 例完全性圆头精子症患者中，2 例新鲜胚胎移植各活产健康男婴 1 名，2 例解冻周期移植活产健康男婴、女婴各 1 名。结论 完全型圆头精子症患者精子形态学异常表型特征明显，ICSI 联合 AOA 是有效的辅助生殖治疗手段。

【关键词】 精子注射，细胞质内； 延时成像； 圆头精子症； 卵子人工激活

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Analysis of sperm phenotype, pathogenic genes and assisted reproductive therapy outcomes in patients with total globozoospermia

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【 Abstract 】 **Objective** To analyze the clinical phenotype, sperm morphological characteristics and assisted reproductive therapy efficiency in patients with total globozoospermia. **Methods** Four male patients with total globozoospermia were collected during November 2019 to May 2022 from Reproductive Medical and Genetic Center, the People's Hospital of Guangxi Zhuang Autonomous Region. Peripheral blood samples were collected for genetic detection and the whole exome sequencing to explore the pathogenic genes. Semen characteristics, sperm morphology and ultrastructure were analyzed. Four patients

were treated with intracytoplasmic sperm injection (ICSI) combined with artificial oocyte activation (AOA). Conventional ICSI cycles (*n*=9) were selected as control group, and the development dynamic parameters were monitored by Time-lapse. The fertilization and embryo development parameters, developmental dynamic parameters and clinical outcomes were analyzed between the two groups. **Results** Four patients were complicated with low sperm motility and increased sperm DNA fragmentation. Sperm morphology analysis and acrosome fluorescence staining represented that all the spermatozoas were with a small round head lacked of acrosome. By the transmission electron microscope, it was observed that round-headed spermatozoas were lacked of acrosome completely, loose chromatin structure, vacuolation and other abnormal changes in the head, mitochondrial sheath in neck were reduced arranged in disorder, and the structure of "9+2" of the flagellar axial filament was incomplete. Of the 4 patients, 1 was homozygous deletion of *DPY*19L2 gene and 1 was homozygous frameshift mutation of *DPY*19L2 gene. There were no significance differences in fertilization rate, two pronuclei fertilization rate, day 3 high-quality embryo rate, day 6 blastocyst formation rate and day 6 high-quality blastocyst formation rate between total globozoospermia group and control group (all *P*>0.05). The developmental dynamic parameters as the time at which the second polar body is extruded, the time when both (or the last) PN disappear, two to six discrete cells in the total globozoospermia group were significantly earlier than those in control group, and the difference was statistically significant (all *P*<0.05). There was no significant difference in the embryo cleavage patterns between the two groups (*P*>0.05). Among the 4 patients with total globozoospermia, 2 live births with signal healthy male baby were achieved by fresh embryo transfer, and 2 live births with one signal healthy male baby and one healthy female baby were achieved by frozen-thawed embryo transfer respectively. **Conclusion** Abnormal morphology characteristics of spermatozoas from patients with total globozoospermia are obvious, patients with total globozoospermia could have favorable clinical outcomes following ICSI combined with AOA.

【**Key words**】 Sperm injection, intracytoplasmic; Time-lapse imaging; Globozoospermia; Artificial oocyte activation

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宫腔观察吸引手术技术在剖宫产瘢痕妊娠治疗中应用的初探

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【摘要】 目的　了解宫腔观察吸引手术技术在剖宫产瘢痕妊娠（cesarean scar pregnancy，CSP）治疗中的应用效果及安全性。方法　回顾性分析 2019 年 4 月至 2022 年 6 月期间于河北医科大学第二医院妇产科采用宫腔观察吸引手术技术作为初始治疗的 7 例 CSP 患者的临床资料。所有患者均使用一次性摄像吸引管同步观察吸引，术前 3 h 放置一次性宫颈扩张器，术后 3 d 复查血 β-人绒毛膜促性腺激素（human chorionic gonadotropin，hCG）及超声检查，必要时进行宫腔镜治疗。结果　7 例 CSP 患者中Ⅰ型 3 例，Ⅱ型 4 例，年龄为（33.9±4.7）岁，范围为 27~40 岁，停经时间范围为 38~47 d，中位时间是 43 d。所有患者手术过程均顺利，术中中位出血量 30 mL，术后中位出血量 20 mL，术后中位出血时间 3 d，无子宫穿孔和术中大出血发生，术后所有患者血 β-hCG 均下降满意，6 例复查超声未见明显异常，1 例Ⅱ型患者因超声提示瘢痕部位强回声伴随丰富血流信号行宫腔镜电切术。结论　宫腔观察吸引手术技术借助其内置于吸引管头端的高清摄像头，能真正做到观察与吸引同步，有望应用于停经≤47 d 的Ⅰ型及部分Ⅱ型 CSP 的治疗。

【关键词】 剖宫产瘢痕妊娠；　宫腔观察吸引手术技术；　一次性摄像吸引管

Preliminary study of application effect of intrauterine observation suction surgery technique in the treatment of caesarean scar pregnancy

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【 **Abstract** 】 **Objective** To study application effect and safety of intrauterine observation suction surgery technique in the treatment of cesarean scar pregnancy (CSP). **Methods** A total of 7 patients with CSP who were treated with intrauterine observation suction surgery technique in Department of Obstetrics and Gynecology, the Second Hospital of Hebei Medical University from April 2019 to June 2022 were analyzed retrospectively. All patients used a disposable camera suction tube to observe the attraction synchronously. A disposable cervical dilator was placed 3 h before operation. Blood β-human chorionic gonadotropin (hCG) and ultrasound were reexamined 3 d after operation, and hysteroscopic treatment was supplemented if necessary. **Results** Seven patients included 3 cases of type Ⅰ CSP and 4 cases of type Ⅱ CSP, the age was (33.9±4.7) years ranging from 27 to 40 years,

menopause ranged from 38 d to 47 d with median time of 43 d. The operation process of all patients was smooth, the median blood loss during operation was 30 mL, the median blood loss after operation was 20 mL, the median bleeding time after operation was 3 d, and there was no uterine perforation and massive bleeding during operation. Three days after operation, blood β-hCG decreased satisfactorily in all patients. Six cases showed no pregnant tissue residue, 1 case underwent hysteroscopic resection due to strong echo with slightly rich blood flow signal at the scar site. **Conclusion** With the help of the high-definition camera built into the suction tube, the observation and suction can be synchronized with the suction technique, and can be applied to the treatment of type I and some type Ⅱ CSP with menopausal time no more than 47 d.

【Key words】 Cesarean scar pregnancy; Intrauterine observation suction surgery technique; Disposable camera suction tube

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·综述·

高龄妊娠对孕产妇心理及子代神经行为发育的影响及相关机制研究进展

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【摘要】 随着生活方式、婚育观念及生育政策的变化，我国高龄孕妇比例快速攀升。高龄妊娠和高龄所致的母体压力状态是孕妇心理健康及其子代神经行为发育的独立危险因素。本文系统阐述了胶质细胞源性神经营养因子、下丘脑-垂体-肾

上腺轴、5-羟色胺系统、催产素等影响高龄孕产妇心理及子代神经行为发育的作用机制及潜在干预手段，目前的干预手段主要包括人工补充剂、抗抑郁药物、体育锻炼、营养素补充等，但疗效有限且部分治疗措施有较高的不良反应发生风险，目前尚缺乏具有针对性的、系统的干预措施。未来研究中应进一步深入探究相关发病机制并提出更加安全有效的干预措施，保障高龄孕产妇心理健康及其子代的长期健康发展。

【关键词】 母亲年龄； 孕产妇健康； 发育障碍； 神经行为学表现； 胶质细胞源性神经营养因子； 血清素； 催产素； 下丘脑-垂体-肾上腺轴

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Research progress on the effect of advanced maternal age on maternal psychology and neurobehavioral development of their offspring and related mechanisms

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【Abstract】 With the changes in lifestyle, marriages and childbearing concepts, and population policies in recent years, the proportion of women with advanced maternal age (AMA) in China is rising rapidly. AMA and maternal stress due to advanced age are considered as independent risk factors for maternal mental health and the neurobehavioral development of their offspring. In this paper, we summarized how the glial cell line-derived neurotrophic factor, the hypothalamic-pituitary-adrenal axis, the 5-HT system and the oxytocin affect the maternal mental health and the neurobehavioral development of their offspring, as well as some potential targeted interventions. Interventions currently being developed include artificial supplements, antidepressants, physical exercise, nutrient supplementation, etc., but they have a limited efficacy and a high risk of side effects, yet there is still a lack of specific and systematic interventions. The relevant pathogenesis should continue to be explored in the future research, and hopefully more effective and safe interventions will be given in the near future to improve the mental health of mothers with AMA and the long-term healthy development of their offspring.

【Key words】 Maternal age; Maternal health; Developmental disabilities; Neurobehavioral manifestations; Glial cell line-derived neurotrophic factor; Serotonin; Oxytocin; Hypothalamic-pituitary-adrenal axis

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·综述·

外泌体治疗宫腔粘连的研究进展

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【摘要】 外泌体是一类细胞外囊泡，是近年来子宫内膜损伤后再生与修复领域的研究热点。外泌体可由多种细胞释放，能通过 miRNA 等多种生物活性物质调节受体细胞功能，从而有效促进组织的再生修复。宫腔粘连（intrauterine adhesions，IUA）是一种常见的由于子宫创伤、感染、遗传因素等导致子宫内膜基底层受损的子宫内膜损伤性疾病，常因宫腔部分或全部闭塞而引起月经异常、不孕或反复流产等临床问题，是女性生育困难原因中不可忽视的一部分，并且现有的治疗措施无法实现满意的子宫内膜损伤后修复效果。因此，近年来有研究对外泌体促进 IUA 中内膜修复、生育力恢复的作用进行新探索，证明了外泌体修复内膜损伤的有效性，并逐渐摸索出其中的作用机制。外泌体凭借抑制细胞凋亡和上皮间质转化及纤维化、促进细胞增殖和血管生成、参与免疫调控等作用，可增加受损内膜的厚度和腺体数量，并提高子宫内膜容受性及生育力，将来有望成为 IUA 的新型治疗手段。本文将对外泌体治疗 IUA 的研究进展进行综述。

【关键词】 外泌体；　上皮间质转化；　宫腔粘连

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Research progress in the treatment of intrauterine adhesions with exosomes

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【Abstract】 Exosomes, a kind of extracellular vesicles, are a research hotspot in the field of regeneration and repair in the circumstance of endometrial injury recently. Exosomes can be released by a variety of cells, and can regulate the function of receptor cells through miRNA and other bioactive substances, thus effectively promoting tissue regeneration and repair. Intrauterine adhesions (IUA) is a common endometrial injury disease resulting from uterine trauma, infection, genetic factors and other causes of damage to the endometrial basal layer. It often causes clinical problems such as abnormal menstruation, infertility and repeated abortion due to partial or total occlusion of the uterine cavity, leading to female reproductive difficulties, and the existing remedies can not achieve satisfactory repair effect concerning endometrial injuries. Therefore, recent studies have been exploring the role of exosomes in promoting endometrial repair and fertility recovery in IUA, proving the effectiveness of exosomes in repairing endometrial damage, and exploring the mechanism. Through inhibiting apoptosis, downregulating the level of epithelial-mesenchymal transition and fibrosis, facilitating cell proliferation, promoting angiogenesis, and regulating immune responses, exosomes can increase the thickness of damaged endometrium and the number of glands, and enhance endometrial receptivity and fertility, thus expected to be a new treatment for IUA in the future. Herein, we will review the research progress in the treatment of IUA with exosomes.

【Key words】 Exosomes; Epithelial-mesenchymal transition; Intrauterine adhesions

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·综述·

高强度聚焦超声消融治疗子宫腺肌病的研究进展

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【摘要】 子宫腺肌病（adenomyosis，ADS）是育龄期妇女常见的良性疾病，主要症状为痛经、月经量增多、子宫增大和不孕等。近年来随着 ADS 确诊患者的年轻化及生育政策的调整，保留生育功能的治疗方法逐渐受到重视。高强度聚焦超声（high-intensity focused ultrasound，HIFU）消融以其非侵入性、高准确性和可重复性等特点，较好地保留了子宫结构与功能的完整性，在保留生育功能的 ADS 治疗中展现出优势。HIFU 消融治疗明显改善 ADS 患者的临床疗效以及妊娠结局，提高 HIFU 消融治疗 ADS 病灶的消融率更有益于上述结果。此外，HIFU 消融相较其他微创治疗在保护生育力方面也具有一定优势。本文围绕 HIFU 消融治疗 ADS 保留生育功能的临床应用和研究总结作一综述。

【关键词】 子宫腺肌病； 妊娠结局； 高强度聚焦超声消融； 生育功能

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Advances of high-intensity focused ultrasound ablation for the treatment of adenomyosis

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【Abstract】 Adenomyosis (ADS) is a common benign disease in women of childbearing age. The main symptoms are dysmenorrhea, increased menstrual volume, uterine enlargement and infertility. In recent years, with the younger age of ADS patients and the adjustment of fertility policy, the treatment of fertility preservation has gradually attracted attention. High-intensity focused ultrasound (HIFU) ablation has the characteristics of non-invasive, high accuracy and repeatability, which better preserves the integrity of uterine structure and function, and shows advantages in the treatment of ADS with fertility preservation. HIFU ablation significantly improves clinical outcomes as well as pregnancy outcomes in patients with ADS, and increasing the ablation rate of HIFU ablation for ADS lesions is more beneficial to these outcomes. In addition, HIFU ablation has some advantages in terms of fertility preservation compared with other minimally invasive treatments. This article reviewed the clinical application and research of HIFU ablation for ADS fertility preservation.

【Key words】 Adenomyosis; Pregnancy outcomes; High-intensity focused ultrasound ablation; Reproductive function

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·综述·

自噬在多囊卵巢综合征发病机制中的研究进展

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【摘要】 多囊卵巢综合征（polycystic ovary syndrome， PCOS）是临床常见的女性内分泌疾病，是导致女性不孕症的原因之一，影响女性健康的多个方面。目前医学界对该病发病机制的研究仍没有明确定论。自噬作为一种进化上保守、高度调节的分解代谢过程，能够影响卵泡生长，调控子宫内膜功能，与 PCOS 中高雄激素血症、胰岛素抵抗、肥胖、慢性炎症、氧化应激等内分泌代谢紊乱密切相关。本文对近几年文献报道的关于自噬在 PCOS 发病机制中的研究情况进行了综述，以期对 PCOS、不孕症等生殖相关疾病的临床诊疗提供新思路。

【关键词】 自噬； 多囊卵巢综合征； 内分泌代谢紊乱； 发病机制

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Research progress of autophagy in pathogenesis of polycystic ovary syndrome

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【Abstract】 Polycystic ovary syndrome (PCOS) is a common clinical female endocrine disease, which is one of the causes of female infertility and affects many aspects of female health. At present, there is still no definite conclusion on the pathogenesis of this disease. As an evolutionarily conserved and highly regulated catabolic process, autophagy can affect follicle growth and regulate endometrial function, and is closely related to endocrine and metabolic disorders such as hyperandrogenemia, insulin resistance, obesity, chronic inflammation and oxidative stress in PCOS. In this paper, the studies on autophagy in the pathogenesis of PCOS reported in recent years were reviewed, in order to provide new ideas for the clinical diagnosis and treatment of PCOS, infertility and other reproductive diseases.

【Key words】 Autophagy; Polycystic ovary syndrome; Endocrine and metabolic disorders; Pathogenesis

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·综述·

基质细胞衰老在子宫内膜蜕膜化及容受性建立中的作用机制

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【摘要】 胚胎着床过程复杂而精密。胚胎质量、子宫内膜容受性以及两者的同步发育是决定胚胎着床的关键因素。蜕膜化是子宫内膜基质细胞转变为分泌型的蜕膜基质细胞的过程，与子宫内膜容受性密切相关。异常蜕膜化可导致胚胎着床失败或不良妊娠结局。最新研究表明子宫内膜蜕膜化中存在子宫内膜基质细胞衰老的现象，一定程度的基质细胞衰老促进蜕膜化和容受性建立，而过度或不足的基质细胞衰老则可能导致蜕膜化异常和容受性受损。本文旨在对基质细胞衰老在子宫内膜蜕膜化及容受性建立中的作用进行综述，以期为容受性相关疾病的发病机制和治疗提供新的启示。

【关键词】 胚胎植入； 细胞衰老； 子宫内膜； 蜕膜化； 子宫内膜容受性

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Potential role of stromal cell senescence in endometrial decidualization and the acquisition of endometrial receptivity

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【Abstract】 Embryo implantation is a complicated and elaborately regulated process. Embryo quality, endometrial receptivity and synchronized embryo-endometrium development are key determinants for embryo implantation. Decidualization refers to the differentiation of endometrial stromal cells into decidual stromal cells with a specific secretory phenotype and is closely related to endometrial receptivity. Abnormal decidualization results in implantation failure or adverse pregnancy events. Recent studies have revealed that endometrial stromal cell senescence takes place in endometrial decidualization. While moderate stromal cell senescence promotes endometrial decidualization and the establishment of endometrial receptivity, excessive or deficient stromal cell senescence could lead to abnormal decidualization and impaired receptivity. This review aims to summarize the potential role of stromal cell senescence in endometrial decidualization and the acquisition of endometrial receptivity to provide new insights in the pathogenesis and treatment of receptivity-associated diseases.

【Key words】 Embryo implantation; Cellular senescence; Endometrium; Decidualization; Endometrial receptivity

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·综述·

人类生殖细胞低温冷冻保存现状与研究进展

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【摘要】 人类生殖细胞低温冷冻作为生育力保存的一种方式，在辅助生殖技术（assisted reproductive technology，ART）发展中起着重要作用，目前该技术已成为生殖医学领域的研究热点之一，并在辅助生殖实践中得到越来越广泛的应用。为提高 ART 的成功率，冷冻保存技术在发展中不断改进，尤其是冷冻策略的选择和冷冻保护剂的改良与优化。冷冻保存技术适用于行 ART 治疗或是因疾病导致的生育力下降而进行的卵母细胞、精子、胚胎冷冻保存的群体，也适用于癌症患者为保存生育力而进行的卵巢及睾丸组织冷冻保存。然而，不同的冷冻方法对于不同生殖细胞类型的冷冻效果并不一致，且目前不同生殖细胞冷冻效果的评价尚缺乏合理有效的标准。本文综述了人类生殖细胞低温冷冻保存技术的发展现状及应用，并探讨了低温保存未来的发展方向。

【关键词】 卵母细胞；　精子；　睾丸组织；　胚胎；　卵巢组织；　低温冷冻保存

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Current status and research progress in the development of cryopreservation of human germ cells

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【Abstract】 Cryopreservation of human germ cells as a form of fertility preservation plays an important role in the development of assisted reproductive technology (ART), which has become one of the research hotspots in the field of reproductive medicine and is increasingly used in assisted reproductive practice. To improve the success rate of ART, cryopreservation techniques are constantly being improved in development, especially the selection of freezing strategies and the improvement and optimization of cryoprotectants. Cryopreservation is indicated for groups undergoing ART or for the freezing and preservation of oocytes, sperm and embryos due to reduced fertility caused by disease. It is also indicated for the cryopreservation of ovarian and testicular tissue for fertility preservation in cancer patients. However, the freezing effect of different freezing methods is not consistent for different germ cell types, and there is a lack of reasonable and valid criteria for evaluating the freezing effect of different germ cells. This paper reviews the current development and application of cryopreservation technology for human germ cells and discusses the future development of cryopreservation.

【**Key words**】 Oocytes; Sperm; Testicular tissue; Embryos; Ovarian tissue; Cryopreservation

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