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·PGT 专栏·

PGT 专栏导读

胚胎植入前遗传学检测（preimplantation genetic testing，PGT）最早由 Edwards 于 1964 年提出。1990 年世界上首例选择排除性连锁疾病的胚胎移植入母体获得妊娠并分娩了健康新生儿，标志着 PGT 技术的诞生。在世界范围内，PGT 自临床应用以来，已经历三十余年，该技术在临床上的有效开展，显著降低了异常新生儿出生的风险，最大程度地阻断遗传疾病的垂直传递。

PGT 在临床应用的过程中，也有了长足的进步，主要表现在两个方面：首先，活检取材经历了由极体（polarbody）—卵裂球（blastomere）—滋养外胚层细胞（trophectoderm，TE）—培养液/囊胚腔液（blastocoel fluid， BF）的过程，其趋势是取材由有创到无创，保证检测结果准确的同时，降低由活检造成的对胚胎发育潜能可能的影响，降低可能的子代表观遗传发生异常，避免由此引起的子代体格、行为和心理发育的异常。其次，检测技术经历了聚合酶链反应（polymerase chain reaction，PCR）—荧光原位杂交（fluorescence *in situ* hybridization，FISH）—微阵列比较基因组杂交（array-based comparative genomic hybridization，array-CGH）—高通量测序（二代测序技术）—单分子测序（三代测序技术）的发展，其趋势是检测范围更加全面，检测发现能力逐渐提升，检测成本逐渐减低。在 PGT 的临床应用中，各类活检方法和检测技术虽存在一定程度的更替，但又互为补充。

国内专家为规范 PGT 的临床应用，相继出台了《高通量基因测序植入前胚胎遗传学诊断和筛查技术规范（试行）》《胚胎植入前遗传学诊断/筛查技术专家共识》《高通量测序技术临床检测规范化应用北京专家共识》《应用胚胎植入前遗传学检测技术阻断常染色体显性多囊肾病遗传的中国专家共识》等规范和共识。目前 PGT 的临床应用分为胚胎植入前非整倍体检测（PGT for aneuploidies，PGT-A）、胚胎植入前单基因遗传病检测（PGT for

monogenic/single gene defects，PGT-M）和胚胎植入前染色体结构重排检测（PGT for chromosomal structural rearrangements，PGT-SR）。PGT-M 和 PGT-SR 在一定程度上逐渐发展成为替代传统产前诊断的方法，最大程度地减少由于产前诊断结果异常带来的终止妊娠的发生，避免由此给女性及家庭带来的身心创伤。同时，虽然 PGT-A 在临床应用受到一定争议，但对于胚胎有染色体非整倍体高风险的夫妻，PGT-A 的广泛开展，为无数家庭在尽可能短的时间获得健康子代提供了可能。

本期专栏邀请生殖学科专家对 PGT 在临床应用中遇到的问题，如嵌合胚胎的取舍和移植后的风险、活检技术的安全性、各种 PGT 检测技术效能的比较、无创 PGT 技术在临床开展的可行性、染色体多态性是否要进行 PGT、PGT 开展中相关的伦理问题、活检/扩增失败的补救措施和如何高效进行罕见/新发单基因病的 PGT-M 等展开讨论，希望为 PGT 在临床上安全有效地应用提供更多的循证医学证据和经验。

感谢各位专家同行的贡献，为无数生殖医学工作者提供“操千曲而后晓声，观千剑而后识器”的途径，为年轻的生殖人“博观而约取，厚积而薄发”作出贡献。

如有不妥之处，恳请各位同仁批评指正。

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·PGT 专栏·

基于囊胚期活检的胚胎植入前非整倍体遗传学检测对高龄女性母婴结局的影响

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【摘要】 目的 探讨基于囊胚期活检的胚胎植入前非整倍体遗传学检测（preimplantation genetic testing for aneuploidies，PGT-A）对高龄女性妊娠结局及子代健康的影响。方法 采用回顾性队列研究，选取 2016 年 1 月至 2018 年 12 月期间在北京大学第三医院妇产科生殖医学中心采用卵胞质内单精子注射（intracytoplasmic sperm injection， ICSI）后行 PGT-A（记为 PGT-A 组）或单纯 ICSI（记为对照组）助孕、年龄≥35 岁、单囊胚解冻移植的患者。同时根据年龄进一步分为 35~37 岁亚组和≥38 岁亚组。主要结局为活产，次要结局包括人绒毛膜促性腺激素（human chorionic gonadotropin，hCG）阳性、临床妊娠、妊娠丢失、妊娠期糖尿病、妊娠期高血压、胎龄、早产、剖宫产、低出生体质量儿、巨大儿、小于胎龄儿及大于胎龄儿等。结果 对于高龄患者，PGT-A 组的活产率显著高于对照组［38.0%（89/234）比 26.8%（237/885），*OR*（95% *CI*）=1.49（1.13~1.97），*P*=0.047］，其流产率显著低于对照组［17.6%（19/108）比 29.0%（116/443），*OR*（95% *CI*）=0.45（0.24~0.85），*P*=0.013］。≥38 岁亚组患者 PGT-A 组的活产率［*OR*（95% *CI*）=3.01（1.67~5.44），*P*<0.001］、hCG 阳性率［*OR*（95% *CI*）=2.08（1.25~3.47），*P*=0.005］、临床妊娠率［*OR*（95% *CI*）=2.39（1.40~4.07），*P*=0.001］均显著高于对照组，且 PGT-A 组的流产率显著低于对照组［*OR*（95% *CI*）=0.34（0.13~0.85），*P*=0.022］；而 35~37 岁亚组患者，其妊娠结局在两组间差异均无统计学意义（均 *P*>0.05）。高龄女性的产科并发症及其新生儿结局发生情况在 PGT-A 组和对照组间差异均无统计学意义（均 *P*>0.05），根据年龄进行的亚组分析也得出了一致结论。结论 基于囊胚期活检的 PGT-A 可显著提高≥38 岁患者在单囊胚解冻移植周期中的 hCG 阳性率、临床妊娠率及活产率，并显著降低流产率，但并未显示 PGT-A 对 35~37 岁患者的妊娠结局有改善效果。此外，PGT-A 的使用并不会增加高龄女性产科并发症及其新生儿不良结局的发生风险。

【关键词】 胚胎植入前非整倍体遗传学检测； 囊胚期活检； 高龄； 妊娠结局； 子代健康

基金项目：国家自然科学基金重点项目（81730038）；北京市科技计划课题（Z191100006619086）

Maternal and perinatal outcomes after preimplantation genetic testing for aneuploidies using blastocyst biopsy for women of advanced age

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【Abstract】 **Objective** To examine the effects of preimplantation genetic testing for aneuploidies (PGT-A) using blastocyst biopsy on maternal and perinatal outcomes for women of advanced age. **Methods** A retrospective cohort study was conducted during January 2016 to December 2018 at Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital. Women who were aged ≥35 years, underwent intracytoplasmic sperm injection (ICSI, control group) or PGT-A after ICSI (PGT-A group) with single frozen-thawed blastocyst transferred were eligible in this study. They were further divided into 35–37 years old subgroup and ≥38 years old subgroup according to age. The primary outcome was live birth, and the secondary outcomes were human chorionic gonadotropin (hCG) positivity, clinical pregnancy, pregnancy loss, hypertension in pregnancy, gestational diabetes mellitus, gestational age, preterm birth, caesarean section, low birth weight, small gestational age, and large gestational age. **Results** For women aged ≥35 years, the live birth rate in PGT-A group was significantly higher than that in control group [38.0% (89/234) *vs*. 26.8% (237/885), *OR*(95% *CI*)=1.49(1.13–1.97), *P*=0.047], the miscarriage rate was significantly lower than that in control group [17.6% (19/108) *vs*. 29.0% (116/443), *OR*(95% *CI*)=0.45(0.24–0.85), *P*=0.013]. We found that for women who aged ≥38 years, the live birth rate [*OR*(95% *CI*)=3.01(1.67–5.44), *P*<0.001], hCG positivity rate [*OR*(95% *CI*)=2.08(1.25–3.47), *P*=0.005], clinical pregnancy rate [*OR*(95% *CI*)=2.39(1.40–4.07), *P*=0.001] in PGT-A group were significantly higher than those in control group, and the miscarriage rate in PGT-A group was significantly lower than that in control group [*OR*(95% *CI*)=0.34(0.13–0.85), *P*=0.022]; for women aged 35–37 years, there were no statistically significant differences in pregnancy outcomes between the two groups (all *P*>0.05). Moreover, there were no statistically significant differences in the rates of obstetric complications and perinatal outcomes for women aged ≥35 years between PGT-A group and control group (all *P*>0.05), and similar results were found in the subgroup analyses for women who aged 35–37 years or ≥38 years. **Conclusion** PGT-A using blastocyst stage biopsy strategy in single blastocyst thaw transferred cycles could significantly improve the rates of hCG positivity, clinical pregnancy, and live birth, and significantly reduce the miscarriage rate for women aged ≥38 years, but could not improve the pregnancy outcomes for women aged 35–37 years. In addition, the use of PGT-A does not increase the risk of obstetric complications and perinatal outcomes for women of advanced age.

【Key words】 Preimplantation genetic testing for aneuploidies; Blastocyst biopsy; Advanced age; Maternal outcomes; Perinatal outcomes

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·PGT 专栏·

染色体多态性：PGT-A 新指征？

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【摘要】 目的　探讨染色体多态性变异是否可以作为胚胎植入前非整倍体检测（preimplantation genetic testing for aneuploidies，PGT-A）的指征。方法　回顾性队列研究分析于郑州大学第一附属医院生殖医学中心 2012 年 1 月 1 日至 2021 年 12 月 31 日期间接受 PGT-A 解冻移植和体外受精-胚胎移植（*in vitro* fertilization and embryo transfer， IVF-ET）新鲜移植助孕患者的临床资料。根据夫妇染色体核型，PGT-A 周期分为女方染色体多态性变异（女方多态组）、男方染色体多态性变异（男方多态组）及双方染色体多态性变异（双方多态组），同期染色体正常夫妇为对照（染色体正常组）；IVF 周期分为女方染色体多态性变异（女方多态组）、男方染色体多态性变异（男方多态组），同期染色体正常夫妇为对照（染色体正常组）；比较组间实验室结果和妊娠结局。结果　PGT-A 周期中，各组间活检胚胎染色体非整倍体率、解冻移植临床妊娠率、早期流产率、活产率差异均无统计学意义（均 $P>0.05$）。IVF 新鲜胚胎移植中，各组间临床妊娠率、早期流产率、活产率差异均无统计学意义（均 $P>0.05$）。IVF 助孕后早期流产患者中，女方多态组、男方多态组和染色体正常组流产组织拷贝数变异（copy number variation，CNV）检测异常率分别为 26.67% （4/15）、57.89% （11/19）、64.59% （363/562），差异有统计学意义（$P=0.010$）。结论　夫妇染色体多态性变异不影响胚胎非整倍体，同时不影响 PGT-A 周期和 IVF 新鲜移植周期妊娠结局，且不增加流产组织染色体异常率。目前无明确证据支持染色体多态性变异可作为 PGT-A 新指征。

【关键词】 妊娠结局；　染色体多态性变异；　胚胎植入前非整倍体检测；胚胎非整倍体；　流产组织拷贝数变异

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Chromosomal polymorphisms: the new indication for PGT-A?

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【 **Abstract** 】 **Objective** To explore whether the chromosomal polymorphism variation is the new indication of preimplantation genetic testing for aneuploidies (PGT-A). **Methods** Clinical data of the patients who received PGT-A frozen-thawed embryo transfer and *in vitro* fertilization-embryo transfer (IVF-ET) fresh embryo transfer from the Center for Reproductive Medicine of the First Affiliated Hospital of Zhengzhou University from January 1, 2012 to December 31, 2021 were analyzed in a retrospective cohort study. According to the karyotype of the couples, PGT-A cycles were divided into female, male and couple chromosome polymorphism variation groups, and couples with normal chromosomes at the same time were included in control group. IVF cycles were divided into female and male chromosome polymorphism variation groups, and the couples with normal chromosomes at the same time were included in control group. The laboratory results and pregnancy outcomes were compared among the groups. **Results** In PGT-A cycles, there were no significant differences in chromosome aneuploidy rate, clinical pregnancy rate after frozen-thawed embryo transfer, early abortion rate and live birth rate among the four groups (all $P>0.05$). In IVF fresh embryo transfer cycles, there were no significant differences in clinical pregnancy rate, early abortion rate and live birth rate among the three groups (all $P>0.05$). Among the early abortion patients after IVF cycles, the abnormal rates of copy number variation (CNV) in the abortion tissues of the female chromosome polymorphism variation group, the male chromosome polymorphism variation group and the normal control group were 26.67% (4/15), 57.89% (11/19) and 64.59% (363/562), respectively, with a statistical difference ($P=0.010$). **Conclusion** Chromosomal polymorphism of couples does not affect the aneuploidy rate of embryos, and does not affect the pregnancy outcomes of PGT-A frozen-thawed embryo transfer cycle and IVF fresh embryo transfer cycle, and does not increase the chromosome abnormality rate of abortion tissues. At present, there is no clear evidence to support that chromosomal polymorphisms as a new indication of PGT-A.

【 **Key words** 】 Pregnancy outcome; Chromosomal polymorphisms; Preimplantation genetic testing for aneuploidies; Embryo aneuploid; Copy number variation of abortion tissue

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PGT-A 后不同发育时间和评级囊胚的移植临床结局及转录组特征分析

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【摘要】 目的　探讨行胚胎植入前遗传学非整倍体检测（preimplantation genetic testing for aneuploidies， PGT-A）后不同发育时间和评级囊胚移植的临床结局，并对其转录组特征进行比较分析。方法　回顾性队列研究分析 2017 年 1 月至 2021 年 12 月期间在山西省妇幼保健院生殖医学中心行 PGT-A 后选择整倍体囊胚移植的患者临床资料，共 295 个移植周期，分别按照囊胚发育时间［第 5 日（day 5，D5）组和第 6 日（day 6，D6）组］ 及囊胚评级（高质量组和一般质量组）进行分组，比较各组囊胚移植临床结局。通过比较来自 GEO 和 ENA 数据平台不同发育时间和评级的囊胚单细胞转录组数据（scRNA-seq），分析不同组间的转录组水平差异。结果　①D5 组和 D6 组男女方年龄、不孕类型、不孕年限、体质量指数（body mass index，BMI）、卵泡刺激素（follicle-stimulating hormone， FSH）、黄体生成素（luteinizing hormone，LH）、雌二醇和获卵数差异均无统计学意义（均 $P>0.05$），两组间 $M_{Ⅱ}$卵率 ［86.35% （2051/2375）比 82.71% （1770/2140），$P=0.001$］、囊胚形成率［68.08%（725/1065）比 62.14%（540/869），$P=0.006$］、着床率［72.78%（115/158）比 52.55%（72/137），$P<0.001$］、临床妊娠率［56.33%（89/158）比 43.80% （60/137），$P=0.032$］和活产率 ［53.80% （85/158）比 40.87% （56/137），$P=0.027$］相比较，D5 组都显著高于 D6 组，两组间流产率、早产率、男性比例和出生体质量差异均没有统计学意义（均 $P>0.05$）；②高质量组和一般质量组男女方年龄、不孕类型、不孕年限、BMI、FSH、LH、雌二醇和获卵数差异均没有统计学意义（均 $P>0.05$），两组间 $M_{Ⅱ}$卵率 ［87.06% （1251/1437）比 83.50%（2570/3078），$P=0.002$］、囊胚形成率［73.38%（499/680）比 61.08%（766/1254），$P<0.001$］、着床率 ［77.90% （74/95）比 56.50% （113/200），$P<0.001$］、临床妊娠率 ［61.05% （58/95）比 45.50% （91/200），$P=0.013$］和活产率 ［56.84% （54/95）比 43.50% （87/200），$P=0.032$］相比较，高质量组都显著高于一般质量组，两组间流产率、早产率、新生儿男性比例和出生体质量差异均没有统计学意义（均 $P>0.05$）；③基于 GEO 和 ENA 数据平台的 scRNA-seq 数据，挖掘 D5 和 D6 囊胚以及高质量和一般质量囊胚内细胞团（inner cell mass，

ICM）和外滋养层（trophectoderm， TE）的差异表达基因（differentially expressed genes， DEGs）。经过 KEGG 富集分析，显示 D5 组较 D6 组 ICM/TE 上调的 DEGs 显著富集在 285/288 个信号通路；高质量组较一般质量组 ICM/TE 上调的 DEGs 显著富集在 207/3 个信号通路。结论　发育 D5 囊胚比发育 D6 囊胚，高质量囊胚比一般质量囊胚都具有较好的着床和继续临床妊娠能力。对不同发育时间和评级的囊胚进行转录组水平分析比较，显示转录组特征具有显著差异。囊胚转录组水平的分析，对囊胚着床及继续临床妊娠能力具有预测价值。

【关键词】　转录组；　胚胎植入前遗传学非整倍体检测；　囊胚发育时间；囊胚评级；　临床结局

Analysis of clinical outcomes and transcriptome characteristics of blastocysts with different developmental time and grades of PGT-A embryo transfer cycles

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【Abstract】　Objective　To explore the clinical outcome of blastocysts with different developmental time and grades of preimplantation genetic testing for aneuploidies (PGT-A) embryo transfer cycles, and to compare and analyze their transcriptome characteristics. **Methods**　The clinical data of patients with euploid blastocyst transplantation selected by PGT-A in Center for Reproductive Medicine of Women Health Center of Shanxi from January 2017 to December 2021 were retrospectively analyzed. A total of 295 transplantation cycles were divided into groups according to the day of embryo blastulation [day 5 (D5) group and day 6 (D6) group] and blastocyst grade (good-quality group and fair-quality group) and their clinical outcomes were compared. By comparing the single-cell RNA sequencing (scRNA-seq) data of blastocysts of different developmental time and grades from GEO and ENA data platforms, the transcriptome level differences among different groups were analyzed. **Results**　1) There were no significant differences in age of male and female, type of infertility, infertility duration, body mass index (BMI), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and number of oocytes retrieved between D5 and D6 groups (all $P>0.05$). The M_{II} oocyte rate [86.35% (2051/2375) *vs.* 82.71% (1770/2140), $P=0.001$], blastocyst formation rate [68.08% (725/1065) *vs.* 62.14% (540/869), $P=0.006$], implantation rate [72.78% (115/158) *vs.* 52.55% (72/137), $P<0.001$], clinical pregnancy rate [56.33% (89/158) *vs.* 43.80% (60/137), $P=0.032$] and live birth rate [53.80% (85/158) *vs.* 40.87% (56/137), $P=0.027$] in D5 group were significantly higher than those in D6 group, and the results of miscarriage rate, preterm birth rate, proportion of male and birth weight between the two groups were not statistically significant. 2) There were no significant differences in age of male and female, type of infertility, infertility duration, BMI, FSH, LH, estradiol and number of oocytes retrieved between good-

quality and fair-quality groups (all *P*>0.05). The M_{II} oocyte rate [87.06% (1251/1437) *vs*. 83.50% (2570/3078), *P*=0.002], blastocyst formation rate [73.38% (499/680) *vs*. 61.08% (766/1254), *P*<0.001], implantation rate [77.90% (74/95) *vs*. 56.50% (113/200), *P*<0.001], clinical pregnancy rate [61.05% (58/95) *vs*. 45.50% (91/200), *P*=0.013] and live birth rate [56.84% (54/95) *vs*. 43.50% (87/200), *P*=0.032] in good-quality group were significantly higher than those in fair-quality group, and the results of miscarriage rate, preterm birth rate, proportion of male and birth weight between the two groups were not statistically significant. 3) Based on the scRNA-seq data from GEO and ENA data platforms, we mined differentially expressed genes (DEGs) in the inner cell mass (ICM) and trophectoderm (TE) of D5 and D6 blastocysts, good-quality blastocysts and fair-quality blastocysts. Compared with D6 group, KEGG enrichment analysis showed that DEGs up-regulated of ICM/TE in D5 group were significantly enriched in 285/288 signaling pathways. DEGs up-regulated of ICM/TE were significantly enriched in 207/3 signaling pathways in the good-quality group compared with the fair-quality group. **Conclusion** In terms of implantation and clinical pregnancy ability, D5 blastocysts were better than D6 blastocysts, and good-quality blastocysts were better than fair-quality blastocysts. Transcriptome level analysis of blastocysts with different developmental time and grades showed significant differences in transcriptome characteristics. The analysis of blastocyst transcriptome level has predictive value for blastocyst implantation and clinical pregnancy ability.

【 Key words 】 Transcriptome; Preimplantation genetic testing for aneuploidies; Day of embryo blastulation; Blastocyst grade; Clinical outcomes

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单基因病临床意义不明变异实施植入前遗传学检测的策略研究

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【摘要】 目的 探讨单基因病临床意义不明变异（variants of uncertain significance，VUS）实施胚胎植入前遗传学检测（preimplantation genetic testing，PGT）的策略。方法 招募 2018 年至 2020 年期间因携带 VUS 前来中信湘雅生殖与遗传专科医院进行生育咨询的单基因病病例，根据美国医学遗传学与基因组学学会（American College of Medical Genetics and Genomics，ACMG）发布的《ACMG 遗传变异分类标准与指南》（以下称 ACMG 指南）及贝叶斯分析法，对 VUS 致病性进行重分析，分类为"致病/可能致病变异" "倾向于致病的 VUS""致病性仍不明确的 VUS"及"倾向于良性的 VUS"。在夫妻双方自主自愿并充分理解风险的原则下，对 VUS 升级为"致病/可能致病变异"及分类为"倾向于致病的 VUS"的家系实施胚胎植入前单基因遗传学检测（preimplantation genetic testing for monogenic disorders， PGT-M）。追踪随访妊娠胎儿、出生孩子的生长发育状况。结果 ①16 例单基因病家系共检出 25 个变异，其中 1 个为致病变异（pathogenic variation，P），3 个为可能致病变异（likely pathogenic variation，LP），21 个为 VUS。重分析后，11 个 VUS 升级为 LP（52.4%），7 个重分类为"倾向于致病的 VUS"（33.3%），2 个 VUS 重分类为"致病性仍不明确的 VUS"（9.5%），1 个 VUS 重分类为"倾向于良性的 VUS"（4.8%）。②14 例单基因病家系进入 PGT-M，包括 VUS 均升级为 LP 的家系 9 例，携带 1 个 LP/P 及 1 个"倾向于致病的 VUS"家系 2 例，只携带"倾向于致病的 VUS"家系 3 例。③PGT-M 术后出生 12 个健康婴孩。根据疾病发病年龄随访出生后代，8 个子代未表现出与先证者相同的症状，4 个子代暂未见疾病症状，因尚未到发病年纪还需要持续随访。结论 针对临床上的 VUS，需要按 ACMG 指南主动寻找新证据并进行重新分析。升级为 P/LP 的 VUS 以及升级为倾向于致病的 VUS 可以在患者知情同意前提下开展 PGT-M，为 VUS 携带者夫妇降低生育单基因病患儿的风险。

【关键词】 胚胎植入前遗传学检测； 单基因病； 临床意义不明变异； 重分类

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Strategic study of preimplantation genetic testing for monogenic disorders with variants of uncertain significance

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【Abstract】 Objective To explore the strategy of preimplantation genetic testing for monogenic disorders (PGT-M) with variants of uncertain significance

(VUS). **Methods** Monogenic disorder couples who carried VUS and sought fertility counseling between 2018 and 2020 in Reproductive and Genetic Hospital of CITIC-Xiangya were recruited in this study. The pathogenicity of VUS was reanalyzed according to the Standards and Guidelines for the Interpretation of Sequence Variants released by the American College of Medical Genetics and Genomics (ACMG) and the Bayesian Classification. Those VUSs were reclassified as "pathogenic/likely pathogenic variants (P/LP)", "likely pathogenic VUS", "variants of uncertain significance", or "likely benign VUS". PGT-M was applied to families with VUS upgraded as "P/LP" or "likely pathogenic VUS" under the principle of couples fully voluntary and understanding the risks. We also followed up the developmental status of fetuses and the health condition of the born children. **Results** 1) A total of 25 variants were detected in 16 families with monogenic disorders, including 1 P, 3 LP, and 21 VUS. After reanalysis, 11 VUS and 7 VUS were upgraded as LP (52.4%) and "likely pathogenic VUS" (33.3%), respectively. Two VUS were still reclassified as "variants of uncertain significance"(9.5%), and 1 VUS was reclassified as "likely benign VUS" (4.8%). 2) PGT-M was implemented for 14 families with monogenic disorders, including 9 families with VUS upgraded as LP, 2 families with one LP/P and one "likely pathogenic VUS", and 3 families with only "likely pathogenic VUS". 3) Twelve healthy babies were born after PGT-M. Following up was done according to the onset age of diseases: 8 offsprings did not show the symptoms as probands, and 4 offsprings had not yet reached the age of onset and need continuous follow-up. **Conclusion** It is necessary to actively search for new evidence and reanalyze the pathogenicity of VUS according to ACMG guidelines before PGT-M. Under fully informed consent of the patients, PGT-M can be carried out for VUS reclassified as "P/LP" and "likely pathogenic VUS", to reduce the risk of recurrence.

【Key words】 Preimplantation genetic testing; Monogenic disorders; Variants of uncertain significance; Reclassification

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·PGT 专栏·

单精子测序技术在新发突变单基因遗传病家系胚胎植入前遗传学检测中的应用

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【摘要】 目的　探讨单精子测序技术在新发突变单基因病家系胚胎植入前遗传学检测（preimplantation genetic testing，PGT）中的应用效果和价值。方法　针对 3 个携带新发突变的常染色体遗传病家系，采用多重置换扩增技术（multiple-displacement amplification， MDA）对单精子进行全基因组扩增（whole genome amplification，WGA），通过检测扩增产物的变异位点以及目的基因上下游 2M 范围内有效单核苷酸多态性位点（single nucleotide polymorphism，SNP）位点信息，构建携带突变的风险单体型与不携带突变的正常单体型。对待测胚胎进行 WGA，产物进行高通量测序，结合单体型信息判断胚胎致病位点的携带状态，选择不携带致病变异的胚胎进行移植。结果　共挑取 16 份有效单精子样本，在原发性高草酸尿症、Kabuki 综合征、遗传性大疱性表皮松解症 3 个新发突变单基因病家系中成功构建单体型。胚胎植入前单基因遗传病检测（PGT for monogenic disorders，PGT-M）结果提示有 10 枚胚胎携带父源致病变异；6 枚胚胎不携带父源致病变异，其中 2 枚胚胎检出染色体拷贝数变异。除原发性高草酸尿症夫妇外，其余两个家系的夫妇共获得 4 枚正常胚胎，移植后均未妊娠。结论　对于家系中男性携带新发突变的夫妇，可以利用单精子测序技术构建单体型，进而进行 PGT。

【关键词】 胚胎植入前遗传学检测；　单基因疾病；　单精子测序；　新发突变

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Clinical application of single-sperm-based SNP haplotyping for PGT of monogenic hereditary disease associated with *de novo* mutations

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【Abstract】 Objective To explore the application value of single-sperm-based single-nucleotide polymorphism (SNP) haplotyping in preimplantation

genetic testing of monogenic disorders (PGT-M) associated with *de novo* mutations. **Methods** Whole genome amplification (WGA) of the isolated single sperm was performed based on the multiple displacement amplification (MDA). WGA products were tested for the pathogenic mutation site and informative polymorphic SNP loci located within 2M upstream or downstream of the target gene to establish a sperm-based SNP haplotype. Biopsy samples obtained from embryos were subjected to WGA and next-generation sequencing (NGS). All embryos were verified via haplotype analysis and normal embryos were selected for transfer. **Results** Totally 16 sperm samples were selected. Haplotypes of the affected male in 3 families with monogenic hereditary diseases including primary hyperoxaluria type 1 (PH1), Kabuki syndrome and Epidermolysis bullosa (EB) were successfully constructed using single sperm cell sequencing. PGT-M results showed that there were 10 embryos carrying paternal pathogenic variations, while the other 6 embryos did not carry paternal pathogenic variations, 2 of them had chromosomal copy number variations (CNVs). Four embryos obtained from 2 families were found to be normal after NGS according to single-sperm-based SNP haplotype analysis. However, no successful pregnancy was obtained. **Conclusion** For males carrying *de novo* mutations, single-sperm-based SNP haplotyping can be applied for PGT to construct paternal haplotype.

【Key words】 Preimplantation genetic testing; Monogenic disease; Single-sperm-based single-nucleotide polymorphism haplotyping; *De novo* mutation

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·PGT 专栏·

PGT 后嵌合型胚胎的移植价值

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【摘要】 辅助生殖技术中进行胚胎植入前遗传学检测（preimplantation genetic testing，PGT）时可以检出一定比例的嵌合型胚胎。嵌合型胚胎移植后有机会获得健康活产，但相比于整倍体胚胎，其妊娠率降低、流产率升高，且其妊娠风险及子代安全性尚不明确。因此，近年来嵌合型胚胎的临床处理备受关注。本文从嵌合型胚胎的发生机制、影响因素，以及移植的临床妊娠结局对 PGT 后嵌合型胚胎的移植价值进行阐述。

【关键词】 胚胎植入前遗传学检测； 嵌合型胚胎； 移植

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Transfer value of mosaic embryos after PGT

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【Abstract】 In the practice of preimplantation genetic testing (PGT), a certain proportion of embryos with chromosomal mosaicism can be identified. Mosaic embryo transfer has a chance leading to a healthy live birth, however, lower implantation rate and higher miscarriage rate were observed compared with euploid embryo transfer. Currently, the risks of pregnancy and offspring are not yet clear. Therefore, clinical management of mosaic embryo transfer has always been a concern. This article commented on the possible value of mosaic embryo transfer after PGT from the prospects of mechanism, influencing factors, and clinical outcomes of mosaic embryo transfer.

【Key words】 Preimplantation genetic testing; Mosaic embryo; Transfer

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扩展性携带者筛查结合 PGT 的临床应用意义和实施策略

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【摘要】 遗传检测技术的进步，促进了携带者筛查技术在生殖领域的蓬勃开展。扩展性携带者筛查与传统的基于指南的携带者筛查相比，可以有效地识别出更多的高危夫妇。扩展性携带者筛查开展后，增加了单基因病胚胎植入前遗传学检测（preimplantation genetic testing，PGT）的转诊数量，丰富了疾病诊断类型。扩展性携带者筛查结合 PGT 技术，正在改变遗传风险评估的临床策略，通过准确识别生殖风险信息，合理安排生育计划，从而预防出生缺陷。

【关键词】 遗传携带者筛查； 遗传学检测； 生殖技术

Clinical implications and implementation strategies of expanded carrier screening combined with PGT

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【Abstract】 Advances in genetic testing field have contributed to the boom in carrier screening technology. Expanded carrier screening can effectively identify more high-risk couples than traditional guideline-based carrier screening. The introduction of extended carrier screening has increased the number of referrals for preimplantation genetic testing (PGT) for monogenic disease and enriched the types of disease diagnosed. Expanded carrier screening combined with PGT technology is changing the clinical strategy of genetic risk assessment and preventing birth defects by accurately identifying reproductive risk information and rationalizing fertility planning.

【Key words】 Genetic carrier screening; Genetic testing; Reproductive techniques

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极体活检在胚胎植入前遗传学检测中的临床应用价值

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【摘要】 极体是卵母细胞减数分裂的副产物，含有和卵细胞相对应的遗传物质，对极体进行遗传学检测可以推测出相应卵细胞的染色体和基因状态。极体活检具有对胚胎损伤小、伦理上易被接受等特点，是一种安全、有效的胚胎植入前遗传学检测（preimplantation genetic testing，PGT）取材方法。极体分析主要用于母源单基因遗传病、染色体非整倍体和染色体结构重排的 PGT，在女方新发变异、家系成员缺失或生殖腺嵌合的单基因病检测、线粒体遗传病的阻断和高龄女性的染色体非整倍体筛查方面具有优势。与囊胚期检测相比，极体检测能够避免囊胚培养失败造成的胚胎浪费，提高胚胎利用率，可能对卵巢功能不全的女性更有利。此外，极体检测将检测时间前移，能够实现新鲜胚胎移植。本文对极体活检在 PGT 中的研究进行整理和归纳，旨在揭示其临床应用价值。

【关键词】 极体； 胚胎植入前遗传学检测； 活检； 单基因病； 染色体非整倍体； 染色体结构重排

Clinical application value of polar body biopsy in preimplantation genetic testing

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【Abstract】 Polar bodies are the byproducts of oocyte meiosis, which contain the corresponding genetic material with the egg cell. Genetic testing of the polar bodies can infer the chromosomal and genetic state of the corresponding egg cell. Polar body biopsy is a safe and effective method for preimplantation genetic testing (PGT), which has the characteristics of less damage to the embryo and easy to be accepted ethically. Polar body analysis is mainly used for PGT of maternal monogenic diseases, chromosomal aneuploidy and structure rearrangement, with significant advantages especially for the females with *de novo* mutations, absent of family members, and gonadal mosaic mutation, preventing the transmission of mitochondrial diseases, and screening chromosomal aneuploidy with advanced age. In addition, compared with blastocyst detection, preimplantation detection in the polar body stage avoids embryo waste caused by failure of blastocyst culturing, improves the utilization of embryos. This characteristic may take more advantages for females with ovarian insufficiency. Moreover, polar body biopsy moves the

detection time forward and makes fresh embryo transfer available. This paper summarized the application of polar body biopsy in PGT aiming to reveal its clinical value.

【**Key words**】 Polar body; Preimplantation genetic testing; Biopsy; Monogenic diseases; Chromosomal aneuploidy; Chromosomal structure rearrangement

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·PGT 专栏·

无创 PGT 技术的临床应用及研究进展

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【摘要】 胚胎植入前遗传学检测（preimplantation genetic testing， PGT）技术广泛应用于辅助生殖技术（assisted reproductive technology， ART）。PGT 可以检测胚胎的单基因遗传病、染色体结构和数目变异，同时能改善胚胎植入效果、临床妊娠结局和活产率。但该技术涉及到的活检过程对胚胎具有一定的侵袭性，同时对设备和人员的要求颇高。而随着从囊胚液和胚胎培养液中发现了可以用于基因分析的游离 DNA，无创 PGT（noninvasive PGT， NiPGT）成为一种有潜力的检测方式，在辅助生殖领域有广阔的应用前景。现就目前 NiPGT 技术的应用及研究的有效性和局限性进行阐述，为临床应用提供依据。

【关键词】 无创胚胎植入前遗传学检测； 囊胚培养液； 胚胎培养液； 游离 DNA

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Noninvasive preimplantation genetic testing: clinical application and progress

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【**Abstract**】 Preimplantation genetic testing (PGT) has been widely used today in assisted reproductive technology (ART). PGT can detect embryonic monogenic genetic diseases, chromosome structure and number abnormalities, and improve clinical outcomes in terms of embryo implantation, clinical pregnancy, and live birth rates. Biopsy procedure in PGT is 'invasive' for embryos and has high requirement for equipment and operators. With the discovery of free DNA for gene analysis in blastocyst fluid and embryo culture fluid and embryo culture fluid, a noninvasive PGT (NiPGT) becomes a potential alternative method. It has a broad application prospect in the field of assisted reproduction. Now we summarize the current application and research progress of NiPGT and analyze its effectiveness and limitations, to provide a basis for clinical applications.

【**Key words**】 Noninvasive preimplantation genetic testing; Culture media of blastocysts; Spent embryo culture media; Free DNA

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·临床研究·

重组人促卵泡激素预充注射笔应用于有多囊卵巢综合征症状/体征患者的前瞻性、观察性研究

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【摘要】 目的 评估在至少有一项多囊卵巢综合征（polycystic ovary syndrome，PCOS）症状/体征的不孕症患者中，PCOS 相关体征/症状组合与卵巢刺激过度反应之间的关系，同时评估使用重组人促卵泡激素（recombinant Human Follitropin Alfa，r-hFSHα）预充注射笔在卵巢过度刺激综合征（ovarian hyperstimulation syndrome，OHSS）高危患者人群中应用的疗效及安全性结局。方法 采用前瞻性、观察性、IV 期研究，于 2015 年 12 月至 2017 年 9 月期间在河北医科大学第二医院、山东大学附属生殖医院、空军军医大学唐都医院、大连市妇女儿童医疗中心、南京市妇幼保健院、江西省妇幼保健院、新疆医科大学第一附属医院、安徽医科大学第一附属医院及内蒙古医科大学附属医院，招募了 1055 例至少具有一种 PCOS 症状/体征的不孕症患者，使用 r-hFSHα 预充注射笔，进行了 4 个月以上的随访观察。评估的主要终点包括受试者出现多囊卵巢，血清睾酮水平升高，月经周期紊乱，出现多毛症，完成取卵。研究的有效性终点包括获卵数、M_{II} 卵数、生化妊娠率、临床妊娠率、着床率。结果 在全分析集中（*n*=997），多囊卵巢率为 54.5%（543/997）；血清睾酮水平为（0.4±0.2） μg/L；月经周期紊乱率为 45.0%（449/997）；多毛症率为 10.5%（105/997）；在有 PCOS 症状或体征患者中，242 例（24.3%）患者获卵超过 15 个，100 例患者（10.0%）获卵超过 20 个，体质量指数每降低 1 kg/m^2，过度反应（获卵数>15）风险增加约 9%，过度反应（获卵数>20）风险增加约 9%。窦卵泡计数每增加 1，过度反应（获卵数>15）风险增加约 6%，过度反应（获卵数>20）风险增加约 4%。促排卵后的平均获卵数为 14.4 个。每移植周期的临床妊娠率为 53.6%（251/468），活产率为 45.3%（212/468），生化妊娠率为 60.9%（285/468），着床率为 39.1%（349/893），鲜胚移植取消率为 24.0%（239/997）。有 1.8%（19/1054）的患者（安全集，*n*=1054）诊断为 OHSS，其中有 8 例（0.8%）轻度，10 例（0.9%）中度，1 例（0.1%）重度。结论 至少有一种 PCOS 症状/体征的患者中，卵巢过度刺激与低体质量指数和高窦卵泡计数相关，使用 r-hFSHα 预充注射笔后，患者获得了较好的临床收益。

【关键词】 生殖技术，辅助； 多囊卵巢综合征； 精准医疗； 控制性卵巢刺激； 真实世界证据

临床试验注册：美国临床试验数据库(NCT02607293)

Application of recombinant Human Follitropin Alfa solution for injection in patients with symptoms/signs of polycystic ovary syndrome: a prospective, observational study

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【**Abstract**】 **Objective** To evaluate the association between polycystic ovary syndrome (PCOS)-related symptom combinations and ovarian stimulation high response in infertile patients with PCOS symptoms and controlled ovarian stimulation treatment by recombinant Human Follitropin Alfa (r-hFSHα) solution for injection, and to evaluate the efficacy and safety outcomes of using the r-hFSHα prefilled injection pen in high-risk patients with ovarian hyperstimulation syndrome (OHSS). **Methods** This prospective, observational, phase Ⅳ study enrolled 1055 patients with at least one symptom/sign of PCOS using the r-hFSHα prefilled pen for over 4 months follow-up observation from December 2015 to September 2017 in the Second Hospital of Hebei Medical University, Center for Reproductive Medicine, Shandong University, Tangdu Hospital of the Air Force Military Medical University, Dalian Maternity and Child Health Care Hospital, Nanjing Maternity and Child Health Care Hospital, Jiangxi Maternity and Child Health Care Hospital, the First Affiliated Hospital of Xinjiang Medical University, the First Affiliated Hospital of Anhui Medical University, the Affiliated Hospital of Inner Mongolia Medical University. The primary endpoints assessed included the development of polycystic ovaries, elevated serum testosterone levels, menstrual cycle disturbances, development of hirsutism, and completion of egg retrieval. The efficacy endpoints of the study included the number of ocoytes retrieved, the number of $M_{Ⅱ}$ oocyte, the biochemical pregnancy rate, the clinical pregnancy rate, and the implantation rate. **Results** In the full analysis set (*n*=997), polycystic ovary rate was 54.5% (543/997), serum testosterone level was (0.4±0.2) μg/L, menstrual cycle disorder rate was 45.0% (449/997), hirsutism rate was 10.5% (105/997). The average number of oocytes retrieved after ovarian stimulation was 14.4. The clinical pregnancy rate per transfer cycle was 53.6%

(251/468), the live birth rate was 45.3% (212/468), the biochemical pregnancy rate was 60.9% (285/468), the implantation rate was 39.1% (349/893), and the fresh embryo transfer cancellation rate was 24.0% (239/997). OHSS incidence was diagnosed in 1.8% (19/1054) of patients (safety set, *n*=1054), including 8 (0.8%) mild cases, 10 (0.9%) moderate cases and 1 (0.1%) severe case. According to the results of exploratory analysis, a decrease in body mass index (BMI) was associated with an increased risk of high response. For every 1 kg/m^2 decrease in BMI, the risk of high response (number of retrieved oocytes >15) increased by approximately 9%, the risk of high response (number of retrieved oocytes >20) increased by approximately 9%. For every 1 increase in antral follicle count (AFC), the risk of high response(number of retrieved oocytes >15) increased by approximately 6% and the risk of high response (number of retrieved oocytes >20) by approximately 4%.

Conclusion Patients with at least one symptom/sign of ovarian hyperstimulation achieved good clinical outcomes with the use of the r-hFSHα prefilled pen, and high response was associated with lower BMI and AFC.

【**Key words**】 Reproductive techniques, assisted; Polycystic ovary syndrome; Precision medicine; Controlled ovarian stimulation; Real-world evidence

Trial Registration: ClinicalTrials.gov (NCT02607293)

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·临床研究·

持久性有机污染物多氯联苯暴露对多囊卵巢综合征患者内分泌紊乱、炎症及氧化应激水平的影响

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【摘要】 目的 分析多囊卵巢综合征（polycystic ovary syndrome， PCOS）患者和非 PCOS 患者在持久性有机污染物（persistent organic pollutants， POPs）多氯联苯（polychlorinated biphenyls， PCBs）暴露、炎症水平和氧化应激水平间的差异，并探究 PCBs 暴露与 PCOS 发生及其与炎症、代谢异常的关联。方法 采用病例-对照研究选取 2013 年 4 月至 2013 年 9 月期间在北京大学第三医院妇产科生殖医学中心接受体外受精-胚胎移植（*in vitro* fertilization and embryo transfer，IVF-ET）的体质量正常 PCOS 患者（PCOS 组，*n*=30）和非 PCOS 患者（对照组，*n*=25），收集受试者的一般资料、临床数据，测定血清中 25 种 PCBs、炎症因子、氧化应激水平，并对污染物、炎症水平和氧化应激水平及临床指标间的相关性进行分析，对 PCBs、炎症因子、氧化应激水平在 PCOS 发病中的作用进行分析，进一步探究睾酮在 PCBs 同系物总水平（∑PCBs）与炎症因子白细胞介素-6（interleukin-6， IL-6）水平之间的中介效应。结果 对 PCBs 的检测显示 PCOS 组中 8 种 PCBs 显著高于对照组（均 *P*<0.05），并且∑PCBs 水平、类二噁英类 PCB 同系物总和（∑dl-PCBs）水平显著高于对照组（*P*=0.037、*P*=0.002）；PCOS 组 IL-6、晚期氧化蛋白产物 （advanced oxidation protein products， AOPPs）、晚期糖基化终末产物（advanced glycation end products， AGEs）水平显著高于对照组（*P*=0.005、*P*=0.021、*P*=0.034）。研究人群中，∑PCBs、∑dl-PCBs、肿瘤坏死因子-α（tumor necrosis factor α，TNF-α）、IL-6、AOPPs、AGEs 都和睾酮呈显著正相关（*r*=0.58，*P*<0.001；*r*=0.53，*P*<0.001；*r*=0.70，*P*<0.001；*r*=0.57，*P*<0.001；*r*=0.69，*P*<0.001；*r*=0.57，*P*=0.003）。多因素回归模型中，∑PCBs（*OR*=1.016，95% *CI*=1.001~1.030，*P*=0.031）、TNF-α（*OR*=2.415，95% *CI*=1.058~5.510，*P*=0.036）、IL-6（*OR*=1.865，95% *CI*=1.126~3.089，*P*=0.015）、AOPP（*OR*=1.155，95% *CI*=1.002~1.332，*P*=0.047）均与 PCOS 的发生风险有关。睾酮在∑PCBs 对 IL-6 的作用中有显著的中介效应（中介效应占比 47.20%）。结论 PCOS 患者血清中 PCBs 水平显著升高，炎症指标和氧化应激水平也高于非 PCOS 患者，睾酮在 PCBs 对 IL-6 的作用中存在中介效应。

【关键词】 多囊卵巢综合征； 持久性有机污染物； 多氯联苯； 炎症； 氧化应激

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Effects of exposure to persistent organic pollutants polychlorinated biphenyls on the levels of endocrine disorders, inflammation and oxidative stress in patients with polycystic ovary syndrome

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【Abstract】 **Objective** To analyze the differences in exposure of persistent organic pollutants (POPs) polychlorinated biphenyls (PCBs), inflammation levels and oxidative stress levels between patients with and without polycystic ovary syndrome (PCOS), and to explore the relationship between PCBs exposure and the incidence of PCOS, and its association with inflammation and metabolic abnormalities. **Methods** This case-control study enrolled normal weight

PCOS patients (PCOS group, *n*=30) and control participants without PCOS (control group, *n*=25) who received *in vitro* fertilization and embryo transfer (IVF-ET) in Reproductive Medicine Center, Department of Obstetrics and Gynecology, Peking University Third Hospital from April 2013 to September 2013, and general information and clinical data of the subjects were collected. The serum levels of 25 kinds of PCBs, inflammatory factors, and oxidative stress indicators were measured. Then we analyzed the correlation between pollutants, inflammation levels, oxidative stress and clinical indicators, and explored the effect of these indicators in the pathogenesis of PCOS. Furthermore, we explored the mediating effect of testosterone in the relationship between the sum of PCB congeners (ΣPCBs) and interleukin-6 (IL-6) levels. **Results** We found that 8 kinds of PCBs were significantly higher in PCOS group (all *P*<0.05), and the levels of ΣPCBs and the sum of dioxin-like-PCBs (Σdl-PCBs) were significantly higher than those in control group (*P*=0.037, *P*=0.002). The inflammatory factor IL-6 was significantly higher in PCOS group than in control group (*P*=0.005). As for oxidative states, advanced oxidation protein products (AOPPs) and advanced glycation end products (AGEs) levels in PCOS group were significantly higher than those in the control (*P*=0.021, *P*=0.034). In studied population, ΣPCBs, Σdl-PCBs, tumor necrosis factor-α (TNF-α), IL-6, AOPPs and AGEs were positively correlated with testosterone (*r*=0.58, *P*<0.001; *r*=0.53, *P*<0.001; *r*=0.70, *P*<0.001; *r*=0.57, *P*<0.001; *r*=0.69, *P*<0.001; *r*=0.57, *P*=0.003). And multiple regression analysis confirmed that ΣPCBs (*OR*=1.016, 95% *CI*=1.001–1.030, *P*=0.031), TNF-α (*OR*=2.415, 95% *CI*=1.058–5.510, *P*=0.036), IL-6 (*OR*=1.865, 95% *CI*=1.126–3.089, *P*=0.015) and AOPPs (*OR*=1.155, 95% *CI*=1.002–1.332, *P*=0.047) were associated with the risk of PCOS. Testosterone had a significant mediation effect in the effect of ΣPCBs on IL-6 (mediation effect accounts for 47.20%). **Conclusion** The level of PCBs in the serum of PCOS patients is significantly increased, and the levels of inflammation and oxidative stress indicators are also higher than those of the control. Testosterone has a mediating effect in the effect of PCBs on IL-6.

【**Key words**】 Polycystic ovary syndrome; Persistent organic pollutants; Polychlorinated biphenyls; Inflammation; Oxidative stress

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授精次数、促排卵方案对宫腔内人工授精临床妊娠率和医疗花费的影响

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【摘要】　目的　探讨经济而有效的宫腔内人工授精（intrauterine insemination，IUI）助孕策略。方法　回顾性队列研究分析 2020 年 1 月 1 日至 2020 年 12 月 31 日期间在北京大学第三医院妇产科生殖医学中心进行夫精 IUI 助孕的 2266 对夫妇的第 1 个 IUI 周期临床资料，根据人工授精的次数分为单次 IUI 组（*n*=2158）和双次 IUI 组（*n*=108），分析两组临床妊娠率和医疗花费的差异。根据是否行促排卵治疗及促排卵药物不同，将患者分为自然周期组（*n*=1163）和促排卵周期组（*n*=1103）。根据促排卵药物不同，促排卵周期组又分为克罗米酚（clomiphene，CC）/CC+人绝经期促性腺激素（human menopausal gonadotropin，hMG）亚组（*n*=324）、来曲唑（letrozole，LE）/LE+hMG 亚组（*n*=670）和 hMG 亚组（*n*=109）。对比分析不同组间 IUI 助孕结局。结果　①单次 IUI 组和双次 IUI 组患者的年龄、体质量指数（body mass index，BMI）、不孕年限、子宫内膜厚度和临床妊娠率差异均无统计学意义（均 *P*>0.05），但双次 IUI 组的医疗花费明显多于单次 IUI 组，其差异具有统计学意义[（1786.06±173.80）元比（3 172.99±174.91）元，*P*<0.001]。②女方因素、男方因素、不明原因不孕、自然周期、促排卵周期的单次 IUI 和双次 IUI 的临床妊娠率差异均无统计学意义（均 *P*>0.05）。单次 IUI 组中，不孕原因的临床妊娠率差异有统计学意义（*P*=0.012）。两两比较检验显示，单次 IUI 者，女性因素不孕与不明原因不孕的临床妊娠率差异有统计学意义（*P*=0.003）；单次 IUI 者，促排卵周期临床妊娠率［14.0%（145/1039）］高于自然周期临床妊娠率［7.8%（87/1119）］，差异有统计学意义（*P*<0.001）；而双次 IUI 者，促排卵周期临床妊娠率与自然周期临床妊娠率差异无统计意义（*P*=0.774）。③CC/CC+hMG 亚组和 LE/LE+hMG 亚组的临床妊娠率［13.9%（45/324）、14.6%（98/670）］明显高于自然周期组[7.9%（92/1163）]，差异均存在统计学意义（*P*=0.001，*P*<0.001）。多因素 logistic 回归分析，应用 CC/CC+hMG、LE/LE+hMG 促排卵是 IUI 临床妊娠率的独立影响因素［*OR*（95% *CI*）=1.794（1.216~2.647），*P*=0.003；*OR*（95% *CI*）=1.892（1.382~2.589），*P*<0.001］。结论　双次 IUI 与单次 IUI 在临床妊娠率相似，但双次 IUI 治疗费用高，故不建议进行双次 IUI。促排卵治疗可以改善临床妊娠率，其中以 LE/LE+hMG 临床妊娠率最佳，安全性良好。

【关键词】　促排卵；　宫内授精次数；　临床妊娠率；　医疗花费

Influences of the intrauterine insemination times and ovulation induction program on the clinical pregnancy rate and medical cost

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【**Abstract**】 **Objective** To explore the economical and effective strategies for patients treated with intrauterine insemination (IUI). **Methods** We retrospectively analyzed in a cohort study the clinical data of the first IUI cycle of 2266 couples who were treated from January 1, 2020 to December 31, 2020 in Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital. According to the times of insemination in one IUI treatment cycle, patients were divided into two groups: single IUI group (2158 cycles) and double IUI group (108 cycles). The differences in clinical pregnancy rate and cost-effectiveness were analyzed. According to the whether treated with ovulation induction and ovulation induction medicines, patients were divided into two groups: natural cycle group (1163 cycles) and ovulation induction cycle group (1103 cycles). The ovulation induction cycle group were further divided into three subgroups according to ovulation induction medicines: clomiphene (CC)/CC+human menopausal gonadotropin (hMG) subgroup (n=324), letrozole (LE)/LE+hMG subgroup (n=670) and hMG subgroup (n=109). IUI outcomes were compared and analyzed in these groups. **Results** 1) There were no significant differences in age, body mass index (BMI), duration of infertility, endometrial thickness and clinical pregnancy rate between single IUI group and double IUI group (all P>0.05). The medical expenses of the double IUI group was significantly higher than that of the single IUI group [(1 786.06±173.80) yuan *vs.* (3 172.99±174.91) yuan, P<0.001]. 2) There was no statistically significant difference in the clinical pregnancy rate between single IUI and double IUI group with female factor, male factor, unexplained infertility, natural cycle and ovulation induction cycle (all P>0.05). For single IUI, there was a significant difference in the clinical pregnancy rate among the three different causes of infertility (P=0.012), and the difference between the female infertility and the unknown cause of infertility was statistically significant (P=0.003). For double IUI, there was no significant difference in the clinical pregnancy rate among the three groups (P=0.477). The clinical pregnancy rate of ovulation induction cycle [14.0% (145/1039)] was higher than that of natural cycle [7.8% (87/1119), P<0.001]. There was no significant difference in clinical pregnancy rate between ovulation induction cycle group and natural cycle group in patients with double IUI (P=0.774). 3) After ovulation induction, the clinical pregnancy rates of CC/CC+hMG and LE/LE+hMG subgroups [13.9% (45/324),14.6% (98/670)] were significantly higher than that of the natural cycle group [7.9% (92/1163); P=0.001, P<0.001]. Ovulation induction with CC/CC+hMG or LE/LE+hMG was an independent factor improving the clinical pregnancy rate of IUI by multivariate logistic regression analysis [OR(95% CI)=1.794(1.216–2.647), P=0.003; OR(95% CI)=1.892(1.382–

2.589), *P*<0.001]. **Conclusion** Double IUI had similar clinical pregnancy rate with the single IUI, but the treatment cost was higher. So the double IUI is not recommended. Ovulation induction therapy could improve the clinical pregnancy rate. Ovulation induction with LE/LE+hMG had the highest clinical pregnancy rate and good security as well.

【Key words】 Ovulation induction; Intrauterine insemination times; Clinical pregnancy rate; Medical cost

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·临床报道·

子宫内膜血流异常是胚胎反复种植失败的相对独立风险因素

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【摘要】 目的 比较胚胎反复种植失败（recurrent implantation failure，RIF）患者与非RIF患者的超声下子宫内膜血流情况。方法 采用前瞻性观察性队列研究，选择2019年2月至2019年7月期间于中山大学附属第一医院生殖医学中心进行冻融胚胎移植（frozen-thawed embryo transfer， FET）周期助孕的不孕症患者，通过经阴道彩色多普勒超声检测85例RIF患者及17例非RIF患者子宫内膜有无内膜下血流，比较未检测出内膜血流信号的患者比例，以及子宫内膜血流搏动指数（pulsatility index， PI）和阻力指数（resistance index， RI）。结果 RIF组和非RIF组相比，超声检测出内膜血流信号的患者比例明显减少［65.88% （56/85）比94.12% （16/17），*P*=0.020］；在能检测出内膜血流信号的患者中，RIF组的PI和RI值明显高于非RIF组（0.895 9±0.182 0比0.779 1±0.271 9，*P*=0.048； 0.575 6±0.078 4比0.511 1±0.130 7，*P*=0.016）；通过单因素logistic回归分析显示能否检测到内膜血流是RIF的独立风险因素（*P*=0.045）。结论 子宫内膜血流异常可能与RIF有关，可能通过降低内膜对胚胎的容受性从而引起RIF的发生。

【关键词】 子宫内膜； 血液供给； 胚胎移植； 多普勒，彩色； 超声检查

Abnormal endometrial blood flow is a relatively independent risk factor for repeated embryo implantation failure

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【**Abstract**】 **Objective** To compare the endometrial blood flow in patients with recurrent implantation failure (RIF) and non RIF patients. **Methods** A prospective cohort study was perfomed. Infertility patients who underwent frozen-thawed embryo transfer (FET) cycles in the Reproductive Medicine Center of the First Affiliated Hospital of Sun Yat-Sen University from February 2019 to July 2019 were included. Transvaginal color Doppler ultrasound was used to detect whether there was subendometrial blood flow in the endometrium of RIF patients (RIF group, *n*=85) and non-RIF patients (non-RIF group, *n*=17). The proportion of patients without endometrial blood flow signal was compared, as well as endometrial blood flow pulsatility index (PI) and resistance index (RI). **Results** Compared with non-RIF group, the proportion of patients without endometrial blood flow signal detected by ultrasound was significantly increased in RIF group [34.12% (29/85) *vs.* 5.88% (1/17), *P*=0.020]. PI and RI values of RIF group were significantly higher than those of non-RIF group (0.895 9±0.182 0 *vs.* 0.779 1±0.271 9, *P*=0.048; 0.575 6±0.078 4 *vs.* 0.511 1±0.130 7, *P*=0.016). Univariate logistic regression analysis showed that endometrial blood flow was an independent risk factors for RIF (*P*=0.045). **Conclusion** Abnormal endometrial blood flow may be related to RIF, which may cause RIF by reducing the receptivity of endometrium to embryo.

【**Key words**】 Endometrium; Blood supply; Embryo transfer ;Doppler, color; Ultrasonic examination

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·个案报道·

造血干细胞移植术后的重度β地中海贫血患者自体移植冻融卵巢组织诱导青春期发育成功病例1例并文献复习

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【摘要】 目的　探索自体移植冻融卵巢组织诱导青少年女性青春期发育的可行性。方法　重度β地中海贫血患儿造血干细胞移植术前于2019年在中山大学附属第六医院生殖医学中心冷冻卵巢组织11片。患儿造血干细胞移植术后复诊出现卵巢早衰，无青春期发育征象，仍无月经初潮。2022年1月20日通过腹腔镜为患者行原位卵巢组织移植术，共移植卵巢组织5片。术后随访患者性激素水平、生长发育情况及月经是否来潮。结果　患者卵巢移植术后5个月现月经初潮。性激素水平表现为卵泡刺激素与黄体生成素明显下降，雌二醇水平明显升高，提示卵巢组织移植成功，卵泡已开始募集及发育。患者彩色超声提示子宫明显增大，子宫内膜增厚，盆腔左侧移植部位探及窦卵泡声像。结论　青春期前儿童通过卵巢组织冷冻保存生育力的临床价值。对已经出现卵巢功能衰竭、青春期发育延迟甚至停滞的患儿通过自体冻融卵巢组织移植可诱导自然的青春期发育，恢复患者的生殖内分泌功能。

【关键词】 造血干细胞移植；　生育力保存；　卵巢组织移植；　重度地中海贫血

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Puberty induction by autograft of cryopreserved ovarian tissue in a patient with β-thalassemia after hematopoietic stem cell transplantation: a case report and literature review

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【 Abstract 】 **Objective** To explore the feasibility of autologous transplantation of frozen-thawed ovarian tissue to induce pubertal development in adolescent females. **Methods** Before hematopoietic stem cell transplantation in patient with severe β-thalassemia, 11 pieces of ovarian tissue were frozen in the Center of Reproductive Medicine, the Sixth Affiliated Hospital of Sun Yat-sen

University in 2019. The patient was diagnosed as premature ovarian failure after hematopoietic stem cell transplantation. There were no signs of puberty development and menarche. Orthotopic ovarian tissue transplantation was performed for the patient through laparoscopy, and a total of 5 pieces of ovarian tissue were transplanted on January 20, 2022. Postoperatively, we followed up the sex hormone levels, growth and development of the patients and menarche. **Results** The patient developed menarche 5 months after ovarian transplantation. The levels of sex hormones showed that follicle-stimulating hormone and luteinizing hormone were significantly decreased, and estradiol levels were significantly increased, indicating that ovarian tissue transplantation was successful, and follicles had begun to recruit and develop. The patient's ultrasonography revealed a markedly enlarged uterus and a thickened endometrium. Antral follicles were detected in the left implantation site of pelvic cavity. **Conclusion** Cryopreservation of ovarian tissue is recommended for fertility preservation in prepubertal children. Autologous frozen-thawed ovarian tissue transplantation can induce natural puberty development and restore the reproductive endocrine function in children with ovarian failure, delayed puberty development or even stagnation.

【 Key words 】 Hematopoietic stem cell transplantation; Fertility preservation; Ovarian tissue transplantation; Thalassemia major

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·综述·

周细胞的研究现状及其在妇产科中的研究展望

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【摘要】 周细胞是围绕在毛细血管内皮细胞外的血管壁细胞。周细胞可以在多种疾病中通过调节血管形态及功能发挥重要作用，如糖尿病视网膜病变、阿尔茨海默症、出血性脑卒中、组织纤维化、肿瘤转移等。此外，周细胞还是间充质祖细胞，可以分化产生（肌）成纤维细胞、血管平滑肌细胞、脂肪细胞、软骨、骨骼和肌肉等。本文将对周细胞的研究现状进行综述，并对子宫中周细胞未来可能的研究方向进行展望。

【关键词】 周细胞； 妊娠； 生殖； 血管渗透性； 胚胎植入； 蜕膜化； 子宫

Research progress of pericytes and its prospect in gynaecology and obstetrics

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【**Abstract**】 Pericytes are microvascular mural cells surrounding the endothelial cells of capillaries. Pericytes play a critical role in various diseases by regulating vascular morphology and function, such as diabetic retinopathy, Alzheimer's disease, hemorrhagic stroke, tissue fibrosis and tumor metastasis. Moreover, pericytes are mesenchymal progenitor cells that can differentiate into fibroblasts, vascular smooth muscle cells, adipose cells, cartilage, bone, and muscle. There are few studies on pericytes during pregnancy, and some existing evidence points to pericytes playing an essential role in some aspects of pregnancy. In this paper, the research progress of pericytes was reviewed, and the future research direction of uterine pericytes was prospected.

【**Key words**】 Pericytes; Pregnancy; Reproduction; Capillary permeability; Embryo implantation; Decidualization; Uterus

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·综述·

子宫内膜容受性转录组学研究进展

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【摘要】 胚胎植入依赖于良好的胚胎质量、子宫内膜容受性，及胚胎-子宫内膜间同步和谐地交流对话。相较于发展较成熟的胚胎培养技术，目前子宫内膜容受性仍缺乏有效的诊断与治疗方法，传统检测方法如胞饮突检测、组织学检测、超声等，其准确性和可重复性饱受质疑。随着组学技术的发展，利用基因表达的整体特征描述、诊疗疾病已成为可能，其在子宫内膜容受性领域也具有较大的研究和临床运用价值。本文就近年来子宫内膜容受性领域转录组学临床研究作一综述，概括子宫内膜容受性相关编码基因、非编码基因研究的基本情况及临床运用情况，为后续研究子宫内膜容受性、指导临床诊疗提供参考。

【关键词】 子宫内膜容受性； 种植窗； 转录组学； 信使 RNA； 非编码 RNA

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Research progress of transcriptomic study in endometrial receptivity

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【 Abstract 】 Embryo implantation is a complex process that relies on elaborate cooperation between the well-qualified embryo and endometrial receptivity, and synchronous and harmonious communication between embryo and endometrium. Compared with the well-developed embryo culturing technology, there is a lack of effective diagnosis and treatment of endometrial receptivity. Traditional diagnostic tools, including pinopode analyzing, histologic dating, ultrasound, etc. are being questioned for accuracy and reproducibility. However, with the great development of omics, describing diseases in a gene expression whole pattern becomes feasible, which shows potential clinical value. The review focuses on the research progress of transcriptomic study in endometrial receptivity and concludes receptivity-related coding and non-coding RNAs, laying foundations for further research and clinical applications.

【 Key words 】 Endometrial receptivity; Window of implantation; Transcriptome profiling; Messenger RNA; Non-coding RNA

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