

·临床研究·

PCOS患者胚胎非整倍体率及整倍体胚胎移植后流产率升高

刘馨然, 揭慧英, 苏姗妮, 周灿权

(中山大学附属第一医院妇产科生殖医学中心, 广东广州 510080)

摘要:【目的】探讨多囊卵巢综合征(PCOS)患者囊胚染色体特征及其妊娠结局,分析PCOS对胚胎非整倍体率及流产风险的影响。【方法】采用回顾性队列研究,纳入中山大学附属第一医院行胚胎植入前遗传学检测(PGT)中非整倍体检测(PGT-A)及单基因遗传病检测(PGT-M)的周期,通过倾向评分匹配筛选出191个PCOS组周期与564个对照组周期。比较两组卵母细胞及胚胎发育潜力、囊胚染色体检测结果及临床结局。根据获卵数将PCOS患者分为 >20 枚组和 ≤ 20 枚组,比较不同卵巢反应水平下整倍体胚胎移植后的妊娠结局。【结果】PCOS组囊胚非整倍体率高于对照组(21.8% vs. 19.0%, $P=0.044$)。PCOS组总体流产率高于对照组(17.2% vs. 10.3%, $P=0.024$)。移植整倍体胚胎后,PCOS组流产率仍高于对照组(17.2% vs. 10.0%, $P=0.019$)。亚组分析显示,获卵数 >20 枚的PCOS患者移植整倍体胚胎后的流产率高于对照组(21.4% vs. 6.7%, $P=0.001$),早期流产率亦升高(15.7% vs. 5.7%, $P=0.011$);而获卵数 ≤ 20 枚亚组与对照组临床结局差异无统计学意义。【结论】PCOS患者囊胚非整倍体率较对照组显著升高。PCOS患者囊胚移植流产率,甚至整倍体囊胚移植后妊娠的流产率均较对照组显著增加,尤其表现在高卵巢反应PCOS患者中。

关键词:多囊卵巢综合征;胚胎植入前遗传学检测;非整倍体;胚胎移植;流产

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Increased Aneuploidy Rates and Euploid-embryo-transfer Miscarriage Rates in PCOS Patients

LIU Xinran, JIE Huiying, SU Shanni, ZHOU Canquan

(Reproductive Medicine Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China)

Correspondence to: ZHOU Canquan; E-mail: zhoucquan@mail.sysu.edu.cn

Abstract:【Objective】To investigate the chromosomal characteristics of blastocysts and pregnancy outcomes in patients with polycystic ovary syndrome (PCOS), and to analyze the impact of PCOS on embryonic aneuploidy rate and the risk of miscarriage.【Methods】The retrospective cohort study was conducted on the preimplantation genetic testing (PGT) in the First Affiliated Hospital of Sun Yat-sen University, including cycles of PGT for aneuploidy (PGT-A) and PGT for monogenic disorders (PGT-M). The 191 PCOS cycles (PCOS group) were matched with 564 control cycles (control group) using propensity score matching. The oocyte and embryo viability, chromosomal testing results of blastocysts, and cumulative clinical outcomes were compared between two groups. Subgroup analysis was performed by stratifying PCOS patients based on oocyte retrieval (>20 vs. ≤ 20). And the pregnancy outcomes after euploid embryo transfer were compared under different levels of ovarian response.【Results】PCOS group showed a significantly higher rate of aneuploidy per blastocyst compared to control group (21.8% vs. 19.0%, $P=0.044$). Clinically, the overall miscarriage rate in the PCOS group was significantly higher than control group (17.2% vs. 10.3%, $P=0.024$), even after euploid embryo transfer (17.2% vs. 10.0%, $P=0.019$). In the PCOS subgroup with > 20 oocytes, the miscarriage rate following euploid embryo transfer was dramatically increased compared to control group (21.4% vs. 6.7%, $P=0.001$), accompanied by higher risks

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作者简介:刘馨然,第一作者,研究方向:生殖医学,E-mail:liuxr35@mail2.sysu.edu.cn;周灿权,通信作者,主任医师,教授,E-mail:zhoucquan@mail.sysu.edu.cn

of early miscarriage (15.7% vs. 5.7%, $P=0.011$). Conversely, the PCOS subgroup with ≤ 20 oocytes showed outcomes comparable to control group. [Conclusions] Patients with PCOS exhibit a significantly higher rate of blastocyst aneuploidy compared to the control group. Furthermore, PCOS is associated with a marked increase in miscarriage rates following blastocyst transfer, even with euploid embryos, particularly among patients with high ovarian response.

Key words: polycystic ovary syndrome; preimplantation genetic testing; aneuploid embryo; embryo transfer; miscarriage

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多囊卵巢综合征(polycystic ovary syndrome, PCOS)是育龄期女性最常见的内分泌疾病,全球患病率约为10%至13%^[1]。该病以慢性无排卵、高雄激素血症及多囊卵巢形态为特征,是导致排卵障碍性不孕的主要原因。辅助生殖技术(assisted reproductive technology, ART)已成为PCOS患者获得妊娠的重要手段。然而,接受体外受精(in-vitro fertilization, IVF)或卵胞浆内单精子注射(intracytoplasmic sperm injection, ICSI)治疗的PCOS患者常伴不理想的临床结局,表现为流产及妊娠期并发症等发生率升高^[2-6]。有研究表明^[7]这些不良结局多与内分泌及旁分泌调节异常导致卵母细胞发育潜能受损有关,进而降低了受精率与胚胎植入率。学者也开始探索PCOS患者的早期流产率高等不良妊娠结局是否与其胚胎非整倍体率相关,关于PCOS患者胚胎染色体稳定性的研究逐渐增多,但目前学术界仍存争议。部分基于胚胎植入前遗传学检测-非整倍体检测(preimplantation genetic testing for aneuploidy, PGT-A)的研究显示^[8],两组间的胚胎整倍体率无显著差异。然而,另有纳入PGT-A+单基因遗传病检测(PGT for monogenic disorders, PGT-M)患者分析^[9]指出,PCOS组囊胚的总体非整倍体率(14.7%)显著低于非PCOS对照组(25.4%)。对于PCOS和对照组患者自然流产组织物染色体报告的分析也有不同。有研究^[10]发现PCOS患者早期自然流产绒毛样本有较低的胚胎非整倍体率,推测流产可能与母体因素有关。另一研究^[11]则表明PCOS是流产组织染色体异常率显著增加的风险因素。有研究提出,除经典的非整倍体外,胚胎嵌合现象亦可能在胚胎发育潜能及妊娠结局中发挥重要作用,但目前关于PCOS患者胚胎嵌合率的研究仍相对有限,也存在争议^[9, 12-13]。近年来PGT在临床中逐渐推广,整倍体

胚胎移植成为评估胚胎与母体因素对妊娠结局影响的重要研究模型。理论上,整倍体胚胎移植能够显著降低由胚胎染色体异常导致的流产风险,但已有研究显示^[2]PCOS患者在整倍体胚胎移植后的流产率仍高于非PCOS患者,提示存在染色体异常以外的其他因素影响胚胎正常生长发育。尽管已有数篇研究尝试从囊胚PGT结果及早期流产组织分析中得出结论,但PCOS是否作为独立因素通过染色体或非染色体机制导致妊娠丢失,仍需深入探索。鉴于此,开展系统性的对比研究,全面评估PCOS患者的胚胎遗传学特征及临床妊娠结局,显得尤为重要。因此,本研究在对患者的基线资料进行匹配后,从整体囊胚及单周期双维度,对PCOS患者与对照组的胚胎整倍体、非整倍体、嵌合体等PGT结果进行系统比较,为阐明PCOS与胚胎染色体异常之间有无关联提供更加全面而可靠的临床证据。在PGT的基础上,本研究对PCOS患者及对照组的临床结局进行进一步比较分析,以期更严谨探讨PCOS患者不良妊娠结局的可能机制。

1 材料与方法

1.1 研究对象与入组标准

本研究为一项临床回顾性研究,数据来源于中山大学附属第一医院生殖医学中心2018年1月1日至2024年12月31日期间所有接受PGT治疗的周期。从本中心资料库收集纳入本研究的各个周期所对应的临床资料有:患者的诊断、夫妻双方年龄、体质指数(body mass index, BMI)、基础性激素、孕产史、促排卵方案、人绒毛膜促性腺激素(human chorionic gonadotropin, hCG)日雌孕激素、获卵数、卵子受精情况、胚胎生长发育情况、PGT结果等。本研究已于2025年6月6日通过本院伦理委员会

审批(伦理批准号:[2025]421),并因研究性质为回顾性分析且不涉及患者干预,免除书面知情同意。

本研究的纳入标准为:①女方年龄20至45岁;②接受PGT-A或同时进行PGT-A+PGT-M;排除标准为:①卵巢储备功能减退(diminished ovarian reserve, DOR);②卵母细胞或精子冷冻保存周期;③先天性肾上腺皮质增生症、甲状腺功能异常等内分泌异常;④子宫内膜异位症及子宫腺肌病患者。PCOS组依据2003年鹿特丹标准进行诊断,即符合以下3项标准中的任意2项:稀发排卵或无排卵、临床或生化高雄激素表现,以及经阴道超声提示多囊卵巢形态,且无其他相关内分泌疾病;对照组为无PCOS临床表现及相关症状的女性。经数据清理与质量控制后,最终共纳入2 227个治疗周期,其中PCOS组192个周期,对照组2 035个周期。

1.2 促排卵周期流程

每个PGT治疗周期开始前,所有夫妇均接受产科优生遗传学咨询,充分了解PGT的优势与局限性,并签署书面知情同意书。卵巢刺激方案依据本中心常规临床实践进行个体化制定,采用外源性促性腺激素(gonadotropin, Gn)进行控制性卵巢刺激,具体方案包括单纯Gn方案、促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)激动剂方案或GnRH拮抗剂方案。根据卵泡发育的数量及直径大小,采用hCG单扳机(trigger)或双扳机方案诱导卵母细胞最终成熟。Gn剂量根据患者卵巢反应情况进行个体化调整。于hCG注射后34~36 h行经阴道超声引导下取卵。所有成熟卵母细胞均采用ICSI方式受精,并于受精后16~18 h通过观察双原核(two pronuclei, 2PN)及双极体确认正常受精。胚胎在卵裂期及囊胚期分别依据形态学标准进行等级评价。

1.3 PGT流程及结果

在遗传学检测方面,单纯进行非整倍体检测者实施PGT-A,而对于存在明确单基因遗传病风险的夫妇则实施PGT-A+PGT-M。所有胚胎均于囊胚阶段进行活检,采用激光辅助方式从囊胚滋养层获5~10个细胞。活检细胞经全基因组扩增技术(whole-genome amplification, WGA)后进行后续遗传学分析。仅行PGT-A的周期采用基于芯片的检测方法,而同时行PGT-A+PGT-M的周期则采用下一代测序(next-generation sequencing, NGS),检测

流程均严格按照标准操作规范及试剂说明书执行。WGA产物经文库构建后在Illumina测序平台进行测序分析,每个样本最低测序读长数不少于100万条,且基因组覆盖率超过4%方纳入后续分析。

本生殖中心根据检测结果对胚胎进行分类:整倍体胚胎定义为嵌合比例低于20%,染色体数目正常;嵌合胚胎定义为同时存在整倍体与非整倍体细胞群体,并根据嵌合比例进一步分为2类:嵌合比例<50%者,在充分知情同意后可考虑移植;嵌合比例≥50%者通常不建议移植;非整倍体胚胎定义为超过80%的细胞存在染色体异常。此外,存在片段性拷贝数变异或多倍体异常的胚胎亦归类为不适宜移植胚胎。因技术原因未获得检测结果,或虽完成活检但因PGT-M结果判定为不可移植的胚胎,统一归类为“无结果”,并在后续分析中予以排除。

1.4 囊胚移植周期流程

所有患者均接受冻融囊胚移植,其中胚胎解冻复苏流程严格按照中心培养室标准进行。子宫内膜准备的具体方案及用药由医生根据现行临床指南^[4]及院内临床结果数据,依据经验决定。移植周期包括自然周期、促排卵周期、人工周期等。其中自然周期及促排卵周期根据患者的月经周期及卵泡发育情况检测黄体生成素(luteinizing hormone, LH)峰值,或使用hCG触发排卵,在通过超声结合血清性激素水平确认排卵后的第5天移植冻融囊胚;胚胎移植后,根据患者的血清孕酮及雌二醇水平决定用药,可服用每天2次地屈孕酮10 mg至移植术后第12天进行妊娠试验确认移植结果。人工周期通过口服、阴道、肌肉注射、经皮给药等单独或联合使用抑制排卵并促进内膜生长,待内膜厚度达标后联用地屈孕酮、雪诺酮、黄体酮等孕激素进行内膜转化;胚胎移植术后根据患者血清孕酮及雌二醇水平决定后续用药。

1.5 结局指标

收集指标包括2PN形成率、囊胚形成率、整倍体率及非整倍体率等。结局指标包括卵母细胞及胚胎发育潜能以及囊胚染色体构成谱,分别在“每周”与“每囊胚”这2个层面进行统计分析。

1.6 倾向性评分匹配分析

为控制潜在混杂因素并提高PCOS组与对照组之间的可比性,本研究采用倾向性评分匹配方法。倾向性评分匹配分析(propensity score matching,

PSM)比例为1:3,不完全匹配后纳入PCOS组191个周期及对照组564个周期。匹配变量包括女性年龄、产次、不孕年限、BMI、ART类型(PGT-A或PGT-A+PGT-M)及卵巢刺激方案。采用标准化均数差(standardized mean difference, SMD)评估匹配后协变量平衡情况,SMD均小于0.1(视为匹配达到良好平衡)。匹配后各协变量差异均无统计学意义($P>0.05$),提示匹配效果良好。

1.7 统计学分析

所有统计分析均采用R软件4.5.1完成。连续变量首先通过Shapiro-Wilk检验进行正态性评价,并结合Levene检验评估方差齐性。若符合正态分布且方差齐,以均数±标准差($\bar{x} \pm s$)表示,组间比较采用Student's *t*检验;若不符合正态分布或方差不齐,则以中位数及四分位数间距 $M(P_{25} \sim P_{75})$ 表示,组间比较采用Mann-Whitney *U*检验。分类变量采

用卡方检验,当理论频数 <5 时采用Fisher精确检验。缺失值采用多重插补链式方程法(multiple imputation by chained equations, MICE)进行处理,共生成5个插补数据集。所有检验均为双侧检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 PSM后基线资料比较

本研究共纳入2 227个治疗周期,其中PCOS组192个周期,对照组2 035个周期。经1:3比例PSM后,最终成功匹配PCOS组191个周期及对照组564个周期。尽管未完全达到严格的1:3匹配比例,但匹配后各基线特征均达到良好平衡($SMD<0.1$),且组间差异无统计学意义($P>0.05$),提示匹配效果可靠(表1)。

表1 PSM后PCOS组与对照组患者基线资料的比较
Table 1 Baseline characteristics of PCOS and control groups after PSM [n(%), M(P_{25} - P_{75})]

Variables	PCOS (n=191)	Control (n=564)	P	SMD
Female age/years	31 (29-33)	31 (28-34)	0.600	0.029
Parity/years	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.556	0.007
Infertility duration /years	1.0 (0.0-3.0)	1.0 (0.0-2.8)	0.105	-0.006
BMI/(kg/m ²)	22.1 (20.3-24.0)	21.6 (20.0-23.4)	0.092	0.068
ART regimen			0.379	-0.011
PGT-A	73 (38.2)	238 (42.2)		
PGT-A+PGT-M	118 (61.8)	326 (57.8)		
Ovarian stimulation protocol			0.847	
Simple Gn protocol	1 (0.5)	3 (0.5)		<0.001
Short GnRH agonist protocol	8 (4.2)	17 (3.0)		0.007
GnRH antagonist protocol	164 (85.9)	497 (88.1)		-0.018
Long GnRH agonist protocol	11 (5.8)	26 (4.6)		0.009
Long-acting GnRH agonist protocol	7 (3.7)	21 (3.7)		0.002

PSM: propensity score matching; PCOS: polycystic ovary syndrome; SMD: standardized mean differences; BMI: body mass index; ART: assisted reproductive technology; PGT: preimplantation genetic testing; Gn: gonadotropin; GnRH: gonadotropin-releasing hormone.

2.2 卵胚生长发育及培养情况比较

PCOS组的获卵数显著高于对照组,单周期优质第3天胚胎率亦明显升高($P<0.001$)。两组在成熟卵母细胞率、ICSI受精率、2PN形成率及囊胚

形成率方面差异均无统计学意义($P>0.05$)。在以单个卵子或胚胎为分析单位的结局指标比较中,两组间亦未观察到显著差异($P>0.05$;表2)。

表2 PSM后PCOS组与对照组卵子及胚胎发育及培养情况的比较

Table 2 Comparison of oocyte and embryo viability outcomes between PCOS and control groups after PSM

[($\bar{x} \pm s$), n(%)]

Outcomes	PCOS (n=191)	Control (n=564)	P
Per cycle			
Oocytes retrieved/n	22.1 ± 10.1	16.9 ± 8.4	<0.001*
MII rate/%	83.1 ± 13.6	82.3 ± 15.0	0.809
ICSI fertilization rate/%	84.6 ± 11.6	82.6 ± 15.4	0.305
2PN rate/%	79.2 ± 13.1	78.4 ± 16.3	0.761
High-quality Day 3 embryo rate/%	41.6 ± 22.3	30.9 ± 24.8	<0.001*
Blastocyst formation rate/%	67.8 ± 23.0	66.6 ± 24.4	0.593
High-quality blastocyst rate/%	39.1 ± 22.1	38.4 ± 24.0	0.752
High-quality blastocyst ratio/%	67.1 ± 23.8	66.6 ± 28.5	0.724
Per oocyte/embryo			
Oocytes retrieved/n	4 218	9 507	-
MII rate/%	3 482 (82.6)	7 783 (81.9)	0.347
ICSI fertilization rate/%	2 928 (84.1)	6 455 (82.9)	0.133
2PN rate/%	2 750 (79.0)	6 105 (78.4)	0.534
High-quality Day 3 embryo rate/%	892 (32.4)	1 887 (30.9)	0.158
Blastocyst formation rate/%	1 866 (67.9)	4 113 (67.4)	0.659
High-quality blastocyst rate/%	1 049 (38.2)	2 372 (38.9)	0.540
High-quality blastocyst ratio/%	1 049 (56.2)	2 372 (57.7)	0.297

PCOS: polycystic ovary syndrome; SD: standard deviation; MII: metaphase II; ICSI: intracytoplasmic sperm injection; 2PN: two pronuclei; * compared with control $P < 0.05$.

2.3 染色体结果比较

在以周期为单位分析PGT结果时,PCOS组的非整倍体率显著高于对照组(20.0% vs. 12.5%, $P=0.016$), <50% 嵌合率亦显著升高[0.0(0.0~14.3) vs. 0.0(0.0~10.0), $P=0.028$],总体嵌合率同样高于对照组(7.1% vs. 0.0%, $P=0.024$)。两组在整倍体率及理论可移植率方面差异均无统计学意义($P > 0.05$)。在以单个卵子或胚胎为单位进行分析时,PCOS组的非整倍体率显著升高(21.8% vs. 19.0%, $P=0.044$)。两组在嵌合率(13.6% vs. 11.9%, $P > 0.05$)及理论可移植率(67.1% vs. 69.2%, $P > 0.05$)方面差异均无统计学意义(表3)。

2.4 囊胚移植临床结局比较

在临床结局方面,PCOS组的总体流产率显著高于对照组(17.2% vs. 10.3%, $P=0.024$);即便在移植整倍体胚胎后,PCOS组的流产率仍高于对照组

(17.2% vs. 10.0%, $P=0.019$)。两组在 β -hCG阳性率、临床妊娠率及活产率方面差异无统计学意义(表4)。

2.5 整倍体囊胚移植不同卵巢反应亚组临床结局比较

在整倍体胚胎移植人群中,获卵数超过20枚的PCOS患者流产率(21.4% vs. 6.7%, $P=0.001$)、早期流产率(15.7% vs. 5.7%, $P=0.011$)以及晚期流产率(5.6% vs. 1.0%, $P=0.034$)均显著高于对照组。而在获卵数不超过20枚的PCOS亚组分析中,各项妊娠结局指标与对照组相比差异均无统计学意义($P > 0.05$;表5)。

3 讨论

本研究在控制多种潜在混杂因素并采用PSM

表3 PSM后PCOS组与对照组囊胚PGT-A结果的比较

Table 3 Comparison of PGT-A results of preimplantation blastocysts between PCOS and control groups after PSM

[($\bar{x} \pm s$), $M(P_{25}-P_{75})$, $n(\%)$]

Outcomes	PCOS	Control	<i>P</i>
Per cycle			
Blastocyst number with PGT result/ <i>n</i>	6.2 ± 3.8	4.9 ± 3.4	<0.001*
Euploidy rate/%	60.0(40.0-77.8)	62.5(43.7-83.3)	0.121
Aneuploidy rate/%	20.0(0.0-33.3)	12.5(0.0-33.3)	0.016*
Mosaicism rate/%	7.1(0.0-20.0)	0.0(0.0-16.7)	0.024*
<50% mosaicism rate/%	0.0(0.0-14.3)	0.0(0.0-10.0)	0.028*
≥50% mosaicism rate/%	0.0(0.0-7.1)	0.0(0.0-0.0)	0.669
Segmental copy number variants rate/%	0.0(0.0-7.1)	0.0(0.0-10.0)	0.268
Polyploidy rate/%	0.0(0.0-0.0)	0.0(0.0-0.0)	0.590
Theoretically transferrable rate/%	66.7(50.0-88.9)	71.4(50.0-100.0)	0.197
Per blastocyst			
Blastocyst number with PGT result/ <i>n</i>	1 174	2 768	-
Euploidy rate/%	689 (58.7)	1 712 (61.9)	0.064
Aneuploidy rate/%	256 (21.8)	525 (19.0)	0.044*
Mosaicism rate/%	159 (13.6)	328 (11.9)	0.160
<50% mosaicism rate/%	100 (8.5)	203 (7.3)	0.228
≥50% mosaicism rate/%	59 (5.0)	125 (4.5)	0.412
Segmental copy number variants rate/%	67 (5.7)	193 (7.0)	0.160
Polyploidy rate/%	3 (0.3)	10 (0.4)	0.766
Theoretically transferrable rate/%	788 (67.1)	1 915 (69.2)	0.202

PCOS: polycystic ovary syndrome; SD: standard deviation; Theoretically transferrable embryos are defined as the number of euploid embryos plus those with <50% mosaicism. Blastocysts with "no result" in PCOS and control groups for abnormal PGT-M results or other reasons were 222 and 475 respectively, which were excluded from the analysis; * compared with control $P < 0.05$.

后,系统描述了PCOS患者单个取卵周期几整体水平囊胚的染色体谱特征。结果显示,PCOS患者在单周期层面及囊胚层面均表现出更高的非整倍体发生率,这可能是导致PCOS患者高流产率的原因之一。另外,在排除非整倍体、嵌合等胚胎导致的流产后,PCOS患者的流产率仍显著高于对照组,提示存在非胚胎染色体因素的其他因素影响胚胎正常生长发育。

在单次取卵周期及单个囊胚这2个分析维度上,我们均观察到PCOS组非整倍体率显著升高。这一结果与Li等^[11]研究相符。她们发现,接受ART治疗的PCOS患者流产组织的染色体异常发生率显著高于对照组,推测卵母细胞发育环境异常

或代谢紊乱状态可能影响染色体分离过程,从而增加胚胎遗传不稳定性。PCOS患者常存在LH水平升高,进而能够扰乱减数分裂的内分泌调控,阻碍第一极体排出^[11]。PCOS患者卵母细胞中调控减数分裂过程中染色体排列和分离的关键基因、相关基因的miRNA表达均与对照组存在差异,可能对胚胎染色体异常有不良影响^[15]。有动物实验研究表明肥胖的表型的小鼠卵母细胞存在线粒体代谢异常,推测其染色体排列异常、纺锤体形成异常和非整倍体卵母细胞比例显著高于对照组的结局与线粒体功能障碍具有密切关联^[16]。研究显示,PCOS患者具有更高的基因组不稳定性,其X染色体的非整倍体比例显著升高,且胰岛素抵抗可能增加这一

表4 PSM后PCOS组及对照组囊胚移植临床结局的比较

Table 4 Comparison of clinical outcomes of embryo transfer between PCOS and control groups after PSM

Outcomes of euploid embryo	PCOS	Control	<i>P</i>
Overall embryo transplantation	249	629	
Positive pregnancy	181 (72.7)	451 (71.7)	0.769
Clinical pregnancy	157 (63.6)	409 (65.5)	0.580
Live birth	114 (49.1)	327 (56.6)	0.055
Miscarriage	27 (17.2)	42 (10.3)	0.024*
Early miscarriage	21 (13.4)	34 (8.3)	0.069
Late miscarriage	6 (3.8)	8 (2.0)	0.228
Euploid embryo transplantation	236	613	
Positive pregnancy	174 (73.7)	443 (72.3)	0.732
Clinical pregnancy	151 (64.5)	402 (66.1)	0.723
Live birth	110 (49.8)	322 (56.8)	0.089
Miscarriage	26 (17.2)	40 (10.0)	0.019*
Early miscarriage	20 (13.3)	33 (8.2)	0.073
Late miscarriage	6 (4.0)	7 (1.7)	0.127

PCOS: polycystic ovary syndrome; * compared with control $P < 0.05$.

表5 PSM后PCOS组与对照组整倍体胚胎移植临床结局(按获卵数20枚分组)

Table 5 Comparison of clinical outcomes of euploid embryo transfer between PCOS and control groups after PSM

(according to oocyte retrieval of 20 cutoff)

[*n* (%), *n*]

Outcomes of euploid embryo	PCOS	Control	<i>P</i>
PCOS Oocyte retrieval ≤ 20	100	318	
Positive pregnancy	74 (74.0)	227 (71.4)	0.703
Clinical pregnancy	62 (62.6)	209 (66.1)	0.603
Live birth	47 (51.7)	161 (55.0)	0.666
Miscarriage	7 (11.3)	27 (12.9)	0.903
Early miscarriage	6 (9.7)	22 (10.5)	0.999
Late miscarriage	1 (1.6)	5 (2.4)	0.999
OHSS	0 (0.0)	0 (0.0)	-
PCOS Oocyte retrieval > 20	136	295	
Positive pregnancy	100 (73.5)	216 (73.2)	0.999
Clinical pregnancy	89 (65.9)	193 (66.1)	0.999
Live birth	63 (48.5)	161 (58.8)	0.066
Miscarriage	19 (21.4)	13 (6.7)	0.001*
Early miscarriage	14 (15.7)	11 (5.7)	0.011*
Late miscarriage	5 (5.6)	2 (1.0)	0.034*

PCOS: polycystic ovary syndrome; Early miscarriage refers to miscarriage at <12 weeks' gestation; Late miscarriage refers to miscarriage at 12 to 28 weeks' gestation; * compared with control $P < 0.05$.

缺陷。部分学者认为胚胎的非整倍体率与患者是否为PCOS无显著相关性^[8, 12]。他们推测PCOS患者的不良生殖结局频发的原因可能与子宫内膜容受性和蜕膜化异常、无排卵导致的孕酮缺乏、慢性炎症和免疫失衡相关,并非由胚胎染色体异常导致。他们对于BMI的研究也指出BMI与胚胎非整倍体发生率无关^[12, 17]。

然而,我们的结果与Luo等^[9]研究存在差异,她们报道PCOS患者的非整倍体率显著低于对照组,一项对于PCOS早期流产绒毛样本的研究^[10]也支持PCOS组拥有更低的非整倍体率这一观点,但目前没有较为清晰的机制分析。造成这一差异的原因可能与研究设计不同,如统计分析方法及纳入排除标准的差异有关。Luo等^[9]研究排除了复发性自然流产和反复种植失败患者,其纳入的PGT队列仅包括PGT-A+PGT-M周期,且未进行倾向性评分匹配。虽然其在混合效应广义线性模型中校正了女性年龄、BMI及生殖中心等因素,但未发现PCOS不同表型与非整倍体或嵌合体风险之间存在关联。Wang等^[12]研究亦未观察到PCOS女性非整倍体或嵌合体风险增加,但该研究年龄上限为37岁,总样本量仅380例,且仅对每位患者质量最佳的3枚囊胚进行PGT-A检测,样本规模及检测胚胎数量均明显少于本研究,可能导致选择偏倚并影响结果稳定性。

在嵌合体分析方面,本研究在单周期层面观察到PCOS患者嵌合率升高,尤其是<50%嵌合比例亚组差异更为明显;但在整体囊胚层面分析时,两组嵌合率差异未达统计学意义。这一结果与Luo等^[9]在单周期层面观察到嵌合率升高的结论相似,但在囊胚层面存在差异。他们推测胚胎存在早期有丝分裂阶段的染色体分离不稳定。

另外,在临床结局方面,PCOS患者即使在移植整倍体胚胎的情况下仍有较对照组更高的流产率,但具体到早期或晚期流产未见显著差异。之前有部分研究显示,PCOS患者整倍体移植的早期流产率显著高于非PCOS组^[2]。尽管研究结果有一定差异,但PCOS患者出现更多的整倍体流产现象可能与母体微环境或胚胎非染色体因素相关。多项研究表明,PCOS患者的子宫内膜容受性存在异常,由孕酮介导的子宫内膜去极化受损^[18-19]。另外有研

究表明PCOS患者的子宫内膜呈现孕酮抵抗性,可能进一步导致黄体支持不足等引发流产^[20]。PCOS患者存在慢性低度炎症状态、细胞因子及免疫调节异常,可能影响母胎界面免疫耐受及胎盘早期形成,从而增加整倍体流产风险^[21-24]。纤维化、菌群失调等也是导致子宫内膜功能障碍的重要因素^[25-26]。PCOS患者可伴随高雄激素血症,研究显示,较高的雄激素水平与早期妊娠丢失风险增加显著相关,她们推测高雄刺激可能通过影响滋养层细胞侵袭、胎盘形成影响胚胎着床。也有可能存在影响颗粒细胞功能、线粒体功能等卵母细胞成熟质量使得胚胎早期发育稳定性发生紊乱^[3]。

本研究显示,当PCOS患者获卵数>20枚时,其整倍体囊胚移植后的流产率显著高于对照组,而获卵数≤20枚的亚组结局无显著差异。这可能提示卵巢高反应状态影响胚胎的发育潜能。已有动物研究表明,卵巢过度刺激可导致纺锤体畸形和DNA链断裂率升高,对卵母细胞质量产生不良影响^[27]。也有研究指出,卵巢反应过高可能与卵母细胞质量下降有关,表现为不熟卵比例增加和卵裂均一性下降^[28]。既往研究发现高浓度雌二醇可能通过作用于卵裂期胚胎而不仅仅是内膜来降低子宫内膜容受作用^[29]。我们推测获卵数高的促排周期中,大量卵泡在促性腺激素刺激下被同步募集,但这些卵泡在发育阶段和成熟程度上常存在明显差异,卵母细胞质量异质性增加,部分可能存在胞质不成熟或发育潜能较低的问题。一项大样本量的回顾性分析模型发现,在IVF周期中,随着获卵数的增加,累计活产率在15~20枚卵子时达到相对稳定的水平,超过20个时活产率有所下降^[30]。因此本研究的结果提示,在PCOS患者促排治疗中,适当控制促排卵药物的应用,避免过高获卵数可能有助于改善最终的妊娠结局。

本研究的优势在于样本量较大,采用倾向性评分匹配控制主要混杂因素,并对PGT结果进行了系统而细化的分层分析,从而较为全面地比较了PCOS与非PCOS患者的胚胎染色体谱,是目前少数探索该方向大样本研究之一。此外,本研究进一步分析了临床结局,对PCOS患者不良妊娠结局发生的可能机制进行了探讨,为未来研究的开展方向奠定了一定基础。然而,本研究亦存在回顾性设计的

固有限制。尽管采用PSM进行校正,PCOS表型如高雄激素水平及胰岛素抵抗程度未被纳入进行亚组分析。此外,所有PGT研究均面临滋养层活检结合NGS检测嵌合体所固有的诊断不确定性,其结果未必完全代表整个胚胎的真实染色体状态。由于观察指标较多,虽在非整倍体率等指标上发现差异,但不排除多重比较带来的假阳性风险。未来仍需开展前瞻性、方法学更加标准化的研究,以验证PCOS胚胎非整倍体率升高及整倍体流产率增加的

结论,并进一步阐明其潜在的胚胎及内膜异常机制。

本研究表明,尽管PCOS患者的胚胎发育潜力与非PCOS对照组相似,但其胚胎染色体非整倍体率较高。PCOS患者在移植整倍体胚胎后,流产率仍高于对照组,且在高获卵数(>20枚)患者中尤为显著。研究提示,除了胚胎染色体异常外,内分泌及代谢紊乱等非胚胎因素在PCOS患者妊娠丢失风险增加中也起重要作用。

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