



宫腔灌注粒细胞集落刺激因子改善薄型子宫内膜 患者内膜及血流参数的前瞻性临床对照试验*

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【摘要】目的 探究粒细胞集落刺激因子(granulocyte colony-stimulating factor, G-CSF)宫腔灌注对薄型子宫内膜患者内膜厚度、容积、血流参数及临床结局的影响。**方法** 本研究为前瞻性非随机同期对照试验,将2021年9月1日至2023年9月1日于绵阳市中心医院生殖中心行冻胚移植(frozen-thawed embryo transfer, FET)的薄型子宫内膜患者,分为实验组(行G-CSF宫腔灌注)和对照组(未行G-CSF宫腔灌注)。将两组患者的一般资料和临床结局进行统计分析,将实验组患者G-CSF灌注前后的内膜厚度、容积及血流参数进行统计分析。**结果** 共纳入83例患者,实验组51例,对照组32例,两组患者基线资料无明显差异。实验组患者临床妊娠率(56.86%)高于对照组(50.00%),自然流产率(27.59%)低于对照组(37.50%),但差异无统计学意义($P>0.05$)。实验组患者G-CSF宫腔灌注后的内膜厚度 $[(0.67\pm 0.1)\text{ cm}]$ 大于灌注前 $[(0.59\pm 0.09)\text{ cm}]$,灌注后的子宫容积 $[(1.84\pm 0.81)\text{ cm}^3]$ 大于灌注前 $[(1.54\pm 0.69)\text{ cm}^3]$,灌注后的VFI (1.97 ± 2.82) 大于灌注前 (0.99 ± 1.04) ,差异均有统计学意义($P<0.05$)。**结论** 宫腔灌注G-CSF可改善薄型子宫内膜患者的内膜厚度、容积及部分血流参数。

【关键词】 宫腔灌注 粒细胞集落刺激因子 薄型子宫内膜 内膜容受性

Effect of Intrauterine Perfusion of Granulocyte Colony-Stimulating Factor on Endometrium and Blood Flow Parameters in Patients With Thin Endometrium: A Prospective Controlled Clinical Trial XU Shaorong¹, MA Qianhong^{2△}, ZHANG Yao¹, AN Yinhua¹, HE Wei¹, MA Ying¹, LI Junlin¹, LI Dan¹, LU Wei¹, MA Qinqin¹, YONG Jiajia¹, LAI Ting¹, SU Lian¹, XIANG Hong¹. 1. Reproductive Medicine Center, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang 621000, China; 2. Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education, Sichuan University, Chengdu 610041, China

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【Abstract】Objective To investigate the effects of intrauterine perfusion with granulocyte colony-stimulating factor (G-CSF) on the endometrial thickness, volume, and blood flow parameters of patients with thin endometrium and their clinical outcomes. **Methods** We designed a prospective non-randomized synchronous controlled trial and recruited patients with thin endometrium who underwent frozen-thawed embryo transfer (FET) at Mianyang Central Hospital between September 1, 2021 and September 1, 2023. They were divided into two groups, an experimental group of patients who received the experimental treatment of intrauterine perfusion with G-CSF and a control group of patients who did not receive the experimental treatment. The general data and the clinical outcomes of the two groups were analyzed and compared. The endometrial thickness, volume and blood flow parameters of patients in the experimental group before and after intrauterine perfusion with G-CSF were analyzed. **Results** The clinical data of 83 patients were included in the study. The experimental group included 51 cases, while the control group included 31 cases. There were no significant differences in the baseline data between the two groups. The clinical pregnancy rate of the experimental group (56.86%) was higher than that of the control group (50.00%) and the rate of spontaneous abortion in the experimental group (27.59%) was lower than that in the control group (37.50%), but the differences were not statistically significant ($P>0.05$). In the experimental group, the postperfusion endometrial thickness $[(0.67\pm 0.1)\text{ cm}]$ was greater than the preperfusion endometrial thickness $[(0.59\pm 0.09)\text{ cm}]$, the postperfusion $[(1.84\pm 0.81)\text{ cm}^3]$ was greater than the preperfusion endometrial volume $[(1.54\pm 0.69)\text{ cm}^3]$, and the postperfusion vascularization flow index (VFI) (1.97 ± 2.82) was greater than the preperfusion VFI (0.99 ± 1.04) , with all the differences being statistically significant ($P<0.05$). **Conclusion** Intrauterine perfusion with G-CSF can enhance the endometrial thickness, volume, and some blood flow

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parameters in patients with thin endometrium.

【Key words】 Intrauterine perfusion Granulocyte colony-stimulating factor Thin endometrium Endometrial receptivity

高质量的胚胎和良好的子宫内膜容受性(endometrial receptivity, ER)是妊娠成功的重要因素。目前临床上评估ER广泛采用的简便可靠的方法是超声测量扳机日/胚胎移植日子宫内膜厚度^[1]。大多数研究将子宫内膜厚度 $\leq 7 \sim 8$ mm定义为薄型子宫内膜^[2-4]。随着三维能量多普勒彩超在人类辅助生殖技术(assisted reproductive technique, ART)领域的广泛应用,子宫内膜容积和血流参数被越来越多地用作ER的评价指标。子宫内膜容积是对内膜厚度的补充描述,能更全面、准确反映内膜的信息,以容积 ≥ 2 mL作为临界值评估ER是大多数生殖医生的共识。子宫内膜血流参数包括内膜血管化指数(vascularization index, VI)、血流指数(flow index, FI)、血管化血流指数(vascularization flow index, VFI)和内膜动脉搏动指数(pulse index, PI)、阻力指数(resistance index, RI)、收缩期峰值/舒张末期血流速度比值(systolic peak velocity/diastolic velocity, S/D)。内膜容积血流指数VI、FI、VFI越高,内膜血管化程度越高、血流灌注越丰富,提示ER越好,内膜动脉PI、RI、S/D值越低,动脉阻力越低、血流灌注越多,提示ER越好^[5]。但鲜有报道改善子宫内膜血流参数的方法。

粒细胞集落刺激因子(granulocyte colony-stimulating factor, G-CSF)能够诱导干细胞增殖、分化,并修复损伤组织。宫腔灌注是临床常用的操作简便、局部高效的治疗方法。宫腔灌注G-CSF作为改善ER的新方法,引起了广泛关注。2011年GLEIEHER等^[6]首次报道宫腔灌注G-CSF用于治疗子宫内膜菲薄的不孕患者并成功妊娠。随后该研究团队继续对薄型子宫内膜患者和子宫内膜厚度正常患者进行研究,发现宫腔灌注G-CSF对薄型子宫内膜患者的厚度有改善作用,但正常子宫内膜患者没能获益^[7-8]。反复种植失败(repeated implantation failure, RIF)患者应用G-CSF能增加子宫内膜厚度^[9]。一项双中心前瞻性双盲随机对照试验发现在宫腔粘连分解术后宫腔灌注G-CSF使子宫内膜厚度显著增加^[10]。

鉴于纳入研究的数量和质量有限,G-CSF宫腔灌注未形成完善的临床治疗标准,且尚无G-CSF对薄型子宫内膜患者内膜血流参数的影响的研究。我们设计了前瞻性、非随机、同期、临床对照试验,以探索宫腔灌注G-CSF对薄型子宫内膜患者ER的影响,主要结局指标为子宫内膜厚度、容积,次要结局指标包括血流参数及临床

结局。

1 资料与方法

1.1 研究对象

对2021年9月1日-2023年9月1日在绵阳市中心医院生殖中心进行FET助孕的薄型子宫内膜患者,采用非随机分组的方式分为实验组和对照组,实验组患者进行G-CSF宫腔灌注治疗,对照组患者未行G-CSF宫腔灌注治疗,其余治疗方案两组患者一致。研究方案通过绵阳市中心医院生物医学伦理委员会批准,批准号S20220323-02。

纳入标准:①既往至少2个周期监测内膜厚度 ≤ 0.7 cm;②该移植周期至少有1枚优质卵裂胚或可移植囊胚;③年龄 ≤ 40 岁;④双侧窦卵泡数(antral follicle count, AFC) ≥ 5 个;⑤抗苗勒管激素(anti-Müllerian hormone, AMH) ≥ 0.5 ng/mL;⑥ $18 \text{ kg/m}^2 \leq$ 体质量指数(body mass index, BMI) $\leq 24 \text{ kg/m}^2$ 。

排除标准:①宫腔粘连/瘢痕;②子宫内膜病变(包括黏膜下肌瘤、内膜息肉、内膜炎、内膜结核等);③对G-CSF过敏,对大肠杆菌表达的其他制剂过敏;④严重肝、肾功能障碍;⑤骨髓性白血病患者;⑥术前常规血液分析提示白细胞增高;⑦有复发性流产(recurrent spontaneous abortion, RSA)和RIF病史。

1.2 胚胎评价及内膜准备

参照Gardner评分系统对卵裂胚和囊胚进行评级。优质卵裂胚指正常受精后第三天细胞数为7~9个、评分为I~II级的胚胎。可移植囊胚指3期以上且内细胞团和滋养层评分不同时为C的囊胚。

FET周期均采用人工激素替代周期(hormone replacement therapy, HRT)准备内膜,人工周期有降调节HRT和HRT两种方案,降调节HRT的患者于月经第2~3天注射长效促性腺激素释放激素激动剂3.75 mg(贝依,上海丽珠制药有限公司),降调28 d后开始口服雌激素(芬吗通红片,荷兰雅培制药有限公司),HRT周期的患者于月经第2~3天开始口服雌激素,采用递增剂量方案,起始剂量4 mg/d,每4 d增加剂量2 mg/d,至8 mg/d。实验组患者在使用雌激素的第13天、15天给予1支(150 μ g/0.9 mL)G-CSF(瑞白,齐鲁制药有限公司)进行宫腔灌注治疗,灌注后48~72 h测量子宫内膜厚度、血流参数和常规血液分析。

1.3 彩超参数

所有研究对象行阴道彩超均由固定的医生在同一台设备(GE公司的Voluson S8彩色多普勒超声诊断仪)进行,尽量减少由操作者和设备引起的误差。测量内膜容积和血流参数选择3D能量多普勒的多平面模式,设置容积角度为20°,共切取6个切面,每个切面均手动勾勒出从宫底部到宫颈内口间的子宫肌层与内膜交界线以内的内膜区域,再由计算机测算出范围并计算出内膜容积的数据,在容积图像采样的同时开启血流信号,利用超声工作站内置的计算机辅助分析软件处理图像自动计算出VI、FI和VFI值。测量内膜动脉血流指数是在内膜与肌层交界区域,选取彩色血流较明亮的内膜动脉,调节取样框,启动频谱多普勒,待出现连续三个以上稳定清晰的频谱后进行手动描迹测量,由内置软件自动计算出PI、RI和S/D比值。

1.4 黄体支持和妊娠确定

移植后给予黄体酮注射液(浙江仙琚制药有限公司)20 mg qd肌内注射+芬吗通黄片2片 bid口服;移植后12/14 d检测血 β -HCG确定是否妊娠,移植后28/30 d超声发现宫内妊娠囊为临床妊娠。

1.5 统计学方法

采用SPSS 26.0进行统计分析,对不符合正态分布的数值变量采用中位数(四分位数间距)进行统计描述,采用非参数检验进行比较。计数资料采用 χ^2 检验。G-CSF灌注治疗前后的指标采用 $\bar{x} \pm s$ 进行描述,采用配对 t 检验进行比较。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料比较

实验组共纳入51例患者,对照组共纳入32例患者,两组患者的年龄、不孕年限、BMI、AFC、AMH等基线资料差异无统计学意义($P > 0.05$),见表1。

2.2 治疗结局比较

2.2.1 实验组与对照组妊娠结局比较

由表2可知,实验组患者临床妊娠率(56.86%)高于对照组(50.00%),自然流产率(27.59%)低于对照组(37.50%),但差异无统计学意义($P > 0.05$)。

2.2.2 实验组G-CSF宫腔灌注前后内膜情况比较

见表3、图1,实验组患者G-CSF宫腔灌注后的内膜厚度[(0.67 $\pm$ 0.1) cm]大于灌注前[(0.59 $\pm$ 0.09) cm],灌注后

表 1 一般资料比较

Table 1 Comparison of the general data

Variables	G-CSF group (n=51)	Control group (n=32)	U	P
Age/yr.	33 (29-36)	32 (29-35)	778.5	0.725
Infertility years/year	4 (2-6)	3 (2-5)	712	0.326
BMI/(kg/m ²)	22.4 (21.2-23.3)	21.4 (20.1-23.5)	722.5	0.381
AFC/case	11 (6.00-22.00)	9 (6.25-11.75)	626.5	0.075
AMH/(ng/mL)	2.82 (1.16-5.57)	1.83 (1.19-3.38)	651.5	0.124

Data were presented as median (P₂₅-P₇₅). BMI: body mass index; AFC: antral follicle count; AMH: anti-müllerian hormone.

表 2 妊娠结局比较

Table 2 Comparison of the pregnancy outcomes

Variables	G-CSF group (n=51)	Control group (n=32)	χ^2	P
Clinical pregnancy	29/51 (56.86%)	16/32 (50.00%)	0.373	0.541
Spontaneous abortion	8/29 (27.59%)	6/16 (37.50%)	0.123	0.725

表 3 实验组G-CSF宫腔灌注前后内膜情况 (n=51)

Table 3 Endometrium thickness, volume and blood flow parameters before and after G-CSF intrauterine perfusion in the experimental group (n=51)

Variables	Preperfusion	Postperfusion	t	P
Thickness/cm	0.59 $\pm$ 0.09	0.67 $\pm$ 0.10	-7.608	<0.001
Volume/cm ³	1.54 $\pm$ 0.69	1.84 $\pm$ 0.81	-4.249	<0.001
VI	5.1 $\pm$ 5.2	5.9 $\pm$ 6.0	-0.728	0.470
FI	16.30 $\pm$ 3.37	16.75 $\pm$ 4.23	-0.713	0.479
VFI	0.99 $\pm$ 1.04	1.97 $\pm$ 2.82	-2.304	0.025
PI	1.04 $\pm$ 0.34	1.04 $\pm$ 0.32	0.047	0.963
RI	0.58 $\pm$ 0.09	0.58 $\pm$ 0.10	0.291	0.772
S/D	2.54 $\pm$ 0.73	2.51 $\pm$ 0.70	0.184	0.855

VI: vascularization index; FI: flow index; VFI: vascularization flow index; PI: pulse index; RI: resistance index; S/D: systolic peak velocity/diastolic velocity.

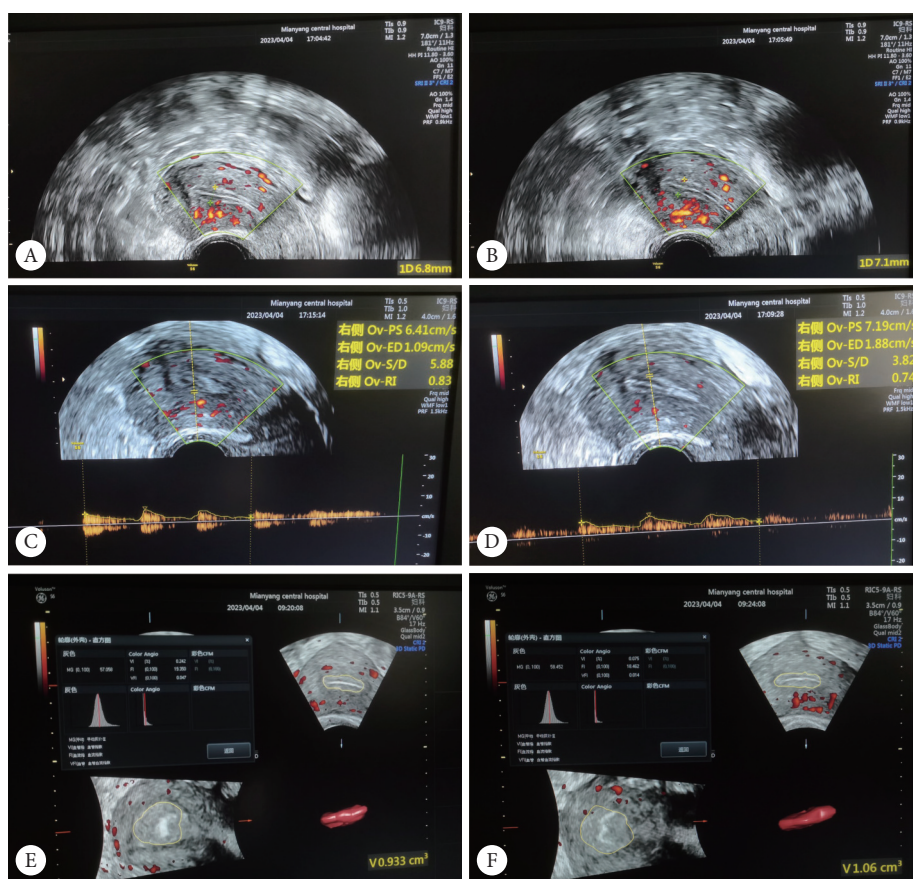


图1 某患者G-CSF灌注前(A、C、E)和灌注后(B、D、F)的内膜厚度(A、B)、容积(C、D)及血流参数(E、F)

Fig 1 The endometrial thickness (A and B), volume (C and D), and blood flow parameters (E and F) of the preperfusion (A, C, and E) and postperfusion (B, D, and F) in a patient

的子宫内膜容积 $[(1.84 \pm 0.81) \text{ cm}^3]$ 大于灌注前 $[(1.54 \pm 0.69) \text{ cm}^3]$,灌注后的VFI (1.97 ± 2.82) 大于灌注前 (0.99 ± 1.04) ,差异有统计学意义($P < 0.05$)。灌注后的VI、FI较灌注前增加,但差异无统计学意义($P > 0.05$),灌注后的内膜动脉PI、RI、S/D值等指标较灌注前无明显差别。

2.3 副反应

实验组51例患者均未出现明显副作用,有1例患者术后1 d觉轻微腰腿酸痛,次日症状缓解;有9例患者灌注后48~72 h查血常规提示白细胞轻微增高,但均小于 $15 \times 10^9 \text{ L}^{-1}$,且在移植前复查均降至正常。

3 讨论

G-CSF是一种刺激骨髓中性粒细胞增殖和分化的细胞因子,目前在临床常规应用于恶性肿瘤化疗过程产生的中性粒细胞减少症,且已通过安全性验证^[11]。G-CSF最早在ART领域的应用可追溯至2000年,研究发现在RIF患者中应用G-CSF能够提高胚胎着床率^[12]。随着G-CSF在ART领域的应用增多,学者对G-CSF影响胚胎着床机制的研究也逐渐增多。G-CSF可能通过免疫调节作用改善胚

胎着床和发育,包括刺激蜕膜巨噬细胞、介导Th1/Th2免疫反应平衡偏向Th2、增加TregT细胞,并且影响着床过程中吞噬及氧化过程^[13-14]。G-CSF是促进胚胎着床和胎盘发育的额外调节因子和保护因子^[15],通过激活PI3K/Akt和Erk信号通路,增加滋养细胞中金属蛋白酶-2的活性和血管内皮生长因子的分泌^[16],以帮助胚胎着床。一项前瞻性双盲随机对照试验发现宫内灌注G-CSF对临床妊娠率、持续妊娠率均有所改善,但差异无统计学意义^[17]。一项纳入1016个周期的meta分析显示,G-CSF可显著提高临床妊娠率(CPR, RR = 1.89, 95%CI 1.53 ~ 2.33)^[18]。本实验发现G-CSF宫腔灌注能改善薄型子宫内膜患者的临床结局,但由于样本量较小,差异无统计学意义。

G-CSF能否改善薄型子宫内膜患者ER尚有争议。有研究发现G-CSF能改善FET周期薄型子宫内膜患者的妊娠结局,但对子宫内膜厚度无明显改变^[19],而另一项回顾性队列研究发现G-CSF能改善薄型子宫内膜患者的内膜厚度,但对妊娠结局无改善^[20]。G-CSF对薄型子宫内膜患者ER的影响机制尚不明确。在小鼠实验中发现,G-

CSF能明显增加间质和腺上皮细胞核抗原(PCNA)的表达,使毛细血管周围血管内皮生长因子受体-2(VEGF-R2)表达明显增加,从而促进子宫内膜的增殖^[21]。G-CSF还可能通过促进子宫内膜血管重塑和减少细胞死亡等机制促进子宫内膜增殖^[22]。本研究发现G-CSF宫腔灌注后的子宫内膜厚度和容积大于灌注前,灌注后的VFI较灌注前增加,且差异有统计学意义($P<0.05$)。G-CSF宫腔灌注后的VI、FI较灌注前增加,但差异无统计学意义($P>0.05$),灌注后的内膜动脉PI、RI、S/D值等指标较灌注前无明显差别。因样本量较小,可能存在假阴性结果。

G-CSF宫腔灌注的用药剂量和时机目前并无统一观点,其用药剂量从100 μg 到300 μg 不等,各中心使用时机也不尽相同,包括优势卵泡直径12 mm时、扳机前6~12 h、扳机日、排卵日、FET周期第14 d、黄体酮给药前1 d、胚胎移植前6~12 h或2~9 d等时机。本研究的灌注时机为内膜接受孕激素作用之前,每次使用1支(150 μg /0.9 mL) G-CSF进行灌注,术中观察使用该剂量进行宫腔灌注能减少药物返流,避免药物浪费。结果表明本研究设计的灌注剂量和时机能改善薄型子宫内膜患者的ER,且不增加患者的经济负担。

本研究行G-CSF宫腔灌注的51例患者均未出现明显的副作用,且实验组患者的自然流产率低于对照组,在一定程度上证明了G-CSF宫腔灌注的安全性。但由于时间关系,本研究仅统计至患者临床妊娠(孕12周),后续会继续随访孕期并发症、产科结局及子代健康问题。目前有多项回顾性队列研究分析了接受G-CSF治疗的患者的新生儿围产期结局,未发现G-CSF导致的产科或新生儿并发症^[23-25]。

我们通过前瞻性临床对照试验,发现在薄型子宫内膜患者中应用G-CSF提高了临床妊娠率,且内膜厚度、容积等主要结局指标较治疗前明显增加,血流参数指标也有所改善。随着G-CSF宫腔灌注的应用越来越广泛,期待设计严谨、质量高、多中心、大样本的随机对照试验,以更深一步地分析与验证G-CSF宫腔灌注的有效性和安全性,以及对内膜血流参数的改善,为薄型子宫内膜患者ER的改善提供更坚实可靠的临床证据。

* * *

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