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地屈孕酮联合环孢素 A 治疗原因不明复发性流产的效果观察 *

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摘要 目的:探讨地屈孕酮联合环孢素 A 治疗原因不明复发性流产的临床效果。方法:选取 2015 年 5 月~2018 年 6 月我院诊治的原因不明复发性流产患者 81 例,根据患者入院先后顺序分为两组,对照组 40 例给予地屈孕酮进行治疗,观察组 41 例在对照组的基础上给予环孢素 A 治疗。比较两组患者的妊娠成功率和妊娠结局,两组患者孕 8 周和孕 10 周的血清绒毛膜促性腺激素(β -HCG)、孕酮(P)、雌二醇(E2)水平以及两组患者孕前 T、B 和 NK 淋巴细胞水平。结果:观察组患者的妊娠成功率为 87.8%,显著高于对照组(67.5%, $P < 0.05$),但两组患者妊娠成功后的早产、分娩孕周相比无统计学差异($P > 0.05$)。观察组患者孕 8 周和孕 10 周的血清 β -HCG 和 E2 水平均显著高于对照组($P > 0.05$),而两组血清 P 水平比较差异无统计学意义($P > 0.05$)。观察组患者孕前 $CD4^+$ 、 $CD4^+/CD8^+$ 和 NK 细胞水平均显著低于对照组, $CD8^+$ 水平显著高于对照组($P > 0.05$),但两组 $CD3^+$ 和 B 细胞水平比较差异无统计学意义($P > 0.05$)。结论:地屈孕酮联合环孢素 A 可显著提高原因不明复发性流产患者孕早期血清 β -HCG 和 E2 水平,抑制患者的免疫功能,提高妊娠成功率,且不影响妊娠结局。

关键词:地屈孕酮;环孢素 A;原因不明复发性流产;效果

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Effect of Dydrogesterone Combined with CsA in the Treatment of Unexplained Recurrent Abortion*

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ABSTRACT Objective: To explore the clinical effect of dydrogesterone combined with CsA in the treatment of unexplained recurrent abortion. **Methods:** 81 cases of unexplained recurrent abortion diagnosed and treated in our hospital from May 2015 to June 2018 were selected, which were divided into two groups according to the sequence of admission. 40 cases of the control group were treated with dydrogesterone, while 41 cases of the observation group were treated with CsA on the basis of the control group. The pregnancy success rate and pregnancy outcome of the two groups were compared, and the levels of serum β -HCG, P and E2 were compared between the two groups at 8 and 10 weeks of gestation, and T, B and NK lymphocyte before pregnancy were compared between the two groups. **Results:** The success rate of pregnancy in the observation group was 87.8%, which was significantly higher than that of the control group (67.5%, $P < 0.05$). But there was no significant difference in the preterm birth or gestational week between the two groups after successful pregnancy ($P > 0.05$). At 8 weeks and 10 weeks of gestation, the levels of serum β -HCG and E2 in the observation group was significantly higher than that in the control group ($P > 0.05$). While there was no significant difference in serum P level between the two groups ($P > 0.05$). The levels of $CD4^+$, $CD4^+/CD8^+$ and NK cells pre-pregnancy in the observation group were significantly lower than those in the control group, and the levels of $CD8^+$ were significantly higher than those in the control group ($P > 0.05$). But there was no statistical difference between the two groups about $CD3^+$ and B cell level ($P > 0.05$). **Conclusion:** Dydrogesterone combined with CsA can improve the level of serum β -HCG and E2 in early pregnancy of patients with unexplained recurrent abortion, inhibit the immune function of patients in active state, and thus improve the success rate of pregnancy without affecting the pregnancy outcome, which is worthy of clinical reference.

Key words: Dydrogesterone; CsA; Unexplained recurrent abortion; Clinical effect

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前言

复发性流产是一种常见病,发病率约为 10%~15%^[1-3]。引发复发性流产的原因有遗传、免疫、内分泌、感染、子宫异常、糖尿病和胚胎畸形等,有 50%以上复发性流产是不明原因的,称为原因不明复发性流产^[4,5]。有研究显示^[6]约 80%的不明原因复发性流产与免疫异常有关,胚胎作为异体移植体,母体会对其产生免疫识别,T 淋巴细胞参与了复发性流产患者免疫功能异常的整个过程,所以 T 淋巴细胞亚群和相关的免疫细胞成为目前研究不明原因复发性流产的热点^[7,8]。另外,Th1/Th2 失衡、自然杀伤细胞毒性升高也与复发性流产的发生密切相关^[9,10]。

复发性流产的常规治疗主要采用黄体酮等激素改善患者机体内环境,提高临床妊娠率,但缺乏针对性,临床效果不理想^[11-13]。环孢素 A 能够抑制患者自身的免疫反应,广泛应用于器官移植中,其在母-胎免疫调节中具有双重作用,既可以抑制母体对胚胎的免疫排斥,也可促进滋养细胞的生成^[14,15]。因此,本研究主要探讨了地屈孕酮联合环孢素 A 治疗原因不明复发性流产的临床效果。

1 资料与方法

1.1 一般资料

选取 81 例西北妇女儿童医院诊治的原因不明复发性流产患者,时间段为 2015 年 5 月~2018 年 6 月,入选标准:①自然流产史≥2 次;②夫妻染色体检查均正常;③病原体筛查正常;④基础性激素、血糖、甲状腺功能正常;⑤男方精液正常。排除标准:①合并生殖系统异常或感染者;②合并内分泌、免疫及遗传疾病者;③合并重要器官功能障碍者。

根据患者入院先后顺序分为两组,对照组 40 例给予地屈孕酮进行治疗,观察组 41 例在对照组的基礎上给予环孢素 A 治疗。对照组患者年龄 28~32 岁,平均 30.31±3.89 岁;孕次 1~4 次,平均 3.12±1.01 次;流产孕周 7~9 周,平均 8.65±1.23 周;平均体质指数 24.52±2.31 kg/cm²。观察组患者年龄 29~32 岁,平均 31.25±4.05 岁;孕次 2~4 次,平均 3.51±1.08

次;流产孕周 7~9 周,平均 8.51±1.03 周;平均体质指数 24.87±3.11 kg/cm²。两组一般资料比较差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

对照组采用地屈孕酮治疗,均采用 B 超检测患者卵泡发育,并指导患者同房,在排卵开始后给予地屈孕酮口服,10 mg/次,3 次/d。在排卵第 16 天检测血 β-hCG 阳性为生化妊娠,在排卵后 30 d 采用 B 超检查宫内妊娠囊为临床妊娠,孕 12 周停药,若在此过程中检查发现胚胎停育或流产则停药。观察组在孕前 30~60 d 给予环孢素 A 口服,50 mg/次,3 次/d 或 2 次/d,在服药 14 d 和 29 d 检测患者的血环孢素 A 浓度,使得血药浓度维持在 80~150 ng/mL。用药时间为 4 周。地屈孕酮的用法同对照组。

1.3 观察指标

①妊娠成功率及妊娠结局,妊娠成功以临床妊娠达 12 周以上为标准。②血清 β-HCG、P 和 E2 水平:分别于孕 8 周和 10 周采集两组患者的空腹静脉血 3 mL,采用全自动生化分析仪 7600(日立公司生产)对患者的血清 β-HCG、P 和 E2 水平进行检测。③孕前 T、B 和 NK 淋巴细胞水平,在环孢素 A 治疗结束后 1 w,孕前分别采集两组患者的空腹静脉血 2 mL,采用 EDTA-NA2 抗凝,采用 FC500 流式细胞仪(BECKMAN 生产)检测淋巴细胞 CD3⁺、CD4⁺、CD8⁺、B 细胞和 NK 细胞的水平。

1.4 统计学方法

采用 SPSS 20.0 软件进行数据分析,计量资料用 $\bar{x} \pm s$ 表示,组间比较行 t 检验;计数资料采用例和百分率表示,组间比较行 χ^2 检验,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组妊娠成功率及妊娠结局的比较

观察组妊娠成功率显著高于对照组($P<0.05$),两组患者妊娠成功后的早产、分娩孕周相比差异无统计学意义($P>0.05$),见表 1。

表 1 两组患者的妊娠成功率及妊娠结局比较

Table 1 Comparison of the pregnancy success rate and pregnancy outcome between the two groups

Groups	n	Successful pregnancy	Abortion	Premature delivery	Delivery gestational age
Control Group	40	27(67.50)	13(32.50)	4(10.00)	34.85±1.79
Observation Group	41	36(87.80)	5(12.20)	1(2.44)	36.21±1.65
χ^2/t	-	4.830		1.998	3.557
P	-	0.028		0.201	0.001

2.2 两组不同时点血清 β-HCG、P 和 E₂ 水平的比较

观察组患者孕 8 周和孕 10 周的血清 β-HCG 和 E₂ 水平均显著高于对照组($P>0.05$),两组血清 P 水平比较差异均无统计学意义($P>0.05$),见表 2。

2.3 两组孕前免疫细胞水平的比较

观察组孕前 CD4⁺、CD4⁺/CD8⁺ 和 NK 细胞水平均显著低于对照组,CD8⁺ 水平显著高于对照组($P>0.05$),两组间 CD3⁺

和 B 细胞水平比较无统计学差异($P>0.05$),见表 3。

3 讨论

原因不明复发性流产患者主要临床症状为阴道流血、分泌物等,从胚胎学的角度分析,母体会对胚胎产生免疫识别,特别是在母体和胎盘尚未完全建立紧密联系的孕早期,此时蜕膜微环境的免疫调节非常重要,而母体的 T 细胞和 NK 细胞在妊娠

免疫中发挥重要作用^[16-18]。孕早期蜕膜淋巴细胞中 NK 细胞占 70%,其数量和功能的异常是复发性流产的重要原因^[19,20]。同时,T 细胞的免疫功能也受到影响,Th1 偏移产生细胞毒性而

导致流产^[21,22]。本研究采用免疫抑制剂环孢素 A 联合地屈孕酮治疗原因不明复发性流产,分析其临床效果及对患者免疫功能的影响。

表 2 两组患者不同时间点血清 β -HCG、P 和 E₂ 水平比较($\bar{x} \pm s$)Table 2 Comparison of the serum β -HCG, P and E₂ levels at different time points between the two groups($\bar{x} \pm s$)

Groups	n	β -HCG(IU/L)		P(ng/mL)		E ₂ (ng/L)	
		8 week of gestation	10 week of gestation	8 week of gestation	10 week of gestation	8 week of gestation	10 week of gestation
Control Group	40	76.05 $\pm$ 21.31	136.85 $\pm$ 32.41	32.12 $\pm$ 8.65	36.98 $\pm$ 10.21	1.83 $\pm$ 0.52	2.22 $\pm$ 0.61
Observation Group	41	93.12 $\pm$ 25.41	155.36 $\pm$ 35.85	33.25 $\pm$ 8.97	37.85 $\pm$ 11.02	2.09 $\pm$ 0.55	2.68 $\pm$ 0.74
t	-	-3.271	-2.436	-0.577	-0.368	-2.185	-3.049
P	-	0.002	0.017	0.566	0.741	0.032	0.003

表 3 两组患者孕前 T、B 和 NK 淋巴细胞水平比较($\bar{x} \pm s$)Table 3 Comparison of the T, B, and NK levels before conception between the two groups($\bar{x} \pm s$)

Groups	n	CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺	Bcell(%)	NKcell (%)
Control Group	40	70.32 $\pm$ 21.33	42.56 $\pm$ 11.35	23.65 $\pm$ 6.52	1.41 $\pm$ 0.47	12.35 $\pm$ 3.26	18.52 $\pm$ 5.31
Observation Group	41	71.25 $\pm$ 20.11	34.85 $\pm$ 10.31	28.51 $\pm$ 6.12	1.13 $\pm$ 0.33	13.21 $\pm$ 3.85	12.45 $\pm$ 3.64
t	-	-0.202	3.202	-3.460	3.096	-1.084	5.987
P	-	0.840	0.002	0.001	0.003	0.282	<0.001

原因不明复发性流产患者的淋巴细胞水平高于正常人,免疫状态也不同于正常人^[23,24]。淋巴细胞可分为若干个亚群,其中 CD8⁺ 为细胞毒性 T 淋巴细胞,具有免疫抑制作用,CD4⁺ 为辅助性 T 淋巴细胞,具有免疫增强的作用,当免疫活动低下时 CD4⁺/CD8⁺ 比值偏低,而当免疫活跃时 CD4⁺/CD8⁺ 比值偏高^[25,26]。在本研究中,观察组患者治疗后的 CD4⁺/CD8⁺ 比值降低,提示母体对胎儿的排斥免疫反应减弱,利于妊娠。NK 细胞一般处于静止状态,是一种非特异性的杀伤细胞,在妊娠的过程中,胚胎作为同种异体的移植物被母体排斥,当 NK 细胞的数量增加时,对胚胎的杀伤作用增强^[27,28]。有研究显示患者的 NK 细胞大于 12% 是发生复发性流产的危险因素^[29]。本研究中,观察组患者的 NK 细胞显著低于对照组,减少了母体对胎儿的攻击,利于妊娠。因此,采用环孢素 A 纠正了患者的免疫状态,减少母体对胎儿的免疫排斥,为妊娠创造良好的环境。

本研究结果显示观察组患者的妊娠成功率显著高于对照组,且孕 8 周和孕 10 周的血清 β -HCG 和 E₂ 水平显著高于对照组,说明环孢素 A 联合地屈孕酮治疗原因不明复发性流产的效果显著。环孢素 A 是一种大环内酯类免疫调节剂,在临床上广泛应用于器官移植后免疫排斥及自身免疫性疾病的预防和治疗,能够抑制钙调素 - 钙神经蛋白信号,进而抑制信号通路及其活性,调节淋巴细胞活性,从而改善患者的免疫状态^[30]。另外,其可抑制肿瘤坏死因子家族成员的表达而抑制免疫反应。地屈孕酮是一种口服孕激素,可支持黄体功能,使增殖期的内膜转化为分泌期,更适合受精卵的着床,创建稳定的环境以便胚胎的植入和发育,同时其还具有一定的免疫抑制作用,可阻止母体对胎儿的免疫排斥反应^[31]。因此,二者联合用药可显著提高患者的妊娠成功率,具有较好的治疗效果。

综上所述,地屈孕酮联合环孢素 A 可提高原因不明复发性流产患者孕早期血清 β -HCG 和 E₂ 水平,抑制患者处于活跃状态的免疫反应,提高妊娠成功率,且不影响妊娠结局。

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