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地屈孕酮联合口服黄体酮胶丸对黄体功能不全先兆流产患者血清抑制素 A、性激素的影响 *

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摘要 目的：探讨地屈孕酮联合口服黄体酮胶丸对黄体功能不全先兆流产患者血清抑制素 A、性激素的影响。**方法：**选择 2018 年 9 月到 2020 年 9 月在我院接受治疗的 125 例黄体功能不全先兆流产患者，采用随机数表法分为试验组（n=63）和对照组（n=62）。对照组给予黄体酮胶丸治疗，试验组在对照组的基础上给予地屈孕酮治疗。比较两组临床疗效、抑制素 A、雌二醇（E_2）、孕酮（P）、人绒毛膜促性腺激素（HCG）、临床症状改善情况、妊娠结局及不良反应发生情况。**结果：**治疗后，两组总有效率比较差异显著（P<0.05）；治疗前，试验组和对照组血清抑制素 A、E_2、P、HCG 比较无显著差异；治疗后试验组和对照组血清抑制素 A、E_2、P、HCG 随着时间的推移而升高，且试验组均高于对照组，差异显著（P<0.05）；试验组止血时间、腹痛改善时间及腰痛改善时间均显著低于对照组，差异显著（P<0.05）；试验组保胎成功率、新生儿体质量及新生儿 Apgar 评分均显著高于对照组，差异显著（P<0.05）；两组不良反应总发生率分别为 7.94%、9.68%（P>0.05）。**结论：** 在黄体功能不全先兆流产患者中应用地屈孕酮联合口服黄体酮胶丸效果显著，可能与其可有效改善血清抑制素 A、性激素水平有关，且不增加不良反应。

关键词：地屈孕酮；黄体酮胶丸；黄体功能不全；先兆流产；抑制素 A；性激素

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Effect of Dydrogesterone Combined with Oral Progesterone Capsule on Serum Statin A and Sex Hormones in Patients with Threatened Abortion with Luteal Insufficiency*

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ABSTRACT Objective: To study Effect of dydrogesterone combined with oral progesterone capsule on serum statin A and sex hormones in patients with threatened abortion with luteal insufficiency. **Methods:** 125 patients with threatened abortion with luteal insufficiency treated in our hospital from September 2018 to September 2020 were divided into experimental group (n=63) and control group (n=62) by random number table method. The control group was treated with progesterone capsule, and the experimental group was treated with dydrogesterone on the basis of the control group. Clinical efficacy, statin A, estradiol (E_2), progesterone (P), human chorionic gonadotropin (HCG), improvement of clinical symptoms, pregnancy outcome and the incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate between the two groups was significantly different (P<0.05). Before treatment, there were no significant differences in serum statin A, E_2, P and HCG between the experimental group and the control group. After treatment, the serum levels of statin A, E_2, P and HCG in experimental group and control group were increased with the passage of time, and the difference was significant(P<0.05). The hemostasis time, improvement time of abdominal pain and improvement time of low back pain in experimental group were significantly lower than those in control group, the differences were significant (P<0.05); The success rate of fetal preservation, neonatal body weight and Apgar score of neonates in experimental group were significantly higher than those in control group (P<0.05). The total incidence of ADR in the two groups was 7.94% and 9.68% (P>0.05). **Conclusion:** In patients with threatened abortion with luteal insufficiency, the application of dydrogesterone combined with oral progesterone capsule has significant effect, which may be related to the effective improvement of serum statin A and sex hormone levels without increasing adverse reactions.

Key words: Dydrogesterone; Progesterone capsule; Luteal insufficiency; Threatened abortion; Statin A; Sex hormones

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前言

先兆流产是妇产科常见疾病，主要是妊娠 28 周前阴道少量出血，继发阵发性腰疼，但胎膜仍然完整，没有妊娠物排除，随着疾病的进展，15%~40%患者出现自然流产，给家庭带来沉重的打击[1-3]。先兆流产的发病机制较为复杂，有研究显示，黄体功能不足是引起先兆流产的重要原因[4]。黄体功能不全先兆流产是孕妇黄体内分泌功能不足引起孕激素分泌不足，导致患者早期流产的情况，因此，补充孕激素是治疗黄体功能不全先兆流产的关键[5,6]。地屈孕酮、黄体酮是目前治疗黄体功能不全先兆流产的常用药物，能有效改善患者性激素，缓解临床症状，但相关报道称其单药使用效果不佳，易导致不良妊娠的发生[7,8]。因此，有学者提出 2 种药物联合治疗可提高治疗效果[9]。本研究旨在探讨地屈孕酮联合口服黄体酮胶丸对黄体功能不全先兆流产患者血清抑制素 A、性激素的影响，以明确地屈孕酮联合口服黄体酮胶丸的治疗效果。

1 资料与方法

1.1 一般资料

选择 2018 年 9 月到 2020 年 9 月在我院接受治疗的 125 例黄体功能不全先兆流产患者，研究已获得我院伦理委员会批准实施。采用随机数表法分为 2 组，试验组 63 例，年龄 20~36 岁，平均(28.56±2.13)岁，孕周 6~12 周，平均(8.25±0.78)周，自然流产史 5 例，习惯性流产 16 例；对照组 62 例，年龄 19~35 岁，平均(28.42±2.12)岁，孕周 6~11 周，平均(8.21±0.78)周，自然流产史 7 例，习惯性流产 15 例。两组基线资料无明显差异，可比较。

纳入标准：(1)停经、早孕症状；(2)基础体温升高；(3)入院前未进行相关治疗者；(4)B 超检查孕囊与孕周符合。排除标准：(1)伴有严重心、肾器官疾病者；(2)伴有严重高血压者；(3)自身免疫性疾病者；(4)实施抗凝、溶栓或降纤治疗的患者；(5)药物、酒精滥用史；(6)依从性较差者；(7)既往精神病史患者；(8) 肝肾功能严重不全者；(9) 病历资料缺失或随访失联者；(10)对本次研究药物过敏者。

1.2 方法

对照组给予黄体酮胶丸治疗(规格：100 mg，生产厂家：天津金耀药业有限公司，国药准字 H12020382)200 mg 口服，1 d 1 次。试验组在对照组的基础上给予地屈孕酮治疗（规格：10 mg，生产厂家：天津金耀药业有限公司，国药准字 H12020382）第一次口服 40 mg，随后每 8h 口服 10 mg。

1.3 观察指标

采集肘静脉血 4 mL，提取血清，采用双抗体夹心酶联免疫吸附法测定抑制素 A、E_2、P、HCG。记录临床症状改善情况、保胎成功率、新生儿体质量及新生儿 Apgar 评分及不良反应情况。

疗效评定标准：显效：阴道流血消失、临床症状消失，胚胎检查正常；有效：临床症状改善，胚胎检查正常；无效：临床症状无明显改善甚至加重。

1.4 统计学分析

以 spss18.0 软件包处理，符合正态分布计量资料用均数±标准差($\bar{x}\pm s$) 表示，组间比较使用独立样本 t 检验，计数资料以率表示，χ^2 检验，$P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床治疗效果评价

治疗后，两组总有效率比较差异显著($P<0.05$)见表 1。

表 1 两组临床治疗效果评价[n(%)]

Table 1 Clinical therapeutic effect evaluation of the two groups[n(%)]

Groups	n	Excellent	valid	Invalid	Total effective rate
Experimental group	63	39(61.90)	19(30.16)	5(7.94)	58(92.06)
Control group	62	26(41.94)	21(33.87)	15(24.19)	47(75.81)
χ^2 value					6.145
P value					0.013

2.2 两组血清抑制素 A、性激素检查结果比较

治疗前，试验组和对照组血清抑制素 A、E_2、P、HCG 比较无显著差异；治疗后试验组和对照组血清抑制素 A、E_2、P、HCG 随着时间的推移而升高，且试验组均高于对照组，差异显著($P<0.05$)，见表 2。

2.3 两组临床症状改善情况比较

试验组止血时间、腹痛改善时间及腰痛改善时间均显著低于对照组，差异显著($P<0.05$)，见表 3。

2.4 两组妊娠结局比较

试验组保胎成功率、新生儿体质量及新生儿 Apgar 评分均显著高于对照组，差异显著($P<0.05$)，见表 4。

2.5 两组用药安全性评价

两组不良反应总发生率分别为 7.94%、9.68%($P>0.05$)见表 5。

3 讨论

先兆流产是产科常见并发症，若不及时治疗则可发展为完全流产，严重影响孕妇健康，近年来其发病率呈上升趋势[10,11]。先兆流产发病机制尚不明确，可能与胚胎、母体等密切相关，其中黄体功能不全是最常见的原因[12]。有研究显示，孕妇黄体功能不全可引起内源孕激素不够，子宫内膜无法及时转换，导致卵巢排卵后孕雌激素明显下降，影响受精卵的正常着床，从而导致先兆流产的发生[13-15]。因此，治疗黄体功能不全先兆流产主要以提高患者体内孕激素水平，维持正常妊娠功能为主[16]。

表 2 两组血清抑制素 A、性激素检查结果比较($\bar{x}\pm s$)

Table 2 Comparison of serum statin A and sex hormone test results between the two groups($\bar{x}\pm s$)

Groups	n	Inhibin A(pg/mL)		E_2(pg/mL)		P(ng/mL)		HCG(IU/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	63	151.25±70.15	399.59±101.14	51.32±9.25	76.09±11.21	14.03±3.51	52.98±5.34	3091.74±614.26	8415.56±904.16
Control group	62	152.08±71.26	289.59±113.47	51.40±9.53	67.58±10.78	14.14±3.48	45.81±4.15	3100.29±625.63	7624.15±854.19
t value		0.066	5.724	0.048	4.325	0.176	8.373	0.077	5.029
P value		0.948	0.000	0.962	0.000	0.861	0.000	0.939	0.000

表 3 两组临床症状改善情况比较($\bar{x}\pm s$,d)

Table 3 Comparison of improvement of clinical symptoms between the two groups($\bar{x}\pm s$, d)

Groups	n	The bleeding time	Abdominal pain improvement time	Duration of improvement in low back pain
Experimental group	63	3.16±0.56	3.57±0.89	3.49±0.78
Control group	62	4.02±1.04	4.26±1.34	4.18±1.25
t value		5.769	3.396	3.709
P value		0.000	0.001	0.000

表 4 两组妊娠结局比较

Table 4 Comparison of pregnancy outcomes between the two groups

Groups	n	Success rate	Neonatal body weight(g)	Apgar score for neonates (points)
Experimental group	63	58(92.06)	2539.75±282.45	9.26±0.95
Control group	62	45(72.58)	2214.26±251.62	8.04±0.85
statistics		8.179	6.799	7.562
P value		0.004	0.000	0.000

表 5 两组用药安全性评价[n(%)]

Table 5 Drug safety evaluation of the two groups[n(%)]

Groups	n	Fatigue	Nausea	Have a headache	Itching	The total incidence of
Experimental group	63	1	1	2	1	5(7.94)
Control group	62	2	1	1	2	6(9.68)
χ^2 value						0.118
P value						0.731

地屈孕酮、黄体酮是治疗黄体功能不全型先兆流产的常见药物,其中地屈孕酮是一种口服孕激素,可与孕激素受体结合,改善子宫内膜容受性,还具有放松平滑肌、抑制子宫收缩等作用,维持子宫正常的机能[17-19]。有研究显示,地屈孕酮能从多方面实现维持妊娠的功能 [20]。黄体酮是卵巢分泌的主要的孕激素,能提高孕妇血液中的孕酮水平,促进子宫充血、内膜增厚,抑制子宫的兴奋,减少子宫收缩,改善因孕激素缺乏引发的临床症状[21,22]。两种药物治疗黄体功能不全先兆流产均有不错的效果,但据临床实验显示,单药治疗黄体功能不全先兆流产效果欠佳,需采用药物联合治疗的方案提高临床治疗效果[23]。有研究显示,黄体酮和地屈孕酮作用机制不相同,两者联合应用具有协同增效的作用[24]。本研究结果显示,联合治疗的患者总有效率高于单药治疗的患者, 且治疗期间未发生明显不良反应,结果提示,地屈孕酮联合口服黄体酮胶丸能提高临床治疗效果,且不会增加药物不良反应。Liang T Z[25]等研究也显示,地屈孕酮联合黄体酮能最大程度维持孕酮水平, 缓解平滑肌痉挛,达到抑制宫缩目的。

有研究显示,抑制素 A 与先兆流产的发生具有密切关系[26]。抑制素 A 由绒毛膜滋养细胞分泌,能影响孕酮的分泌,促进滋养细胞的生长及新生血管内皮细胞的迁移,提高早期着床部位

新生血管的形成，同时还能抑制垂体前叶促卵泡激素的释放，改善部胚囊的血流灌注，调节卵泡的生成，从而促进胚囊的发育[27]。有研究显示，血清抑制素 A 在先兆流产中表达较低，提示胎盘组织发育异常，对胎儿的生长发育造成影响[28]。有研究显示，促进孕妇体内性激素水平的转化可促进孕激素的形成，维持孕妇状态，促进黄体的生长，避免胎儿受到母体淋巴细胞的侵袭[29]。E_2、P、HCG 是临床常见的性激素指标，E_2 是一种甾体雌激素，其在母体内呈增长趋势，则反映胎盘和胎儿的功能良好，其水平降低则预示着胎儿存在流产的风险[30]。P 是由卵巢黄体和滋养层细胞释，具有调节子宫平滑肌的通透性，减轻子宫平滑肌收缩的作用，能确保胚胎在子宫内正常生长，其水平高低对胚胎发育有着重要意义[31]。HCG 是一种糖蛋白激素，由滋养层合体细胞释放，随着孕周的延长而升高，能促进妊娠黄体继续生长，有助于胚胎正常发育，评估先兆流产妊娠结局[32]。有研究显示，先兆流产患者 HCG 水平低于正常妊娠者，而黄体功能不足患者 HCG 增长缓慢，甚至还会出现下降趋势，影响胚胎正常发育[33]。国外研究也显示，E_2、P、HCG 在先兆流产中呈低表达，参与了疾病的发展，可作为诊治疾病的标志物[34]。本研究结果显示，治疗后患者血清抑制素 A、E_2、P、HCG 明显升高，且地屈孕酮与黄体酮胶丸联合治疗的患者高于对照组，结果提示，地屈孕酮联合黄体酮胶丸可提高患者体内性激素水平，保障妊娠正常功能。Mccluggage W G[35]等研究也显示，地屈孕酮联合黄体酮胶丸的疗效较单药治疗效果更佳，能提高患者体内性激素水平。分析其原因可能是因为地屈孕酮联合黄体酮胶丸可发挥药物协同作用，可减轻对胚胎排斥反应，抑制子宫收缩，改善激素水平，加快胚胎生长发育。本研究结果还显示，地屈孕酮与黄体酮胶丸联合治疗的患者止血时间、腹痛改善时间及腰痛改善时间均显著低于对照组，且保胎成功率、新生儿体质量及新生儿 Apgar 评分均显著高于对照组，提示，联合用药的方案能改善黄体功能不全先兆流产患者临床症状，提高保胎成功率。分析其原因可能是因为地屈孕酮可与孕激素受体结合，维持子宫正常的机能，有利于受精卵着床；黄体酮则可避免母体发生胚胎排斥，抑制平滑肌兴奋性，协助胚胎成功着床，减轻母体对滋养层组织，控制病情发展，加快症状改善。

综上所述，在黄体功能不全先兆流产患者中应用地屈孕酮联合口服黄体酮胶丸效果显著，有助于改善血清抑制素 A、性激素水平。

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（上接第 668 页）

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