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熊脱氧酸治疗妊娠期肝内胆汁淤积症的临床效果分析 *

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摘要 目的:探讨熊脱氧酸治疗妊娠期肝内胆汁淤积症(ICP)的临床效果及其可能机制。**方法:**选择 2013 年 8 月到 2018 年 2 月在我院诊治的 ICP 患者 105 例作为研究对象,根据治疗方法分为对照组 50 例和研究组 55 例,对照组给予腺苷蛋氨酸治疗,研究组给予腺苷蛋氨酸联合熊脱氧酸治疗,检测和比较两组的临床总有效率,治疗前后的血清肿瘤坏死因子 α(TNF-α)、白细胞介素 12(IL-12)、甘胆酸(CG)和总胆汁酸(TBA)水平的变化及妊娠结局。**结果:**所有患者都顺利分娩,无死亡产妇与胎儿。研究组的总有效率为 98.2%,显著高于对照组(88.0%),差异有统计学意义(*P<0.05*)。两组治疗后的血清 CG、TBA、IL-12 及 TNF-α 水平均显著低于治疗前(*P<0.05*),且研究组以上指标均明显低于对照组(*P<0.05*)。研究组的剖宫产、早产、新生儿窒息、产后出血、羊水粪染等发生率显著低于对照组(*P<0.05*)。**结论:**熊脱氧酸治疗 ICP 能有效提高治疗效果,改善妊娠结局,这可能与其降低血清患者 TNF-α、IL-12、CG、TBA 水平有关。

关键词:熊脱氧酸;妊娠期肝内胆汁淤积症;腺苷蛋氨酸;TNF-α;IL-12

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Analysis of the Clinical Effect of Ursodeoxycholic Acid on the Intrahepatic Cholestasis of Pregnancy*

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ABSTRACT Objective: To investigate the clinical effect and its possible mechanism of ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy (ICP). **Methods:** 105 cases of ICP patients treated in our hospital from August 2013 to February 2018 were selected and divided into the control group (50 cases) and the study group(55 cases) according to different treatment methods. The control group was treated with adenosylmethionine, and the study group was treated with adenosylmethionine combined with ursodeoxycholic acid. The total clinical efficiency, the level of tumor necrosis factor-alpha (TNF-α), interleukin-12(IL-12), Cholyglycine (CG), total bile acid (TBA) before and after treatment and the pregnancy outcome were examined and compared between two groups. **Results:** All the patients were smoothly delivery and there was no dead parturients and fetus, the total effective rates in the study group was 98.2%, which was significantly higher than that of the control group (88%)(*P<0.05*). The serum levels of CG, TBA, TNF-α and IL-12 after treatment were significantly lower than those before treatment (*P<0.05*), which were lower in the study group than those in the control group (*P<0.05*). The incidence of caesarean section, premature delivery, neonatal asphyxia, postpartum hemorrhage and meconium stained amniotic fluid in the study group were significantly lower than those in the control group (*P<0.05*). **Conclusion:** Ursodeoxycholic acid can effectively improve the therapeutic effect and the pregnancy outcome in the treatment of ICP, which may be related to the reduction of TNF-α, IL-12, CG and TBA levels in the serum.

Key words: Ursodeoxycholic acid; Intrahepatic cholestasis of pregnancy; Adenosylmethionine; TNF-α; IL-12

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前言

妊娠期肝内胆汁淤积症(ICP)是妊娠中晚期特有的并发症,临床上主要表现为皮肤瘙痒和黄疸[1,2]。我国 ICP 主要发病在长江流域和东北少数地区,该病的发生与药物、环境、遗传、雌激素代谢异常等多种因素有关[3,4],可引起早产、死胎、胎膜早破、胎儿宫内窘迫、死产等,终止妊娠可以从根本上阻止病情的发展,但会造成早产儿增加[5,6]。

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ICP 药物治疗的目的是缓解宫缩、降低胆酸、恢复肝功能等。腺苷蛋氨酸是一种天然分子,可增加磷脂酰胆碱的合成,有利于保持细胞膜的流动性,增加硫酸盐的生物学活性,降低血清总胆汁酸(total bile acid,TBA)的毒性[7-10],但是长期应用效果并不理想。熊脱氧酸对肝脏有保护功能,能降低母血肝胆酸浓度,促使胎儿和胎盘中甘胆酸(Cholyglycine,CG)的排泄[11,12]。目前研究表明机体炎症因子如白细胞介素 12(interleukin-12,IL-12)、肿瘤坏死因子 α(tumor necrosis factor-alpha,TNF-α)也参与了 ICP 病程和肝损伤的进展[13,14]。本研究主要探讨了熊脱氧酸治疗 ICP 对患者血清 TNF-α、IL-12 表达的影响,现总结报道如下。

1 资料与方法

1.1 研究对象

选择 2013 年 8 月到 2018 年 2 月在我院诊治的 ICP 患者 105 例作为研究对象,纳入标准:符合 ICP 的诊断标准;单胎妊娠;年龄 20~40 岁;患者签署知情同意书;依从性良好,配合研究,产检资料完整;医院伦理委员会批准了此次研究;孕周 >28 周且 <32 周。排除标准:合并其他类型肝、胆疾病的患者;临床资料缺项者;患有遗传性或免疫性疾病者;合并其他妊娠并发症的患者;药物过敏者。根据治疗方法将所有患者分为研究组 55 例与对照组 50 例,两组患者的一般资料比较差异均无统计学意义(*P>0.05*),具有可比性,见表 1。

表 1 两组患者的一般资料比较

Table 1 Comparison of the general information between the two groups

Group	Cases	Age(year)	Gestational weeks(week)	Course of the disease (d)	Parity (time)	Gravidity (time)
Study group	55	26.34± 2.11	30.92± 1.26	45.72± 6.24	1.24± 0.21	2.81± 0.44
Contorl group	50	25.88± 3.13	30.71± 1.87	45.74± 6.31	1.21± 0.36	2.87± 0.52
P		0.385	0.506	0.987	0.599	0.524

1.2 治疗方法

对照组:给予腺苷蛋氨酸治疗,行静滴腺苷蛋氨酸(生产厂家:hospira S. P. A;批准文号:国药准字 J20150070;生产批号:21S048E02,42S148E02,55G198E02,727648E02;规格:500 mg),5%葡萄糖 500 mL+ 腺苷蛋氨酸针 500 mg,1 次 /d。

研究组:在对照组治疗的基础上给予熊脱氧酸治疗,每次口服熊脱氧酸 (生产厂家:Dr. Falk Pharma GmbH; 批准文号:H20150365; 生产批号:13L11751L,14G08096L,15C09095L,16G13387L,17K03760L;规格:250 mg)300 mg,1 次 /d;

两组均连续治疗直到分娩。

1.3 观察指标

(1)疗效评价标准:显效:瘙痒症状显著缓解,皮肤黄疸消退;有效:瘙痒和黄疸症状缓解;无效:临床症状无改善或加重。(显效 + 有效)/ 组内例数× 100.0%= 总有效率。(2)治疗前后采静脉血并对患者的血清做离心处理,分离血清,通过放射免疫分析法检测血清 CG、TBA 水平, 采用酶联免疫法检测血清 IL-12、TNF-α 水平,试剂盒购于深圳晶美有限公司,严格按照试剂盒操作标准进行。(3)记录两组的新生儿窒息剖宫产、早产等妊娠结局。

1.4 统计学分析

用 SPSS 22.00 软件对数据进行分析,计量资料以($\bar{x}\pm s$)表示,组间比较采用 t 检验,计数资料以%表示,组间比较采用 x^2 检验,以 *P<0.05* 为差异具有统计学意义。

2 结果

2.1 两组治疗总有效率的对比

所有患者都顺利分娩,无死亡产妇与胎儿,研究组的总有效率为 98.2%,显著高于对照组(88.0%),差异有统计学意义(*P<0.05*),见表 2。

表 2 两组治疗总有效率对比

Table 2 Comparison of the total effective rate between two groups

Groups	Cases	Excellent	Effective	Invalid	Total effective rate
Study group	55	50	4	1	54(98.2%)
Contorl group	50	30	14	6	44(88.0%)
P					0.037

2.2 两组治疗前后血清 CG、TBA 水平的变化对比

两组治疗后的血清 CG、TBA 水平与治疗前相比均显著降低,且研究组血清 CG、TBA 水平显著低于对照组,差异具有统计学意义(*P<0.05*)。见表 3。

2.3 两组治疗前后血清 IL-12、TNF-α 水平的变化对比

两组治疗后的血清 IL-12、TNF-α 水平均显著低于治疗前,研究组血清 IL-12、TNF-α 水平明显低于对照组,差异具有统计学意义(*P<0.05*),见表 4。

2.4 两组的妊娠结局对比

研究组的早产、新生儿窒息、羊水粪染等妊娠结局的发生率显著低于对照组(*P<0.05*),见表 5。

表 3 两组治疗前后血清 CG、TBA 水平的变化对比(μmol/L,均数± 标准差)

Table 3 Comparison of the changes of serum CG and TBA levels between the two groups before and after treatment (μmol/L, $\bar{x}\pm s$)

Groups	Cases	CG prior treatment	posttreatment	TBA prior treatment	posttreatment
Study group	55	73.55± 14.29	23.49± 8.48*^	31.48± 9.28	12.48± 6.33*^
Contorl group	50	73.81± 16.03	35.49± 14.10*	31.00± 10.11	20.48± 5.11*

注:与治疗前对比,*$P<0.05$;治疗后与对照组对比,^$P<0.05$.

表 4 两组治疗前后血清 CG、TBA 水平的变化对比(μmol/L,均数± 标准差)

Table 4 Comparison of the changes of serum CG and TBA levels between the two groups before and after treatment(μmol/L, $\bar{x}\pm s$)

Groups	Cases	IL-12 prior treatment	Posttreatment	TNF-α prior treatment	Posttreatment
Study group	55	56.78± 5.69	12.48± 3.10*^	117.30± 11.84	40.68± 8.92*^
Contorl group	50	55.67± 5.88	27.44± 3.89*	118.49± 11.89	66.78± 7.11*

注:与治疗前对比,*$P<0.05$;治疗后与对照组对比,^$P<0.05$.

表 5 两组的妊娠结局对比[例(%)]

Table 5 Comparison of the pregnancy outcome between the two groups[n(%)]

Groups	Cases	Cesarean section	Premature birth	Neonatal asphyxia	Postpartum hemorrhage	Meconium stained amniotic fluid
Study group	55	22(40.0%)	8(14.5%)	7(12.7%)	3(5.5%)	1(1.8%)
Contorl group	50	45(90.0%)	28(56.0%)	21(42.0%)	17(34.0%)	9(18.0%)
P		0.00	0.000	0.001	0.000	0.005

3 讨论

ICP 是妊娠期特有的肝脏疾病之一,是发生在妊娠中晚期的以皮肤瘙痒和黄疸为主的临床疾病。ICP 的病因和发病机制未明,可能与雌孕激素、免疫反应和环境因素等有关;该病的病理改变主要为肝细胞内胆汁淤积、TBA 排泄障碍[15-17]。ICP 的药物治疗目标是缓解临床症状,降低 CG、TBA 浓度,从而降低高胆酸水平所致的胎儿窘迫、死胎的发生,改善妊娠结局[18]。

腺苷蛋氨酸是一种存在于所有生物体内的生理性化合物,可通过甲基化导致雌激素失活,使雌激素无法破坏胆汁、胆盐成分;同时也有助于恢复膜的流动性,促进 CG、TBA 经硫酸化的途径转化,改善胆汁酸代谢系统的解毒功能[19]。熊脱氧酸是黑熊汁的主要成份,在人体胆汁中占 TBA 的 3%,属亲水性胆汁酸。熊脱氧酸进入人体后通过与内源性胆汁酸竞争起到细胞保护作用,促进胆汁分泌作用,增加胎儿胆红素的排泄[20,21]。本研究结果显示所有患者都顺利分娩,无死亡产妇与胎儿,研究组的总有效率为 98.2%,显著高于对照组(88.0%);两组治疗后的血清 CG、TBA 水平显著低于治疗前, 且研究组以上指标低于对照组。相关研究表明熊脱氧酸是可增加磷脂酰胆碱的合成,可以促进 TBA 以硫酸化的途径代谢,降低细胞膜胆固醇 / 磷脂的比值,从而提高机体系统对 TBA 的代谢与解毒[22]。熊脱氧酸也可以改善牛磺型和甘氨型疏水性 TBA 的转运途径,减少肝细胞的损害,降低细胞的毒性作用[23]。

胆红素有着较强的细胞毒性, 能提高 TBA 的细胞毒作用[24]。ICP 会导致肝内胆管胆酸盐沉积,促使血清胆红素增高。TNF-α 是重要的炎性细胞因子,有多种生物活性,主要由单核 - 巨噬细胞分泌,与体内其他细胞因子共同参与全身炎性[25,26]。TNF-α 也可参与 ICP 肝脏的损伤过程,可以促进雌激素在胎盘的合成和分泌,加重 ICP。IL-12 是一种由 NK 细胞、激活的巨噬细胞和树突状细胞产生的细胞因子,可促进干扰素的产生和 Th1 型细胞的免疫应答[27]。研究表明 IL-12 参与了胎膜早破合并有绒毛膜羊膜炎发病过程,母体血清中 IL-12 水平与胎膜早破宫内感染的发生呈正相关[28,29]。本研究显示两组治疗后的血清 IL-12、TNF-α 与治疗前相比显著降低, 且研究组以上指标低于对照组。药理研究显示熊脱氧酸能够替代疏水性胆汁酸,恢复母儿间正常的跨滋养层胆汁酸的转运,降低其细胞毒性,恢复胆汁的正常转运系统,通过糖皮质激素受体途径产生的免疫调节功能,从而抑制 IL-12、TNF-α 的释放[30]。

ICP 与子痫、妊娠期高血压等已成为影响妊娠结局的主要原因,本研究显示研究组的剖宫产、早产、新生儿窒息、产后出血、羊水粪染等发生率显著低于对照组,主要原因在于熊脱氧酸能能抑制肠道对胆酸的重吸收,降低血清胆酸水平,改善胎儿环境,也可促进黄疸消退,显著改善临床症状,使得早产和新生儿窒息的发病率降低。

总之,熊脱氧酸治疗 ICP 能有效提高治疗效果,改善妊娠结局, 这可能与其降低血清患者 TNF-α、IL-12、CG、TBA 水平有关。

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