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思美泰联合熊去氧胆酸对妊娠期肝内胆汁淤积症患者的影响 *

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摘要 目的:探讨思美泰联合熊去氧胆酸对妊娠期肝内胆汁淤积症患者的影响。**方法:**选取我院 2015 年 2 月至 2016 年 2 月收治妊娠期肝内胆汁淤积症患者共 94 例,按随机法分为观察组(47 例)对照组(47 例)。对照组采用思美泰＋地塞米松,观察组采用思美泰＋熊去氧胆酸。观察两组患者治疗前后血清总胆汁酸(TBA)、总胆红素(TB)、丙氨酸转氨酶(ALT)、门冬氨酸转氨酶(AST)、瘙痒评分及妊娠结局、围生儿情况。**结果:**治疗后,两组患者 TBA、TB、ALT 及 AST、瘙痒评分水平均较治疗前下降,观察组下降更明显,差异具有统计学意义(P<0.05);观察组患者早产率 19.15%(9/47)、剖宫产率 27.66%(13/47)、羊水污染率 10.64%(5/47)及胎儿窘迫率 12.77%(6/47)均分别显著低于对照组 40.43%(19/47)、57.45%(27/47)、21.28%(10/37)、19.15%(9/47),其中早产率及剖宫产率比较差异具有统计学意义(P<0.05)。**结论:**思美泰联合熊去氧胆酸能明显改善妊娠期肝内胆汁淤积症患者胆汁酸、肝酶水平及妊娠结局。

关键词:思美泰;熊去氧胆酸;妊娠期肝内胆汁淤积症;胆汁酸;肝酶

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Effect of Transmetil combined with Ursodeoxycholic Acid on the Patients with Intrahepatic Cholestasis of Pregnancy*

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ABSTRACT Objective: To study the effect of transmetil combined with ursodeoxycholic acid on the patients with intrahepatic cholestasis of pregnancy (ICP). **Methods:** 94 patients with intrahepatic cholestasis of pregnancy admitted in our hospital from February 2015 to February 2016 were selected and randomly divided into the observation (47 cases) and control groups (47 cases). The control group was treated by using transmetil+dexamethasone, while the observation group was treated by transmetil combined with ursodeoxycholic acid. The TBA (total bile acid), TB (total bilirubin), ALT (alanine aminotransferase), AST (aspartate aminotransferase), pruritus score before and after the treatment and pregnancy outcome as well as perinatal outcome were compared between two groups. **Results:** After treatment, the TBA, TB, ALT and AST levels and pruritus score of both groups were lower than those before treatment, but the observation group decreased more significantly (P＜0.05), the rate of premature labor 19.15%(9/47), cesarean section rate27.66%(13/47), amniotic fluid pollution rate10.64%(5/47) and fetal distress rate12.77%(6/47) of observation group were lower than the control group 40.43%(19/47), 57.45%(27/47), 21.28%(10/37), 19.15%(9/47) there were significant differences in the rates of preterm labor and the rate of cesarean section (P＜0.05). **Conclusion:** Transmetil combined ursodeoxycholic acid could significantly improve the bile acid, liver enzyme levels and pregnancy outcome of patients with ICP.

Key word: Transmetil; Ursodeoxycholic acid; Intrahepatic cholestasis of pregnancy; Bile acid; Liver enzyme

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前言

妊娠期肝内胆汁淤积症(Intrahepatic cholestasis of pregnancy,ICP)又称为妊娠瘙痒症,临床特征表现为黄疸、皮肤瘙痒及肝功能指标异常等,主要发生于妊娠晚期,其发病率仅次于病毒性肝炎[1,2]。ICP 对孕妇母体伤害较小,主要对围生儿预后产生影响,如导致早产、胎儿窘迫及死胎等,严重危害胎儿健康。近年来, 围生儿的发病率及死亡率逐渐上升,ICP 的治疗受到医学重视,采取合适的治疗方法提高该病治疗效果对保证孕妇及胎儿健康具有重要意义[3,4]。目前,该病的发病机制尚不确切,在临床治疗中无特效药物治疗。我院通过思美泰联合熊去氧胆酸进行治疗,明显改善患者胆汁酸及肝酶等指标,现报道如下。

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1 资料与方法

1.1 一般资料

选择 2015 年 2 月至 2016 年 2 月我院妇产科收治的 94 例 ICP 患者，通过随机法将患者平均分为观察组及对照组。观察组患者年龄 23~38 岁，平均(28.3± 3.4)岁，孕周为 17~26 周，平均(22.5± 5.8)周；对照组患者年龄 22~39 岁，平均(29.1± 3.3)岁，孕周 16~25 周，平均(21.8± 5.7)周。入选标准：① 符合妊娠期肝内胆汁淤积症诊疗指南(2015)[5]诊断标准：空腹血总胆汁酸水平上升，且总胆汁酸(TBA)水平≥ 10 μmol/L；② 妊娠期间存在皮肤瘙痒、黄疸等不适症状；③ 血清总胆红素(TB)、丙氨酸转氨酶(ALT)、门冬氨酸转氨酶(AST)水平轻、中度升高。排除标准：① 病毒性肝炎引起的肝功能异常；② 具有严重心、脑、肺、肾等疾病患者；③ 具有急性脂肪肝、糖尿病及全身感染等特殊疾病患者；④ 入院时胎动异常、羊水过少及孕周较长可能随时终止妊娠患者。本研究由患者签署知情同意书，由我院伦理协会监督进行，患者一般资料比较无明显差异(P>0.05)。

1.2 方法

对照组：思美泰(规格 0.5g，批号 150113，厂家：HospiraS.P.A.)1.0 g 加入 50 g/L 葡萄糖注射液 500 mL 进行静脉滴注，1 次 /d+ 地塞米松(规格 0.75 mg，批号 150103，厂家：广东三才石岐制药有限公司) 口服，剂量 4 mg，3 次 /d，7 d 后将用量逐渐减少，减少至原药量 1/3。

观察组：思美泰 1000 mg 加入 50 g/L 葡萄糖注射液 500 mL 进行静脉滴注，1 次 /d+ 熊去氧胆酸(规格 50 mg，批号 150127，厂家：江苏黄河药业股份有限公司)100 mg 口服，3 次 /d。两组患者治疗时间均为 3 周或至患者分娩，治疗期间每 1~2 天进行胎心监测，每周检测肝功能情况。

1.3 观察指标

观察两组患者治疗前后 TBA、TB、ALT、AST、瘙痒评分的变化，并对妊娠结局围生儿情况进行比较。

TBA、TB、ALT、AST 的检测使用日本 OIYMPUS AU5400 型全自动生化分析仪检测。瘙痒评分使用 Ribaha(1991)[6]评分标准，得分越高，表示瘙痒症状越明显。

1.4 统计学分析

数据用 spss18.0 软件包进行处理，计量资料用均数± 标准差($\bar{x}$± s)表示，并采用 t 检验，计数资料的比较采用 x^2 检验，等级资料的比较采用秩和检验，以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组患者治疗后 TBA 及 TB 水平的比较

治疗前，两组患者在 TBA 及 TB 水平比较差异无统计学意义(P＞0.05)，两组患者治疗后 TBA 及 TB 水平均较治疗前下降(观察组：t=20.654，11.571，P<0.05；对照组：t=12.249，8.859，P<0.05)，但观察组下降更明显(t=8.328，5.572，P<0.05)。见表 1。

表 1 两组患者治疗前后 TBA 及 TB 水平的比较($\bar{x}$± s)

Table 1 Comparison of the TBA and TB levels before and after treatment between two groups($\bar{x}$± s)

Groups	Amount (n)	TBA		t	P	TB		t	P
		Before treatment	After treatment			Before treatment	After treatment		
Observation group	47	37.13± 6.25	14.41± 4.22	20.654	0.000	41.12± 13.24	18.35± 2.59	11.571	0.000
Control group	47	36.24± 7.21	21.49± 4.02	12.249	0.000	42.68± 13.47	23.64± 5.97	8.859	0.000
t		0.639	8.328			0.566	5.572		
P		0.524	0.000			0.572	0.000		

2.2 两组患者治疗前后 ALT 及 AST 水平的比较

治疗前，两组患者在 ALT、AST 水平差异无统计学意(P＞0.05)，两组患者治疗后 ALT 及 AST 水平均较治疗前下降(观察组：t=33.136，13.154，P<0.05；对照组：t=27.161，9.808，P<0.05)，但观察组下降更明显(t=4.772 ，4.284 ，P<0.05)。见表 2。

表 2 两组患者治疗前后 ALT 及 AST 水平比较($\bar{x}$± s)

Table 2 Comparison of the ALT and AST levels before and after treatment between two groups($\bar{x}$± s)

Groups	Amount (n)	ALT		t	P	AST		t	P
		Before treatment	After treatment			Before treatment	After treatment		
Observation group	47	146.27± 16.23	46.72± 12.68	33.136	0.000	134.73± 42.25	48.27± 15.66	13.154	0.000
Control group	47	152.21± 14.87	61.68± 17.35	27.161	0.000	134.82± 44.12	64.76± 21.24	9.808	0.000
t		1.850	4.772			0.010	4.284		
P		0.067	0.000			0.992	0.000		

2.3 两组患者治疗前后瘙痒评分的比较

治疗前，两组患者在瘙痒评分差异无统计学意(P＞0.05)，治疗后，两组患者均得到下降(观察组：t=24.292，P<0.05；对照组：t=21.688，P<0.05)，但观察组结果比对照组低((t=14.238，P<0.05)。见表 3。

2.4 两组患者妊娠结局及围生儿比较

观察组患者早产率、剖宫产率、羊水污染率及胎儿窘迫率分别为 19.15%、27.66%、10.64%、12.77% 均低于对照组 40.43%、57.45%、21.28%、19.15%，其中早产率及剖宫产率比较差异具有统计学意义(x^2=5.0866，8.5296，P<0.05)。见表 4。

表 3 两组患者治疗前后瘙痒评分比较

Table 3 Comparison of the Pruritus score before and after treatment between two groups

Groups	Amount(n)	Pruritus score		t	P
		Before treatment	After treatment		
Observation group	47	2.51± 0.65	0.20± 0.05	24.292	0.000
Control group	47	2.53± 0.64	0.47± 0.12	21.688	0.000
t		0.150	14.238		
P		0.880	0.000		

表 4 两组患者妊娠及围生儿结局比较【例(%)】

Table 4 Comparison of the pregnancy and perinatal outcomes between two groups[n(%)]

Groups	Amount(n)	Premature birth	CEsarean section	Amniotic fluid pollution	Fetal distress
Observation group	47	9(19.15)	13(27.66)	5(10.64)	6(12.77)
Control group	47	19(40.43)	27(57.45)	10(21.28)	9(19.15)
x^2		5.086	8.529	1.983	1.205
P		0.024	0.003	0.159	0.272

3 讨论

ICP 是妊娠中、晚期属一种特发性疾病,发病原因尚未完全阐明,有学者认为其与妊娠期体内雄性激素水平升高、遗传、缓解原因、硫唑嘌呤药物的服用等有关[7,8],首发症状为皮肤瘙痒,表现程度不一,病情严重的还会发生恶心、呕吐、食欲降低等。该病易增加早产、流产率及产后出血的风险,而且会增加围生儿发病率及死亡率,对母婴均不利[9,10]。

思美泰又名腺苷蛋氨酸,在人体内转甲基化和转硫基化的过程中所产生的作用较大,可使肝细胞膜中的磷脂甲基化增加,促进肝细胞中谷胱甘肽的合成及肝内胆汁的输送,从而使体内胆汁酸的水平降低,避免由雌激素所造成的胆汁淤积,还可发挥降酶、护肝等作用[11-13]。熊去氧胆酸主要是由鹅脱氧胆酸代谢所生成,在胆汁中亲和力较强,可在小肠中产生竞争性,对内源性胆汁酸的吸收得到抑制,使血清胆酸的浓度得到降低,从而对患者的肝功能、瘙痒症状加以改善[15,16]。常青等[14]学者的动物实验结果显示熊去氧胆酸改善胆汁酸水平及肝功能的效果比地塞米松优异。由此我们推测思美泰联合熊去氧胆酸在治疗 ICP 患者的效果可能更好。

本研究结果显示思美泰联合熊去氧胆酸治疗的患者 TBA、TB、ALT、AST 的下降程度及瘙痒症状的改善情况更加明显,患者体内 TBA、TB 降低,ALT、AST 水平也会随之降低,胆盐沉积得到减少,瘙痒症状得到改善。Zhang L 等[17,18]众多研究在患者中给予思美泰联合熊去氧胆酸的治疗,结果显示患者在治疗后胆汁酸、肝酶均得到显著下降。此外,有研究显示高浓度的胆酸可使绒毛膜静脉收缩作用增加,对胎儿的血灌注、氧供造成严重影响,促进胎儿窘迫的发生[19,20]。思美泰和熊去氧胆酸都可使血清胆酸的浓度降低,从而对胎儿、胎盘的代谢环境进行改善,预防胎儿窘迫、早产等不良事件的发生。本研究结果也证明此观点,思美泰联合熊去氧胆酸的患者在经过治疗后早产率、剖宫产率、羊水污染率、胎儿窘迫的发生情况均较少。

综上所述,思美泰联合熊去氧胆酸治疗 ICP 患者可使其胆汁酸、肝酶等指标得到明显改善,减轻瘙痒症状,提高妊娠结局及围生儿情况,效果优异。

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