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多烯磷脂酰胆碱对妊娠期肝内胆汁淤积症患者血清 IL-17, TNF- α , TGF- β 水平的影响 *

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摘要 目的:分析多烯磷脂酰胆碱对妊娠期肝内胆汁淤积症患者血清白细胞介素-17(IL-17)、肿瘤坏死因子- α (TNF- α)、转化生长因子- β (TGF- β)水平的影响及临床疗效。**方法:**选择我院2014年6月~2016年6月收治的102例妊娠期肝内胆汁淤积症患者,按抽签法分为对照组与观察组,各51例。对照组行常规治疗,观察组在对照组治疗基本上加以多烯磷脂酰胆碱治疗,比较两组治疗前后IL-17、TNF- α 、TGF- β 、血管内皮生长因子(VEGF)、总胆汁酸(TBA)、直接胆红素(DBiL)、总胆红素(TBiL)、谷草转氨酶(AST)、谷丙转氨酶(ALT)、瘙痒评分的变化、有效率及妊娠结局。**结果:**治疗后,观察组血清IL-17、TNF- α 、TGF- β 、VEGF、TBA、DBiL、TBiL、AST、ALT水平及瘙痒评分均显著低于对照组,有效率明显高于对照组,不良妊娠结局率显著低于对照组,差异均有统计学意义($P<0.05$)。**结论:**多烯磷脂酰胆碱可有效提高妊娠期肝内胆汁淤积症的临床疗效,降低血清IL-17、TNF- α 、TGF- β 水平,改善妊娠结局。

关键词:妊娠期肝内胆汁淤积症;多烯磷脂酰胆碱;白细胞介素-17;肿瘤坏死因子- α ;转化生长因子- β ;临床疗效

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Effects of Polyene Phosphatidyl Choline on the Serum Levels of IL-17, TNF- α and TGF- β of Patients with Intrahepatic Cholestasis During Pregnancy*

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ABSTRACT Objective: To analyze the effect of polyene phosphatidyl choline on the serum interleukin-17 (IL-17), tumor necrosis factor- α (TNF- α), transforming growth factor beta- β (TGF- β) of patients with intrahepatic cholestasis during pregnancy. **Methods:** 102 cases of patients with intrahepatic cholestasis during pregnancy from June 2014 to June 2016 were selected and divided into control group and observation group according to the draw method with 51 cases in each group. The control group was treated by routine treatment, while the observation group was treated by polyene phosphatidyl choline based on the control group. The serum IL-17, TNF- α , TGF- β , vascular endothelial growth factor (VEGF) and total bile acid (associates), direct bilirubin (DBiL), total bilirubin (TBiL), straw transfer ammonia enzyme (AST), alanine aminotransferase (ALT) levels, pruritus score, efficient and pregnancy outcome were compared between two groups. **Results:** The serum IL-17, TNF- α , TGF- β , VEGF, TBA, DBiL, TBiL, AST, ALT levels and pruritus score of observation group were significantly lower than those the control group, the effective rate was higher than that of the control group, the adverse pregnancy outcome rate was lower than that of the control group ($P<0.05$). **Conclusion:** Polyene phosphatidyl choline could effectively enhance the efficacy of intrahepatic cholestasis during pregnancy, decrease the serum IL-17, TNF- α , TGF- β levels and improve the pregnancy outcome.

Key words: Intrahepatic cholestasis disease during pregnancy; Polyene phosphatidyl choline; Interleukin-17; Tumor necrosis factor- α ; Transforming growth factor- β ; Curative effect

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前言

妊娠期肝内胆汁淤积症是妊娠期间的一种特发性疾病,胆汁酸及肝酶升高、皮肤瘙痒是其主要特征,对于母体的影响比较小,但可严重危害围产儿的预后,造成胎儿窘迫、早产、死亡

等^[1]。目前,临床研究显示免疫失衡可能与妊娠期肝内胆汁淤积症的发病有关,血清白细胞介素-17(IL-17)、肿瘤坏死因子- α (TNF- α)、转化生长因子- β (TGF- β)是免疫调节因子,可介导机体免疫反应^[2,3]。妊娠期肝内胆汁淤积症尚无特效治疗,熊去氧胆酸等常规药物治疗的效果并不理想^[4]。近年来研究报道多烯

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磷脂酰胆碱可利于患者肝脏排毒功能的改善,降低不良妊娠结局的危险性^[9]。因此,本研究就妊娠期肝内胆汁淤积症患者使用多烯磷脂酰胆碱治疗对血清生化指标的影响及疗效展开了分析如下。

1 资料与方法

1.1 一般资料

选择我院 2014 年 6 月~2016 年 6 月收治的 102 例妊娠期肝内胆汁淤积症患者,入选标准:① 单胎,头正位,初产妇;② 此前未接受相关治疗;③ 孕前无急性慢性肝胆病史;④ 无其他妊娠合并症。排除标准:① 心、肝肾等主要脏器不全;② 伴恶性肿瘤;③ 对本研究药物过敏者。本研究已签署家属及患者知情同意书,且通过医院伦理委员会许可,按抽签法予以分组。对照组年龄 23~33 岁,平均 (27.58±1.56) 岁;孕周 28~36 周,平均 (32.41±1.16) 周;病情程度:有 37 例轻度,有 14 例重度。观察组年龄 24~31 岁,平均 (26.73±1.65) 岁;孕周 27~36 周,平均 (31.85±1.23) 周;病情程度:有 34 例轻度,有 17 例重度。两组基线资料比较差异均无统计学意义($P>0.05$),具有比较性。

诊断标准:妊娠中晚期出现皮肤瘙痒症状,且以四肢、手脚掌为主;血清总胆汁酸(TBA)水平在 10 $\mu\text{mol/L}$ 以上;谷草转氨酶(AST)、谷丙转氨酶(ALT)高于正常值;妊娠是皮肤瘙痒及生化指标异常的唯一诱因。

1.2 治疗方法

嘱患者适当卧床休息,治疗前 3 天口服 0.75 mg 地塞米松(0.75 mg/片),以促胎肺成熟,期间配合高渗葡萄糖、能量合剂、微生素类等治疗,必要时予以吸氧。对照组行常规治疗,将 1g 思美泰(500 mg/支)与 250 mL 5%葡萄糖注射液稀释(250 mL:25g),予以患者静脉滴注,每天 1 次;口服 250 mg 熊去氧胆酸(50 mg/片),早晚各 1 次。观察组基于对照组加用多烯磷脂酰胆碱治疗,将 15 mL 多烯磷脂酰胆碱与 500 mL 5%葡萄糖注射

液稀释,予以患者静脉滴注,每天 1 次。两组均连续 10 天用药,定期实施无创胎心监护,并复查超声,若发生胎儿窘迫、胎盘功能显著减退、羊水过少等需及时终止妊娠,并记录妊娠结局。

1.3 观察指标

1.3.1 指标检测 采集患者治疗前及治疗结束时外周静脉血 2 mL,行肝素抗凝后常规分离血清待检。使用酶联免疫法检测 IL-17,使用化学比浊法检测 TNF- α ,使用放射免疫法检测 TGF- β 。使用电化学发光法检测血管内皮生长因子(VEGF)、TBA。直接胆红素(DBiL)、总胆红素(TBiL)、AST、ALT 使用全自动生化分析仪检测。

1.3.2 瘙痒程度评估 参照相关文献评估患者治疗前及治疗结束时瘙痒程度,总分为 4 分,0 分表示无瘙痒;1 分表示偶尔发作;2 分表示间断性瘙痒;3 分表示间断性瘙痒且伴症状波动;4 分表示持续性瘙痒,日夜未见改变。

1.3.3 疗效评估 治愈:瘙痒症状消失,血清 TBA 在 10 mmol/L 以下;显效:瘙痒症状基本消失,TBA 在 10 mmol/L 以上,但降低程度超过 2/3;好转:瘙痒症状显著缓解,TBA 降低程度在 1/2~2/3;无效:瘙痒症状未见明显改善,TBA 无改变或者上升,治愈+显效+好转=有效。

1.4 统计学分析

选择 SPSS18.0 行数据统计,用均数 $\pm$ 标准差($\bar{x} \pm s$)表示计量资料,组间比较用 t 检验,用 $[(n)\%]$ 表示计数资料,用 χ^2 检验比较,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者治疗前后血清 IL-17、TNF- α 、TGF- β 水平比较

治疗前,两组血清 IL-17、TNF- α 、TGF- β 水平比较差异无统计学意义($P>0.05$);治疗后,两组血清 IL-17、TNF- α 、TGF- β 水平均较治疗前显著降低,且观察组以上指标明显低于对照组,差异有统计学意义($P<0.05$),见表 1。

表 1 两组患者治疗前后血清 IL-17、TNF- α 、TGF- β 水平比较($\bar{x} \pm s$)

Table 1 Comparison of the serum IL-17, TNF- α and TGF- β levels between the two groups before and after the treatment ($\bar{x} \pm s$)

Items	Time	Control group(n=51)	Observation group (n=51)
IL-17(ng/L)	Before treatment	5.71 $\pm$ 0.81	5.67 $\pm$ 0.84
	After treatment	3.44 $\pm$ 0.49 ^a	2.11 $\pm$ 0.30 ^{ab}
TNF- α (ng/L)	Before treatment	28.63 $\pm$ 4.09	27.80 $\pm$ 3.97
	After treatment	20.46 $\pm$ 2.92 ^a	13.42 $\pm$ 1.91 ^{ab}
TGF- β (ng/L)	Before treatment	2.93 $\pm$ 0.41	2.96 $\pm$ 0.44
	After treatment	3.87 $\pm$ 0.55 ^a	5.79 $\pm$ 0.82 ^{ab}

Note: Compared with control group ^a $P<0.05$; Compared with before treatment ^b $P<0.05$.

2.2 两组患者治疗前后血清 VEGF、TBA 水平比较

治疗前,两组血清 VEGF、TBA 水平比较差异均无统计学意义($P>0.05$);治疗后,两组血清 VEGF、TBA 水平均较治疗前显著降低,且观察组以上指标明显低于对照组,差异均具有统计学意义($P<0.05$),见表 2。

2.3 两组患者治疗前后血清 DBiL、TBiL、AST、ALT 水平比较

治疗前,两组血清 DBiL、TBiL、AST、ALT 水平比较需要无统计学意义($P>0.05$);治疗后,两组血清 DBiL、TBiL、AST、ALT 水平均较治疗前显著降低,且观察组以上指标明显低于对照

组,差异有统计学意义($P<0.05$),见表 3。

2.4 两组患者治疗前后瘙痒评分比较

治疗前,两组瘙痒评分比较差异无统计学意义($P>0.05$);治疗后,两组瘙痒评分均较治疗前显著降低,且观察组明显低于对照组,差异有统计学意义($P<0.05$),见表 4。

2.5 两组患者疗效比较

治疗后,观察组有效率为 94.1%,显著高于对照组,差异有统计学意义($P<0.05$),见表 5。

表 2 两组患者治疗前后血清 VEGF、TBA 水平比较($\bar{x} \pm s$)Table 2 Comparison of the serum VEGF and TBA levels between the two groups before and after the treatment ($\bar{x} \pm s$)

Items	Time	Control group(n=51)	Observation group (n=51)
VEGF(ng/L)	Before treatment	102.50± 14.64	104.96± 15.20
	After treatment	71.48± 10.21 ^b	51.30± 7.32 ^{ab}
TBA(mmol/L)	Before treatment	65.75± 9.67	67.46± 10.93
	After treatment	12.30± 1.74 ^b	9.11± 1.25 ^{ab}

Note: Compared with control group ^aP<0.05; Compared with before treatment ^bP<0.05.

表 3 两组患者治疗前后血清 DBiL、TbiL、AST、ALT 水平比较($\bar{x} \pm s$)Table 3 Comparison of the serum DBiL, TbiL, AST and ALT levels between the two groups before and after the treatment ($\bar{x} \pm s$)

Items	Time	Control group(n=51)	Observation group (n=51)
DBiL(μ mol/L)	Before treatment	17.60± 2.51	16.83± 2.40
	After treatment	9.12± 1.30 ^b	4.70± 0.67 ^{ab}
TbiL(μ mol/L)	Before treatment	39.40± 5.62	37.52± 5.36
	After treatment	27.51± 3.93 ^b	17.60± 2.51 ^{ab}
AST(U/L)	Before treatment	167.98± 23.99	165.37± 22.82
	After treatment	82.43± 11.77 ^b	54.26± 7.75 ^{ab}
ALT(U/L)	Before treatment	242.65± 34.66	244.70± 33.95
	After treatment	105.69± 15.09 ^b	95.43± 13.63 ^{ab}

Note: Compared with control group ^aP<0.05; Compared with before treatment ^bP<0.05.

表 4 两组患者治疗前后瘙痒评分比较($\bar{x} \pm s$)Table 4 Comparison of the pruritus score between the two groups before and after the treatment ($\bar{x} \pm s$)

Items	Time	Control group(n=51)	Observation group (n=51)
Pruritus score(points)	Before treatment	3.45± 0.49	3.38± 0.53
	After treatment	2.52± 0.36 ^b	1.32± 0.18 ^{ab}

Note: Compared with control group ^aP<0.05; Compared with before treatment ^bP<0.05.

2.6 两组患者不良妊娠结局比较

观察组羊水污染、胎儿窘迫、剖宫产、早产、新生儿窒息率

均显著低于对照组,差异有统计学意义(P<0.05),见表 6。

表 5 两组患者疗效比较[例(%)]

Table 5 Comparison of the clinical effect between two groups [n(%)]

Items	Control group (n=51)	Observation group (n=51)
Cure	17(33.3%)	29(56.9%)
Markedly	10(19.6%)	14(27.5%)
Better	12(23.5%)	5(9.8%)
invalid	12(23.5%)	3(5.9%)
Effective rate	39(76.5%)	48(94.1%) ^a

Note: Compared with control group ^aP<0.05.

表 6 两组患者不良妊娠结局比较[例(%)]

Table 6 Comparison of the adverse pregnancy outcome between two groups [n(%)]

Items	Control group (n=51)	Observation group (n=51)
Amniotic fluid pollution	8(15.7%)	3(5.9%) ^a
Fetal distress	9(17.6%)	2(3.9%) ^a
Cesarean section	22(43.1%)	12(23.5%) ^a
Premature delivery	17(33.3%)	6 (11.8%) ^a
Neonatal asphyxia	20(39.2%)	8(15.7%) ^a

Note: Compared with control group, ^aP<0.05.

3 讨论

妊娠期肝内胆汁淤积症存在复发性,症状可于分娩后快速缓解,也可于下次妊娠或者服用雌激素避孕药后再次发病,可引起系列的临床症状,同时增加围产儿的病死率^[6]。尽快减轻瘙痒症状、降低血清 TBA 水平、恢复肝功能、改善妊娠结局是其主要治疗目的^[7]。思美泰可经生理性疏基化何物前体及甲基供体参与机体的主要代谢反应从而发挥治疗目的^[8]。熊去氧胆酸作为一种亲水性胆汁酸,对肝脏可起到多重的保护作用,可发

挥疏水性胆汁酸的替代作用,使其细胞毒性降低^[9],同时也可调节母体与胎儿之间的跨滋层胆汁酸的转运,导致血清中孕激素硫酸化的代谢产物降低,从而利于肝胆管系统功能恢复正常;也可起到一定的抗氧化应激、细胞凋亡的功效,进而改善胎儿预后^[10]。本研究结果显示思美泰结合熊去氧胆酸治疗后生化指标、瘙痒症状虽有一定改善,但不良妊娠结局率仍较高。

多烯磷脂酰胆碱是临床上治疗多种肝病的常用药物,是人工合成磷脂,能够增强肝细胞对自由基、药物、病毒等防御能

力^[11]。研究显示母胎之间的免疫耐受平衡是决定妊娠成功的关键,病理妊娠多伴程度不一的免疫耐受失衡^[12]。IL-17 主要由 Th17 型 T 细胞分泌,可起到激活免疫的作用。TGF- β 主要来自于调节性 T 细胞,二者水平稳定可保持机体免疫状态平衡,一旦失衡可诱导自身免疫反应,引起肝细胞出现免疫受损,从而使胆汁酸代谢出现障碍,诱导肝内形成胆汁淤积^[13]。TNF- α 可利于单核细胞及中性粒细胞产生黏附,增强机体的免疫反应,导致内皮细胞损伤,进一步损伤肝功能,也可引起胎盘绒毛滋养细胞出现坏死、凋亡,诱导胎盘功能出现损伤,从而对胎儿的生长发育构成影响^[14]。本研究结果显示多烯磷脂酰胆碱治疗后血清 IL-17、TNF- α 、TGF- β 水平显著下降,表明多烯磷脂酰胆碱可降低 IL-17、TNF- α 、TGF- β 水平过度分泌,促进机体细胞因子的动态平衡,抑制机体产生过度的炎症反应,从而利于机体免疫功能的恢复^[15]。

临床研究显示 TBA 具有一定的细胞毒性,能够使线粒体膜与细胞膜产生损伤,增加生物膜通透性,进而使肝酶由细胞外溢出,增加其血清浓度,进一步影响肝功能^[16]。高浓度 TBA 可导致胎盘绒毛血管产生痉挛,增加其静脉血管的阻力,使血管通透性受到影响,使 VEGF 表达上调,进一步增加血管通透性^[17]。IL-17、TNF- α 、TGF- β 水平过高可促进血管平滑肌的收缩,使胎盘供血系统出现坏死,引起胎儿窘迫^[18]。而且 TBA、VEGF、TBA、AST、ALT 等水平升高能够使胎儿结肠的机械运动加重增加羊水污染的可能性,还可增加子宫收缩,引起早产^[19]。本研究结果显示多烯磷脂酰胆碱治疗后血清 TBA、VEGF、DBIL、TBIL、AST、ALT 水平均明显降低,表明其可改善肝功能,考虑与其可结合肝细胞膜,利于肝细胞的再生,从而恢复肝功能。同时,经多烯磷脂酰胆碱治疗后的患者瘙痒评分、有效率明显优于常规治疗者,表明多烯磷脂酰胆碱能够有效改善患者的临床症状。此外,多烯磷脂酰胆碱治疗后不良妊娠结局率较低,考虑与其治疗更能利于生化指标的恢复,从而改善妊娠结局有关。

综上所述,多烯磷脂酰胆碱可有效提高妊娠期肝内胆汁淤积症的临床疗效,降低血清 IL-17、TNF- α 、TGF- β 水平,改善妊娠结局。

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