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妊娠期肝内胆汁淤积症患者血清总胆汁酸水平与炎症因子、Th17/Treg 平衡及母婴结局的关系研究 *

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摘要 目的:分析妊娠期肝内胆汁淤积症(ICP)患者血清总胆汁酸(TBA)水平与炎症因子[肿瘤坏死因子- α (TNF- α)、白介素-12(IL-12)、白介素-6(IL-6)]、Th17/Treg 平衡及母婴结局的关系。**方法:**选取 2018 年 1 月-2020 年 12 月期间我院收治的 ICP 患者 94 例为 ICP 组,另选取同期来我院产检的 90 例正常妊娠妇女为对照组,对照组孕妇于体检当日、ICP 组于入院次日在早晨空腹状态下抽取外周静脉血,应用流式细胞仪测定 Th17、Treg 细胞比率,采用全自动生化分析仪对血清 TBA 水平进行检测与分析,采用酶联免疫吸附法检测 TNF- α 、IL-6、IL-12 水平。根据 ICP 孕妇血清 TBA 水平分为低 TBA 组($<40 \mu\text{mol/L}$, 58 例)与高 TBA 组($\geq 40 \mu\text{mol/L}$, 36 例),观察两组围生儿结局、产妇妊娠结局、新生儿并发症发生率。**结果:**ICP 组的 TBA、TNF- α 、IL-6、IL-12、Th17、Th17/Treg 均高于对照组,Treg 低于对照组($P<0.05$)。低 TBA 组剖宫产率低于高 TBA 组,阴道自然分娩率高于高 TBA 组($P<0.05$),两组阴道助产率组间对比差异无统计学意义($P>0.05$)。低 TBA 组胎儿宫内发育迟缓率、胎儿宫内窘迫率低于高 TBA 组($P<0.05$)。两组新生儿窒息率、围生儿死亡率组间对比差异无统计学意义($P>0.05$)。低 TBA 组新生儿并发症总发生率低于高 TBA 组($P<0.05$)。Pearson 线性相关分析结果显示,血清 TBA 与 TNF- α 、IL-6、IL-12、Th17/Treg 比值呈正相关($P<0.05$)。**结论:**ICP 患者的 TBA 水平越高,母婴不良结局发生率越高,此外,ICP 患者具有明显的炎症反应和 Th17/Treg 平衡情况,促进疾病进展。

关键词:妊娠期;肝内胆汁淤积症;总胆汁酸;炎症因子;Th17/Treg 平衡;母婴结局

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The Study of Relationship between Serum Total Bile Acid Level, Inflammatory Factor, Th17/Treg Balance and Maternal and Infant Outcomes in Patients with Intrahepatic Cholestasis during Pregnancy*

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ABSTRACT Objective: To analyze the relationship between serum total bile acid (TBA) level and inflammatory factors [tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), interleukin-6 (IL-6)], Th17/Treg balance and maternal and infant outcomes in patients with intrahepatic cholestasis during pregnancy (ICP). **Methods:** 94 patients with ICP in our hospital from January 2018 to December 2020 were selected as ICP group, 90 normal pregnant women who were examined in our hospital at the same time were selected as control group. Peripheral venous blood was extracted from pregnant women in the control group on the day of physical examination and in the ICP group on the day after admission on a fasting basis in the morning, the ratio of Th17 and Treg cells was measured by flow cytometry. The serum TBA level was detected and analyzed by automatic biochemical analyzer. TNF- α , IL-6 and IL-12 levels were detected by enzyme-linked immunosorbent assay. According to the serum TBA level of ICP pregnant women, the patients were divided into low TBA group ($<40 \mu\text{mol/L}$, 58 cases) and high TBA group ($\geq 40 \mu\text{mol/L}$, 36 cases). The perinatal outcome, maternal pregnancy outcome and incidence of neonatal complications were observed in the two groups. **Results:** TBA, TNF- α , IL-6, IL-12, Th17, Th17/Treg in ICP group were higher than those in control group, and Treg was lower than that in control group ($P<0.05$). The cesarean section rate in low TBA group was lower than that in high TBA group, and the vaginal natural delivery rate was higher than that in high TBA group ($P<0.05$). There was no significant difference in vaginal midwifery rate between the two groups ($P>0.05$). The rate of fetal intrauterine growth retardation and fetal distress in low TBA group were lower than those in high TBA group ($P<0.05$). There was no significant difference in neonatal asphyxia rate and perinatal mortality rate between the two groups ($P>0.05$). The total incidence of neonatal complications in low TBA group was lower than that in high TBA group ($P<0.05$). Pearson linear correlation analysis showed that serum TBA was positively correlated with TNF- α , IL-6, IL-12 and Th17/Treg ratio ($P<0.05$). **Conclusion:** The higher the TBA level of patients with ICP, the higher the incidence of adverse outcomes between maternal and infant. In addition, patients with ICP have obvious inflammatory response and

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Th17/Treg balance, which promotes the progress of the disease.

Key words: Pregnancy; Intrahepatic cholestasis; Total bile acid; Inflammatory factors; Th17/treg balance; Maternal and infant outcomes

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前言

妊娠期肝内胆汁淤积症(ICP)是妊娠晚期常见的并发症之一,其主要特征为总胆汁酸(TBA)水平上调、皮肤瘙痒不止^[1]。既往研究证实 ICP 除了会影响孕妇生活质量外,还会增加胎儿不良妊娠结局的发生,如新生儿窒息、胎儿宫内窘迫、围生儿死亡等^[2]。相关研究认为^[3],ICP 主要是由母体、胎儿胎盘胆酸转运异常所致的疾病。血清 TBA 是胆固醇代谢产物,临床常用于检测 ICP^[4]。随着研究的深入,有观点提出^[5],ICP 的发生与妊娠期母体免疫调节失衡、炎症反应有关,具体为母胎界面免疫细胞、细胞因子调节紊乱,上调了辅助性 T 细胞(Th)17 的表达,并降低调节性 T 细胞(Treg)表达^[6]。也有学者发现肿瘤坏死因子- α (TNF- α)、白介素-6(IL-6)可能参与了 ICP 肝损伤的过程^[7]。本研究通过探讨 ICP 患者血清 TBA 水平与炎症因子、Th17/Treg 平衡及母婴结局的关系,以期临床该病防治提供数据支持。

1 资料与方法

1.1 临床资料

选取 2018 年 1 月-2020 年 12 月期间我院收治的 ICP 患者 94 例为 ICP 组,研究方案获得我院伦理学委员会批准进行。纳入标准:(1)均符合《妊娠期肝内胆汁淤积症诊疗指南(2015)》相关标准^[8];(2)单胎妊娠;(3)临床资料完整;(4)所有受试者及其家属均签署知情同意书。排除标准:(1)肝胆疾病、免疫系统疾病、糖尿病等妊娠合并症;(2)由其他皮肤病引起的皮肤瘙痒;(3)急性感染患者;(4)合并有慢性炎症性疾病者。ICP 患者年龄 21~36 岁,平均(27.38 $\pm$ 3.16)岁;初产妇 55 例,经产妇 39 例;孕周 30~37 周,平均(34.74 $\pm$ 1.49)周;体质指数 24~36 kg/m²,平均(29.38 $\pm$ 2.09)kg/m²。另选取同期来我院产检的 90 例正常妊娠妇女为对照组,收集患者数据,年龄 20~38 岁,平均(28.19 $\pm$ 2.35)岁;初产妇 53 例,经产妇 37 例;孕周

31~36 周,平均(33.92 $\pm$ 1.53)周;体质指数 25~38 kg/m²,平均(29.17 $\pm$ 1.65)kg/m²。两组一般资料对比无差异($P>0.05$),均衡可比。

1.2 方法

对照组孕妇于体检当日、ICP 组于入院次日在早晨空腹状态下抽取 6 mL 外周静脉血,分为 2 管,1 管血液标本应用流式细胞仪(贝克曼 EPICS X 型)测定 Th17、Treg 细胞比率。另一管经 3500 r/min 离心 8 min,离心半径 10.5 cm,留取上清液置于冰箱中备用。采用全自动生化分析仪(日立 7060 型)对血清 TBA 水平进行检测与分析。采用酶联免疫吸附法(试剂盒购自上海酶联生物科技有限公司)检测 TNF- α 、IL-6、白介素-12(IL-12)水平。

1.3 围生期情况

根据 ICP 孕妇血清 TBA 水平分为低 TBA 组(<40 μ mol/L,58 例)与高 TBA 组($\geq$ 40 μ mol/L,36 例),观察两组产妇产后结局,包括阴道助产、阴道自然分娩、剖宫产。围生儿结局包括胎儿宫内发育迟缓或宫内窘迫、围生儿死亡、新生儿窒息。新生儿并发症有新生儿病理性黄疸、新生儿吸入性肺炎、新生儿缺血缺氧性脑病、新生儿颅内出血。

1.4 统计学方法

经 SPSS20.0 软件行数据分析。计量资料以($\bar{x}\pm s$)表示,行 t 检验。用率表示计数资料,行 χ^2 检验。经 Pearson 线性相关分析妊娠期 ICP 患者血清 TBA 水平与炎症因子、Th17/Treg 平衡及母婴结局的相关性。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 对照组、ICP 组 TBA、炎症因子、Th17、Treg 细胞比率、Th17/Treg 比值对比

ICP 组的 TBA、TNF- α 、IL-6、IL-12、Th17、Th17/Treg 均高于对照组,Treg 低于对照组($P<0.05$),详见表 1。

表 1 对照组、ICP 组 TBA、炎症因子、Th17、Treg 细胞比率、Th17/Treg 比值对比($\bar{x}\pm s$)

Table 1 Comparison of TBA, inflammatory factors, Th17, Treg cell ratio and Th17/Treg ratio between the control group and the ICP group($\bar{x}\pm s$)

Groups	TBA(μ mol/L)	TNF- α (pg/mL)	IL-6(pg/mL)	IL-12(pg/mL)	Th17(%)	Treg(%)	Th17/Treg
Control group(n=90)	14.32 $\pm$ 2.01	22.56 $\pm$ 4.62	18.91 $\pm$ 3.32	21.49 $\pm$ 4.76	1.08 $\pm$ 0.24	5.72 $\pm$ 0.36	0.19 $\pm$ 0.03
ICP group(n=94)	74.26 $\pm$ 9.93	97.91 $\pm$ 9.47	83.97 $\pm$ 10.34	77.51 $\pm$ 9.28	1.53 $\pm$ 0.26	4.41 $\pm$ 0.39	0.35 $\pm$ 0.07
t	45.284	39.274	42.485	40.562	18.364	16.932	15.364
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000

2.2 低 TBA 组与高 TBA 组围生儿结局、产妇产后结局对比

低 TBA 组胎儿宫内发育迟缓率、胎儿宫内窘迫率低于高 TBA 组($P<0.05$)。两组新生儿窒息率、围生儿死亡率组间对比差异无统计学意义($P>0.05$)。低 TBA 组剖宫产率低于高 TBA

组,阴道自然分娩率高于高 TBA 组($P<0.05$),两组阴道助产率组间对比差异无统计学意义($P>0.05$)。详见表 2。

2.3 低 TBA 组与高 TBA 组新生儿并发症发生率对比

低 TBA 组新生儿并发症总发生率低于高 TBA 组($P<0.05$)。

详见表 3。

2.4 分析血清 TBA 与炎症因子、Th17/Treg 比值的相关性

Pearson 线性相关分析结果显示, 血清 TBA 与 TNF- α 、IL-6、IL-12、Th17/Treg 比值呈正相关($P<0.05$), 详见表 4。

表 2 低 TBA 组与高 TBA 组围生儿结局、产妇产后结局对比 [例(%)]

Table 2 Comparison of perinatal outcomes and maternal pregnancy outcomes between low TBA group and high TBA group [n(%)]

Groups	Neonatal asphyxia	Fetal intrauterine growth retardation	Perinatal death	Fetal distress	Cesarean section	Vaginal natural delivery	Vaginal midwifery
Low TBA group(n=58)	1(1.72)	2(3.45)	0(0.00)	3(5.17)	26(44.83)	27(46.55)	5(8.62)
High TBA group(n=36)	2(5.56)	6(16.67)	1(2.78)	8(22.22)	25(69.44)	9(25.00)	2(5.56)
χ^2	1.055	4.985	1.628	6.249	5.424	4.366	0.201
P	0.304	0.026	0.202	0.012	0.020	0.037	0.654

表 3 低 TBA 组与高 TBA 组新生儿并发症发生率对比 [例(%)]

Table 3 Comparison of neonatal complications between low TBA group and high TBA group [n(%)]

Groups	Neonatal intracranial hemorrhage	Neonatal hypoxic ischemic encephalopathy	Neonatal pathological jaundice	Neonatal aspiration pneumonia	Total incidence rate
Low TBA group (n=58)	0(0.00)	1(1.72)	2(3.45)	1(1.72)	4(6.89)
High TBA group (n=36)	1(2.78)	2(5.56)	2(5.56)	3(8.33)	8(22.22)
χ^2					4.685
P					0.030

表 4 分析血清 TBA 与炎症因子、Th17/Treg 比值的相关性

Table 4 Analyzes the correlation between serum TBA and inflammatory factors, Th17 / Treg ratio

Item	TBA	
	r	P
IL-6	0.436	0.000
IL-12	0.429	0.003
TNF- α	0.451	0.000
Th17/Treg	0.467	0.000

3 讨论

现临床有关 ICP 的发病机制不明, 既往观点认为相关因素有: ① 激素: 女性妊娠时, 体内雌激素水平上升, 抑制机体内 Na⁺-K⁺-ATP 酶活性, 无法持续有效的为脏器供给能量, 引发 TBA 代谢障碍^[9]。同时也有研究证实^[10], 过高的雌激素水平可升高肝细胞膜内磷脂、胆固醇水平, 降低胆酸通透性。② 遗传: 母亲或姐妹伴 ICP 病史的女性, 其 ICP 发病风险明显增加^[11]。③ 药物: 部分降低胆管胆汁运转类药物可能引发 ICP^[12]。④ 环境: ICP 发病具有明显的季节特征, 通常情况下冬季发病率最高^[13]。TBA 是诊断 ICP 的重要实验室指标, ICP 产妇发病后, TBA 水平会异常升高^[14]。本次研究中 ICP 组的 TBA 高于对照组, 产妇产后血清内的 TBA 表达水平会影响胎儿的发育和生长, 但目前针对不同 TBA 水平影响 ICP 母婴结局的研究报道较少。

本次研究中将 ICP 产妇分为低 TBA 组和高 TBA 组, 结果显示, 低 TBA 组阴道自然分娩率高, 且低 TBA 组围生儿不良结局发生率、新生儿并发症总发生率均低于高 TBA 组, 分析原因可能是因 TBA 长时间过高引起的代谢损伤^[15]。ICP 发病时,

高水平的 TBA 可通过胎盘运转至胎儿, 导致胎儿的 TBA 水平维持较高水平, 同时胎盘血窦间隙存在的胆盐积聚, 胎儿 TBA 的母体回流量也相应降低, 造成恶性循环, 引起胎儿 TBA 淤积^[16,17]。胎儿体内高水平的 TBA 会促使胎盘静脉收缩, 影响胎儿生长发育, 最终引起胎儿宫内发育迟缓、胎儿宫内窘迫等不良结局的发生^[18,19]。此外, 在 ICP 发病期间, 产妇会发生不良情况, 如脂肪及脂溶性维生素吸收障碍等, 间接导致新生儿并发症发生率升高^[20]。

炎症反应、免疫功能改变与 ICP 的发生关系密切, 上述病理改变可能会破坏孕妇免疫微环境, 出现病理性妊娠反应^[21,22]。TNF- α 、IL-6、IL-12 属于多功能炎症因子^[23], Th17 主要分泌白介素 -17, 白介素 -17 过表达可刺激免疫系统, 导致母体免疫排斥胎儿^[24]。Treg 主要分泌白介素 -35, 可延缓炎症进展, 在调节免疫应答中有关键作用^[25]。本研究中 ICP 组的 TNF- α 、IL-6、IL-12、Th17、Th17/Treg 均高于对照组, Treg 低于对照组, 考虑正常水平 Treg 可抑制 Th17 细胞活化及增殖, 引起免疫耐受机制受损, 造成 ICP 发病。TNF- α 、IL-6、IL-12 介导的 ICP 机制可概括为以下几个方面: 促进分泌免疫细胞因子, 产生炎性反应;

促进胎盘组织分泌雌激素,进一步造成雌-孕激素分泌失衡,ICP加重;诱导中性粒细胞、线粒体产生氧自由基,形成脂质过氧化损伤^[26-28]。Pearson 线性相关分析结果显示,血清 TBA 与 TNF- α 、IL-6、IL-12、Th17/Treg 比值呈正相关,提示 ICP 患者 TBA、炎症反应、Th17/Treg 平衡均参与着疾病进展,可能是 TBA 通过对核转录因子- κ B 的调控触发炎症信号传导级联反应,导致分泌大量炎症因子,初始 CD4⁺T 细胞被诱导分化为 Th17,抑制 Treg 细胞分化,机体免疫受损加重,进一步加重 ICP^[29,30]。

综上所述,ICP 产妇伴有明显的 TBA 水平升高,炎症反应增强,Th17/Treg 平衡失衡情况,且 ICP 产妇 TBA 水平越高,新生儿并发症及母婴不良结局发生率越高,故应积极观察 ICP 产妇 TBA、炎症反应、Th17/Treg 平衡情况,以随时了解产妇病情,给予准确的干预治疗,以改善母婴结局。

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