

妊娠期肝内胆汁淤积症患者血清肝胆酸、总胆汁酸水平及血浆凝血功能检测的临床诊断意义*

朱 婷, 吕艳关

(扬州大学附属淮安市妇幼保健院检验科, 江苏淮安 223002)

摘要:目的 探讨妊娠期肝内胆汁淤积症(intrahepatic cholestasis of pregnancy, ICP)患者血清肝胆酸(courage acid, CG)、总胆汁酸(total bile acid, TBA)水平及血浆凝血功能检测的临床诊断意义。方法 随机选择31例妊娠期肝内胆汁淤积症患者(ICP组)及31例正常妊娠孕妇(对照组)作为研究对象,分别检测两组血清CG, TBA, 丙氨酸氨基转移酶(alanine aminotransferase, ALT)、门冬氨酸氨基转移酶(aspartate aminotransferase, AST)以及血浆凝血酶原时间(prothrombin time, PT)、活化部分的凝血活酶时间(activated partial thromboplastin time, APTT)、凝血酶时间(thrombin time, TT)、纤维蛋白原(fibrinogen, FIB)和D-二聚体(D-Dimer, D-D),并对结果进行统计学分析。结果 ①ICP组CG水平(27.14 ± 18.63 mg/L)和TBA水平(50.93 ± 29.69 μ mol/L)均高于对照组(1.14 ± 0.30 mg/L, 2.96 ± 1.61 μ mol/L),差异具有统计学意义($t=7.73, 9.04$, 均 $P<0.01$),与正常对照组相比,ICP组血清CG和TBA表达水平明显增高。②ICP组血清ALT, AST水平分别为 109.01 ± 84.47 U/L和 96.15 ± 80.51 U/L,对照组血清ALT, AST水平分别为 13.27 ± 5.07 U/L和 18.24 ± 4.69 U/L,差异均具有统计学意义($t=6.29, 5.39$, 均 $P<0.01$)。③ICP组FIB, D-D水平分别为 4.61 ± 1.12 g/L和 2.41 ± 1.69 mg/L,对照组FIB, D-D水平分别为 3.41 ± 0.32 g/L和 1.45 ± 0.87 mg/L,差异均具有统计学意义($t=6.10, 2.91$, 均 $P<0.01$),但两组之间PT, APTT和TT水平比较差异无统计学意义($t=0.49, 0.93, 1.20$, 均 $P>0.05$)。结论 ICP患者血清CG, TBA水平升高及凝血功能的改变,对ICP的早期诊断及监测具有重要的临床意义。

关键词:妊娠期肝内胆汁淤积症;肝胆酸;总胆汁酸;凝血功能

中图分类号:R714.255;R446.11 文献标志码:A 文章编号:1671-7414(2019)04-079-04

doi:10.3969/j.issn.1671-7414.2019.04.019

Clinical Significance of Serum Hepatocholic Acid, Total Bile Acid Level and Plasma Coagulation Function Test in Patients with Intrahepatic Cholestasis During Pregnancy

ZHU Ting, LÜ Yan-guan

(Department of Laboratory Clinical, Huai'an Women

& Children Hospital, Affiliated to Yangzhou University, Jiangsu Huai'an 223002, China)

Abstract: Objective To investigate the clinical significance of serum courage acid (CG), total bile acid (TBA) and plasma coagulation function in intrahepatic cholestasis during pregnancy. **Methods** 30 patients with intrahepatic cholestasis of pregnancy (ICP group) and 30 cases of normal pregnant women (control group) were randomly selected as the study subjects. Indexes including CG, TBA, ALT, AST, PT, APTT, TT, FIB and D-D were detected, and the results were compared. **Results**

①The levels of CG (27.14 ± 18.63 mg/L) and TBA (50.93 ± 29.69 mol/L) in ICP group were higher than those in the control group (1.14 ± 0.30 mg/L, 2.96 ± 1.61 mol/L), and the difference were statistically significant ($t=7.73, 9.04$, all $P<0.01$). Compared with the normal control group, the CG and TBA expression in ICP group were significantly increased. ②The serum ALT and AST levels of the ICP group were 109.01 ± 84.47 U/L and 96.15 ± 80.51 U/L, and the serum ALT and AST levels in control group were 13.27 ± 5.07 U/L and 18.24 ± 4.69 U/L, respectively. The differences were all statistically significant ($t=6.29, 5.39$, all $P<0.01$). ③The levels of FIB and D-D in ICP group were 4.6 ± 1.12 g/L and 2.41 ± 1.69 mg/L, respectively and the levels of FIB and D-D in control group were 3.4 ± 0.32 g/L and 1.45 ± 0.87 mg/L, respectively. The differences were all statistically significant ($t=6.10, 2.91$, all $P<0.01$). However, there were no significant differences in PT, APTT, TT levels between the two groups ($t=0.49, 0.93, 1.20$, all $P>0.05$). **Conclusion** Elevated serum CG and TBA levels and changes of coagulation function in patients with intrahepatic cholestasis during pregnancy have important clinical significance for the early diagnosis and monitoring of ICP.

Keywords: intrahepatic cholestasis of pregnancy; courage acid(CG); total bile acid(TBA); coagulation function

* 作者简介:朱 婷(1991—),女,硕士,检验师,研究方向:临床检验诊断学, E-mail:1550532156@qq.com。

通讯作者:吕艳关(1981—),男,硕士,副主任技师,研究方向:临床免疫学诊断, E-mail:lyyanguan@163.com。

妊娠期肝内胆汁淤积症(intrahepatic cholestasis of pregnancy, ICP)是一种妊娠中、晚期特有的并发症,主要表现为轻至重度的皮肤瘙痒,多伴有转氨酶、胆红素的轻度至中度升高,在妊娠结束后症状往往可自行消失^[1-2]。ICP孕妇一般预后较好,顽固性瘙痒和较高的产后出血易感性是产妇发病的主要原因。另一方面,ICP与胎儿早产、窘迫或突然宫内死亡有关,进而可导致胎儿发病率和死亡率的增加^[3]。目前,我国有近4%~5%的孕妇发生ICP,为临床上高发疾病,而常规产前监测无法预防,因此早期准确的诊断和适当的医疗干预对于改善胎儿的预后具有重要的临床意义^[4]。本研究检测ICP患者血清肝胆酸(CG),总胆汁酸(TBA)的表达量及凝血参数凝血酶原时间(PT)、活化部分的凝血活酶时间(APTT)、凝血酶时间(TT)、纤维蛋白原(FIB)、D-二聚体(D-D),了解上述指标在ICP中的临床诊断价值。

1 材料与方法

1.1 研究对象 选择2017年6月~2018年12月在淮安市妇幼保健院产科住院治疗的ICP患者31例,年龄20~45岁,平均年龄 28.27 ± 4.62 岁,孕周16~42周;同时选取我院正常妊娠孕妇31例作为对照组,年龄21~43岁,平均年龄 27.56 ± 4.23 岁,孕周16~42周。两组研究对象年龄、孕周等一般资料比较,差异无统计学意义($P > 0.05$)。入选标准:ICP患者妊娠前无肝胆疾病及皮肤病;妊娠中晚期有皮肤瘙痒症状;并发黄疸或肝功能损害,且无任何其他并发症。

1.2 试剂和仪器 贝克曼 AU5800 生化分析仪及其配套试剂,希森美康 CS-5100 凝血分析仪及其配套试剂。

1.3 方法 所有研究对象均于清晨空腹采集外周静脉血 2 ml,置于枸缘酸钠抗凝管中混匀后,3 500 r/min 离心 5 min,用 Sysmex CS-5100 检测相关凝血指标 PT, APTT, TT, FIB 和 D-D。另抽取静脉血 3 ml,将血液标本置于促凝管中,3 500 r/min 离心 10 min,取上清液于 4℃ 冰箱保存。采用贝克曼 AU5800 生化分析仪检测血清 CG, TBA, ALT 和 AST 水平;所有操作严格遵守仪器作业指导书(SOP)。

1.4 统计学分析 各组年龄和孕周的比较采用单因素方差分析(F检验),两组样本均数的比较采用 *t* 检验。所有统计分析均用 SPSS22.0 软件完成,计量资料采用均数±标准差($\bar{x} \pm s$)表示, $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组血清 CG, TBA 及其他肝功能水平比较

见表1。与正常对照组相比,ICP组血清CG, TBA表达水平明显增高,差异均具有统计学意义。ICP组和对照组血清ALT, AST水平比较,差异也均具有统计学意义($t=6.29, 5.39$, 均 $P < 0.01$)。

2.2 两组血浆凝血功能比较 见表2。ICP组FIB, D-D水平比正常对照组明显增高,差异均具有统计学意义($t=6.10, 2.91$, 均 $P < 0.01$)。但是,两组之间PT, APTT, TT水平比较差异无统计学意义(均 $P > 0.05$)。

表1 两组血清CG, TBA, ALT, AST水平比较($\bar{x} \pm s$)

项 目	对照组($n=31$)	ICP组($n=31$)	<i>t</i> 值	P值
CG(mg/L)	1.14 ± 0.30	27.14 ± 18.63	7.73	<0.01
TBA($\mu\text{mol/L}$)	2.96 ± 1.61	50.93 ± 29.69	9.04	<0.01
ALT(U/L)	13.27 ± 5.07	109.01 ± 84.47	6.29	<0.01
AST(U/L)	18.24 ± 4.69	96.15 ± 80.51	5.39	<0.01

表2 两组血浆凝血功能比较($\bar{x} \pm s$)

项 目	对照组($n=31$)	ICP组($n=31$)	<i>t</i> 值	P值
PT(s)	11.06 ± 0.73	11.19 ± 1.19	0.49	>0.05
FIB(g/L)	3.41 ± 0.32	4.61 ± 1.12	6.10	<0.01
APTT(s)	26.82 ± 2.63	27.59 ± 3.66	0.93	>0.05
TT(s)	17.49 ± 1.19	18.05 ± 2.53	1.20	>0.05
D-D(mg/L)	1.45 ± 0.87	2.41 ± 1.69	2.91	<0.01

3 讨论 妊娠期肝内胆汁淤积症(ICP)是一种病因不明的常见妊娠并发症,其发生可能与遗传、环境、激素或免疫等因素有关^[5],但其确切机制至今

仍未阐明。目前,临床上尚无确切的药物治疗ICP患者,对于受其影响严重的孕妇来说,加强实验室早期监测并及时采取适当的治疗方法或终止妊娠

至关重要。

CG是一种通过肝细胞进行有效合成的结合型胆酸,主要以蛋白结合形式存在于血清中,在正常成人外周血中含量甚微,始终维持在低浓度水平。ICP时由于肝脏血流量减少,肝细胞受损,蛋白合成减弱,进而可导致血清CG浓度增高。TBA是肝细胞损伤最为敏感的一项血清学指标,能够反映肝脏的合成与代谢,在各类肝脏疾病诊断中均具有较高的价值^[6]。ICP的显著特点就是易在孕妇及胎儿体内蓄积高浓度TBA,但因其对组织、胎盘、细胞均具有毒性,从而可致围产儿预后不良或宫内缺氧^[7]。本次研究结果显示:ICP组与对照组之间,血清CG、TBA及其他肝功能水平具有显著性差异,与正常对照组相比,ICP患者血清CG、TBA表达水平明显增高,孕妇肝功能受损比较严重,因此血清CG、TBA可以作为ICP患者病情诊断及评估的重要指标。

肝脏是大多数凝血因子合成的重要场所,ICP患者因其肝功能可能受损,进而存在凝血因子的合成异常。有研究显示,ICP患者由于凝血功能异常出现微循环障碍,可能引发胎儿在子宫内缺氧或酸中毒,严重危害胎儿的健康^[8-9]。PT、APTT、TT、FIB和D-D是目前临床上常用的监测出血性疾病的重要参数,对了解孕妇及ICP患者体内凝血功能具有一定的临床意义。PT主要反映外源性凝血系统状况,延长见于凝血因子、纤维蛋白原、维生素K缺乏及严重肝病等,其明显缩短则主要见于血液呈高凝状态;APTT主要反映内源性凝血系统状况,血浆因子Ⅷ、Ⅸ和Ⅺ水平减低可导致其增高,而相关凝血因子增加可致使其缩短^[10]。TT反映纤维蛋白原转变为纤维蛋白的时间,当纤维蛋白原活性下降时,其往往会延长^[11]。FIB主要反映纤维蛋白原的含量,同时也是预测产后出血最有意义的因素^[12]。D-D则可以诊断和预测静脉血栓栓塞事件的发生,从而对妊娠期相关并发症的监测及抗血栓治疗具有重要意义^[13]。本文通过两组血浆凝血功能比较发现,PT、APTT和TT水平差异无统计学意义,但ICP组FIB、D-D水平比对照组明显增高,提示ICP患者凝血功能可能发生异常,动态监测其凝血功能具有重要临床意义。

综上所述,妊娠期胆汁淤积症患者CG、TBA水平变化显著,存在凝血功能的改变,常规检测CG、TBA水平及凝血功能对ICP的诊断具有重要临床意义。

参考文献:

- [1] TRAN T T, AHN J, REAU N S. ACG clinical guideline: liver disease and pregnancy[J]. *Am J Gastroenterol*, 2016, 111(2): 176-194.
- [2] GEENES V, CHAPPELL L C, SEED P T, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study[J]. *Hepatology*, 2014, 59(4): 1482-1491.
- [3] 何涓, 冯国芳. 妊娠期肝内胆汁淤积症血液流变学和凝血时间变化及意义[J]. *中国妇幼保健*, 2005, 20(8): 991-993.
HE Yin, FENG Guofang. Hemorheology and coagulation time variety of intrahepatic cholestasis of pregnancy and its significance [J]. *Maternal and Child Health Care of China*, 2005, 20(8): 991-993.
- [4] 谢芸芸, 卢立全, 王鹏. 血清肝胆酸及总胆汁酸联合检测在妊娠期肝内胆汁淤积症中的临床意义[J]. *国际检验医学杂志*, 2016, 37(19): 2734-2735.
XIE Yunyun, LU Liquan, WANG Peng. Clinical significance of joint detection with cholyglycine and total bile acid intrahepatic cholestasis during pregnancy [J]. *International Journal of Laboratory Medicine*, 2016, 37(19): 2734-2735.
- [5] OZKAN S, CEYLAN Y, OZKAN O V, et al. Review of a challenging clinical issue: intrahepatic cholestasis of pregnancy [J]. *World J Gastroenterol*, 2015, 21(23): 7134-7141.
- [6] 白利芬, 李慧, 王兴宁. 联合检测 PA、TBA 与肝穿刺活检在慢性肝炎中的临床价值[J]. *现代检验医学杂志*, 2015, 30(4): 50-52.
BAI Lifeng, LI Hui, WANG Xingning. Clinical value of combined detection of prealbumin total bile acid and liver biopsy in chronic hepatitis [J]. *Journal of Modern Laboratory Medicine*, 2015, 30(4): 50-52.
- [7] 朱文芳, 韩双, 邹爱民, 等. 血清 TBA 和 CG 检测在妊娠期肝内胆汁淤积症早期诊断及围产儿不良结局影响的临床意义[J]. *现代检验医学杂志*, 2017, 32(6): 112-114.
ZHU Wenfang, HAN Shuang, ZOU Aimin, et al. Clinical significance of detecting serum TBA and CG in early diagnosis of intrahepatic cholestasis of pregnancy and perinatal adverse outcomes influence [J]. *Journal of Modern Laboratory Medicine*, 2017, 32(6): 112-114.
- [8] 李蕾, 赵新颜, 欧晓娟, 等. 妊娠期肝内胆汁淤积症的临床分析[J]. *中华肝脏病杂志*, 2013, 21(4): 295-298.
LI Lei, ZHAO Xinyan, OU Xiaojuan, et al. Clinical analysis of intrahepatic cholestasis of pregnancy [J]. *Chinese Journal of Hepatology*, 2013, 21(4): 295-298.
- [9] 姜金华, 杨朋. 130 例妊娠期肝内胆汁淤积症的临床分析[J]. *中国妇幼保健*, 2012, 27(33): 5419-5420.
JIANG Jinhua, YANG Peng. Clinical analysis of 130 cases with intrahepatic cholestasis of pregnancy [J].

- Maternal and Child Health Care of China, 2012, 27 (33):5419-5420.
- [10] BABIKER H I, AWOODA H A, ABDALLA S E. Prothrombin time, activated partial thromboplastin time and platelets count in pregnant females and postpartum period with deep venous thrombosis[J]. Int J Hematol Disord, 2014, 1(1):41-44.
- [11] SARNAIK A, KAMAT D, KANNIKESWARAN N. Diagnosis and management of bleeding disorder in a child[J]. Clin Pediatr (Phila), 2010, 49(5):422-431.
- [12] NAKASHIMA A, OGITA K, CHITA M, et al. Serum fibrinogen levels could be an index of successful use of balloon tamponade in postpartum hemorrhage [J]. J Perinat Med, 2018, 46(1):53-57.
- [13] CHAN W S, LEE A, SPENCER F A, et al. D-dimer testing in pregnant patients: towards determining the next level' in the diagnosis of DVT [J]. J Thromb Haemost, 2010, 8(5):1004-1011.
- 收稿日期:2019-04-03 修回日期:2019-04-13
-
- (上接78页)时间,并在日常诊疗过程中,加强对环境的消毒处理,保持病房的干净整洁,以防交叉污染;在耐碳青霉烯类肺炎克雷伯菌(CRE)的问题上,临床医师不容忽视,应多加关注并正确合理的用药。
- 参考文献:
- [1] 许红利. 神经外科患者临床感染细菌分布和耐药性监测[J]. 临床合理用药杂志, 2016, 9(3B):102-103.
- XU Hongli. Monitoring of bacterial infection distribution and drug resistance in patients with neurosurgery [J]. Chinese Journal of Clinical Rational Drug USA, 2016, 9(3B):102-103.
- [2] 张梅, 刘娜, 牟娜, 等. 神经外科住院患者院内感染病原菌分布特点及耐药性分析[J]. 现代预防医学, 2015, 42(14):2651-2653.
- ZHANG Mei, LIU Na, MU Na, et al. Analysis of the distribution characteristics and drug resistance of pathogenic bacteria for nosocomial infections in neurosurgical patients[J]. Modern Preventive Medicine, 2015, 42(14):2651-2653.
- [3] SUN Wenjia, CHEN Hongbin, LIU Yudong, et al. Prevalence and characterization of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates from 14 cities in China[J]. Antimicrob Agents Chemother, 2009, 53(9):3624-3649.
- [4] 马万红, 韩世波. 重型颅脑损伤并发肺部感染病原菌分布及预防措施[J]. 现代医药卫生, 2014, 30(7):1031-1032.
- MA Wanhong, HAN Shibo. Distribution and preventive measures of pathogenic bacteria in patients with severe craniocerebral injury complicated with pulmonary infection [J]. Journal Modern Medicine and Health, 2014, 30(7):1031-1032.
- [5] 雷三喜. 神经外科医院感染的高危因素及控制对策[J]. 中国社区医师, 2016, 32(4):53, 55.
- LEI Sanxi. Analysis of high risk factors and control measures of nosocomial infection in department of neurosurgery[J]. Chinese Community Doctors, 2016, 32(4):53, 55.
- [6] DURANTE-MANGONI E, ZARRILLI R. Global spread of drug-resistant *Acinetobacter baumannii*: molecular epidemiology and management of antimicrobial resistance[J]. Future Microbiol, 2011, 6(4):407-422.
- [7] 卢丽明, 邱芳华. 2012~2014年血流感染的病原菌分布及耐药性分析[J]. 国际检验医学杂志, 2016, 37(24):3385-3387, 3390.
- LU Liming, QIU Fanghua. Distribution and drug resistance analysis of pathogens from bloodstream infections during 2012~2014[J]. International Journal of Laboratory Medicine, 2016, 37(24):3385-3387, 3390.
- [8] 周静, 陶丽. 西安市第四医院2012~2014年多重耐药菌的临床分布分析[J]. 现代检验医学杂志, 2016, 31(2):127-129.
- ZHOU Jing, TAO Li. Analysis of clinical distribution of multi drug resistant from 2012 to 2014[J]. Journal of Modern Laboratory Medicine, 2016, 31(2):127-129.
- [9] 胡付品, 郭燕, 朱德妹, 等. 2017年CHINET中国细菌耐药性监测[J]. 中国感染与化疗杂志, 2018, 18(3):241-251.
- HU Fupin, GUO Yan, ZHU Demei, et al. Antimicrobial resistance profile of clinical isolates in hospital across China: report from the CHINET surveillance program, 2017[J]. Chinese Journal of Infection and Chemotherapy, 2018, 18(3):241-251.
- [10] 樊华, 刘丽, 左晶晶, 等. 呼吸病房产超广谱 β -内酰胺酶肺炎克雷伯菌的耐药性及脉冲场电泳分析[J]. 实用医学杂志, 2017, 33(20):3462-3466.
- FAN Hua, LIU Li, ZUO Jingjing, et al. Antibiotic resistance and PFGE of genotyping of *Klebsiella pneumoniae* from neonatal ward infections[J]. Journal of Practical Medicine, 2017, 33(20):3462-3466.
- 收稿日期:2019-03-28 修回日期:2019-04-15