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未足月胎膜早破合并绒毛膜羊膜炎孕妇血清淀粉样蛋白 A、血小板激活因子水平的表达及临床意义 *

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摘要 目的：检测未足月胎膜早破合并绒毛膜羊膜炎（HCA）孕妇血清淀粉样蛋白 A（SAA）、血小板激活因子（PAF）水平，并探讨其临床意义。**方法：**选择从 2013 年 7 月到 2017 年 7 月，在我院接受治疗的 165 例胎膜早破孕产妇作为研究对象。165 例患者中，未足月胎膜早破者 80 例（未足月胎膜早破组），足月胎膜早破者 85 例（足月胎膜早破组），再根据是否合并 HCA 分为合并 HCA 胎膜早破组 43 例和未合并 HCA 胎膜早破组 122 例。另选取同期在我院体检的 80 例健康孕产妇志愿者作为正常组，对比各组血清 SAA 和 PAF 水平，分析合并与未合并 HCA 胎膜早破组的妊娠结局，利用受试者工作特征（ROC）曲线分析血清 SAA 和 PAF 对未足月胎膜早破是否合并 HCA 的诊断价值。**结果：**未足月胎膜早破组及足月胎膜早破组的血清 SAA 和 PAF 水平均明显高于正常组，且未足月胎膜早破组又高于足月胎膜早破组，差异有统计学意义（*P<0.05*）。未足月胎膜早破组 80 例患者中 HCA 发生率为 35.00%（28/80），明显高于足月胎膜早破组的 17.65%（15/85），差异有统计学意义（*P<0.05*）。合并 HCA 胎膜早破组的血清 SAA 和 PAF 水平均明显高于未合并 HCA 胎膜早破组，差异有统计学意义（*P<0.05*）。合并 HCA 的未足月胎膜早破患者血清 SAA 和 PAF 水平高于未合并 HCA 的未足月胎膜早破患者（*P<0.05*）。合并 HCA 的胎膜早破组的产后大出血、剖宫产以及新生儿肺炎的发生率均明显高于未合并 HCA 胎膜早破组，差异有统计学意义（*P<0.05*）。根据 ROC 曲线分析可知，血清 SAA 和 PAF 对未足月胎膜早破是否合并 HCA 的诊断价值较高。**结论：**血清 SAA、PAF 水平在未足月胎膜早破合并 HCA 孕妇中明显升高，二者对此种合并症具有较高的诊断价值。临床诊疗过程中可将 SAA 及 PAF 纳入到指标监测体系中，从而为临床治疗提供指导。

关键词：未足月胎膜早破；绒毛膜羊膜炎；血小板激活因子；淀粉样蛋白 A；妊娠结局；诊断价值

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Expression and Clinical Significance of Serum amyloid Protein A and Platelet Activating Factor in Pregnant Women with Preterm Premature Rupture of Fetal Membranes Complicated with Chorioamnionitis*

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ABSTRACT Objective: To detect the expression of serum amyloid protein A (SAA) and platelet activating factor (PAF) in pregnant women with premature rupture of fetal membranes complicated with chorioamnionitis (HCA), and to explore its clinical significance. **Methods:** 165 pregnant women with premature rupture of fetal membranes who were treated in our hospital from July 2013 to July 2017 were selected as research subjects. Among 165 patients, there were premature rupture of fetal membranes (premature rupture of fetal membranes group) with 80 case, and there were full-term premature rupture of fetal membranes (full-term premature rupture of fetal membranes group) with 85 cases. According to whether the combined HCA, the patients were divided into combined HCA premature rupture of fetal membranes group with 43 cases and uncombined HCA premature rupture of fetal membranes group with 122 cases. Another 80 healthy pregnant women volunteers who were received physical examination in our hospital during the same period were selected as the normal group. The serum levels of SAA and PAF were compared in each group, the pregnancy outcomes of the combined HCA and uncombined HCA premature rupture of fetal membranes group were analyzed. The diagnostic value of serum SAA and PAF in combined with HCA in patients with preterm premature rupture of fetal membranes were analyzed by receiver operating characteristic (ROC) curve. **Results:** The levels of serum SAA and PAF in premature rupture of fetal membranes group and full-term premature rupture of fetal membranes group were significantly higher than those in the normal group, and the premature rupture of fetal membranes group was higher than that in the full-term premature rupture of fetal membranes group, the differences are statistically significant(*P<0.05*). The incidence of HCA of 80 patients in premature rupture of fetal membranes group was 35.00%(28/80), which was significantly higher than 17.65%(15/85) in the full-term premature rupture of fetal membranes group, the differences are statistically significant (*P<0.05*). The

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levels of serum SAA and PAF in combined HCA premature rupture of fetal membranes group were significantly higher than those in uncombined HCA premature rupture of fetal membranes group, the differences are statistically significant (*P<0.05*). The serum levels of SAA and PAF in patients with premature rupture of membranes without HCA were higher than those in patients without HCA (*P<0.05*). The incidence of postpartum hemorrhage, cesarean section and neonatal pneumonia in combined HCA premature rupture group was significantly higher than that uncombined HCA premature rupture of fetal membranes group, the differences are statistically significant (*P<0.05*). According to the ROC curve analysis, the serum SAA and PAF had a higher diagnostic value of in the diagnosis of combined with HCA in patients with preterm premature rupture of fetal membranes. **Conclusion:** The levels of serum SAA and PAF are increased significantly in preterm premature rupture of fetal membranes complicated with HCA, and the two have high diagnostic value for this complication. In the process of clinical diagnosis and treatment, SAA and PAF can be included in the index monitoring system, so as to provide guidance for clinical treatment.

Key words: Premature rupture of fetal membranes; Chorioamnionitis; Platelet activating factor; Amyloid protein A; Pregnancy outcome; Diagnostic value

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前言

胎膜作为预防孕产妇机体发生上行性感染的一种天然屏障,若其发生破裂,则将致使母体及胎儿发生感染或其他并发症,此时母体可出现产褥期感染或败血症,而胎儿在宫内感染易导致宫内窘迫或早产等,严重时还会导致死胎,对母体及胎儿均具有较为严重的危害[1,2]。对于未足月胎膜早破而言,如处理不当,则可能出现羊膜腔感染,发生绒毛膜羊膜炎(chorioamnionitis,HCA),最终对产妇及胎儿均可造成不良影响[3,4]。有报道指出,未足月胎膜早破合并 HCA 的患者起病隐匿,在早期的临床症状并不显著,而当检测出明显异常时,则可能已对孕产妇及新生儿产生了严重影响[5,6]。因此,寻找快速优质的诊断手段具有重要的意义。血小板激活因子(platelet activating factor,PAF)属于磷脂介质,其可对机体的多个细胞和器官产生作用,与机体的感染或炎症等因素密切相关[7,8]。血清淀粉样蛋白 A(Serum Amyloid protein A,SAA)是机体中可与高密度脂蛋白进行结合的一类急性时相性蛋白,其在受到感染刺激后,能在 5-6h 即可合成并大量分泌,但其半衰期仅为 50 min,若机体内的抗原被清除之后,SAA 则将逐渐降低到正常的水平[9]。本研究通过探讨未足月胎膜早破合并 HCA 孕妇血清 SAA、PAF 水平的表达及临床意义,旨在为临床诊治提供数据参考,现报道如下。

1 资料和方法

1.1 临床资料

选择从 2013 年 7 月到 2017 年 7 月,在我院接受治疗的 165 例胎膜早破孕产妇作为研究对象。纳入标准:(1)所有患者均符合第八版《妇产科学》中关于胎膜早破的诊断标准[10];(2)单胎妊娠;(3)患者或其家属对于此次研究均已经知情,并已签署了同意书。排除标准:(1)有其他类别的妊娠期并发症者和合并症者;(2)胎位不正者;(3)入组前已使用过药物者;(4)资料缺失者。165 例患者中,合并 HCA 的胎膜早破者 43 例(合并 HCA 胎膜早破组),未合并 HCA 的胎膜早破者 122 例(未合并 HCA 胎膜早破组);未足月胎膜早破者 80 例(未足月胎膜早破组),足月胎膜早破 85 例(足月胎膜早破组)。另选同期在我院体检的 80 例健康孕产妇志愿者作为对照组,各组的一般资料信息整体比较后显示的差异无统计学意义(*P>0.05*),但未足月胎膜早破组的孕周和正常组相比有显著性意义,是客观情况的真实体现,详见表 1。此外,此次研究已经得到了我院伦理委员会的评审通过。

表 1 各组一般资料的对比

Table 1 Comparison of general information in each group

Groups	n	Age(year)	Gestational times(times)	Gestational week(week)
Normal group	80	28.14± 1.60	1.72± 1.14	38.95± 1.57
Premature rupture of fetal membranes group	80	27.94± 1.33	2.01± 0.34	32.39± 1.28a
Full-term premature rupture of fetal membranes group	85	28.03± 1.54	1.70± 1.20	38.92± 1.30
Combined HCA premature rupture of fetal membranes group	43	27.98± 1.41	1.83± 0.47	38.84± 1.42
Uncombined HCA premature rupture of fetal membranes group	122	28.01± 1.39	1.81± 0.32	38.91± 1.54
F		0.238	1.912	2.987
P		0.917	0.108	0.058

Note: the overall analysis is one-way ANOVA. The multiple comparison was LSD-t test, and the significant marker a was *P* compared with the normal group (*P < 0.05*).

1.2 研究方法

各组受试者于分娩前一天清晨抽取静脉血 5 mL,给予 15 min 3000 r/min 的离心之后,提取出血清,通过双抗体夹心酶联免疫吸附法测定各组血清 SAA 和 PAF 水平,有关试剂盒均购自美国的 B&D 公司,操作时严格根据说明书进行。待产妇分娩后统计其与新生儿的妊娠结局。组织学 HCA 的检测为每个高倍镜视野当中出现 5-10 个中性粒细胞。HCA 诊断标准为[11]:(1)产时母亲发热,且体温≥ 37.8℃;(2)伴有以下任一项即可明确诊断:① 产妇心动过速(100～120 次 /min);② 胎儿心动过速(≥ 160 次 /min);③ 产妇子宫紧张且有压痛;④ 羊水有异味;⑤ 产妇的白细胞计数>(15～18)× 10^9/L。

1.3 统计学方法

通过 SPSS21.0 统计软件分析数据。计数数据以率(%)表示,比较采用 x^2 检验。计量资料以($\bar{x}\pm s$)表示,比较采用单因素方差分析(多组比较)或两独立样本 t 检验(两组比较)。此外,通过 ROC 曲线分析血清 SAA 和 PAF 对未足月胎膜是否早破合并 HCA 的诊断价值,*P<0.05* 为差异有统计学意义。

2 结果

2.1 各组血清 SAA 和 PAF 水平的对比

各组的血清 SAA 和 PAF 水平相比,差异有统计学意义(*P<0.05*)。未足月胎膜早破组及足月胎膜早破组的血清 SAA 和 PAF 水平均明显高于正常组,且未足月胎膜早破组又高于足月胎膜早破组,差异有统计学意义(*P<0.05*),详见表 2。

表 2 各组血清 SAA 和 PAF 水平的对比($\bar{x}\pm s$)

Table 2 Comparison of serum SAA and PAF levels in each group($\bar{x}\pm s$)

Group	n	SAA(mg/L)	PAF(pg/mL)
Normal group	80	6.39± 2.07	15.31± 2.14
Premature rupture of fetal membranes group	80	23.45± 6.85[a]	23.66± 3.91[a]
Full-term premature rupture of fetal membranes group	85	11.19± 7.26[ab]	18.78± 3.19[ab]
F		177.157	140.602
P		0.000	0.000

Note: the overall analysis is one-way ANOVA. Multiple comparisons were LSD-t test. Significant markers a and b were compared with normal group and non-full-term group respectively (*P < 0.05*).

2.2 未足月胎膜早破组及足月胎膜早破组的 HCA 发生率对比

未足月胎膜早破组 80 例患者中 HCA 发生率为 35.00%(28/80),明显高于足月胎膜早破组的 17.65%(15/85),差异有统计学意义(x^2= 6.440,*P*=0.011)。

2.3 合并与未合并 HCA 的胎膜早破组的血清 SAA 和 PAF 水平对比

合并 HCA 胎膜早破组的血清 SAA 和PAF 水平均明显高于未合并 HCA 胎膜早破组,差异有统计学意义(*P<0.05*),见表 3。

表 3 合并与未合并 HCA 的胎膜早破组的血清 SAA 和 PAF 水平对比($\bar{x}\pm s$)

Table 3 Comparison of serum SAA and PAF levels in premature rupture of membranes with and without HCA($\bar{x}\pm s$)

Groups	n	SAA(mg/L)	PAF(pg/mL)
Combined HCA premature rupture of fetal membranes group	43	25.83± 5.21	24.37± 2.89
Uncombined HCA premature rupture of fetal membranes group	122	13.94± 3.88	19.72± 2.63
t		13.687	9.713
P		0.000	0.000

2.4 合并与未合并 HCA 的胎膜早破者的妊娠结局对比

合并 HCA 胎膜早破组的产后大出血、剖宫产以及新生儿肺炎的发生率均明显高于未合并 HCA 胎膜早破组,差异有统计学意义(*P<0.05*),见表 4。

表 4 合并与未合并 HCA 的胎膜早破者的妊娠结局对比【例(%)】

Table 4 Comparison of pregnancy outcome of premature rupture of membranes with and without HCA[n(%)]

Groups	n	Postpartum hemorrhage	Cesarean section	Neonatal pneumonia
Combined HCA premature rupture of fetal membranes group	43	8(18.60)	23(53.49)	7(16.28)
Uncombined HCA premature rupture of fetal membranes group	122	3(2.46)	36(29.51)	2(1.64)
x^2		10.852	7.959	10.527
P		0.001	0.005	0.001

表 5 合并与未合并 HCA 的未足月胎膜早破患者的血清 SAA 和 PAF 水平($\bar{x}\pm s$)

Table 5 serum SAA and PAF levels in patients with preterm premature rupture of membranes combined with or without HCA($\bar{x}\pm s$)

Groups	n	SAA(mg/L)	PAF(pg/mL)
Merge HCA	28	26.41± 4.78	25.12± 2.52
Unmerged HCA	52	14.65± 4.35	16.34± 3.18

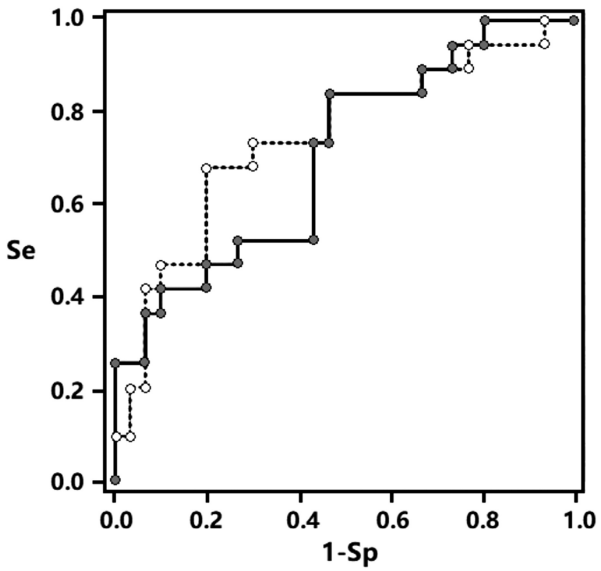

图 1 血清 SAA 和 PAF 对未足月胎膜早破是否合并 HCA 的 ROC 曲线

Fig. 1 ROC curve of serum SAA and PAF in preterm premature rupture of membranes with HCA

Note: The solid line is the ROC curve of SAA for the diagnosis of premature rupture of membranes with HCA, and the dotted line is the ROC curve of PAF for the diagnosis of premature rupture of membranes with HCA.

2.5 血清 SAA 和 PAF 对未足月胎膜早破合并 HCA 的 ROC 曲线分析

合并 HCA 的未足月胎膜早破患者血清 SAA 和 PAF 水平高于未合并 HCA 的未足月胎膜早破患者($P<0.05$),见表 5。由于未足月胎膜早破对孕胎影响更大，临床上比较重视其合并 HCA 的诊断预测及干预。故以未足月胎膜早破合并 HCA 患者资料(赋值 1)及未足月胎膜早破未合并 HCA 患者资料(赋值 0)为样本,将血清 SAA 和 PAF 水平数据划分适当组段,建立 ROC 分析模型。分析结果知:SAA 对未足月胎膜早破是否合并 HCA 的诊断临界值为 17.56 mg/L,灵敏度为 63.57%,特异度为 75.03%,曲线下面积为 0.704。血清 PAF 对未足月胎膜早破是否合并 HCA 的诊断临界值为 22.72 pg/mL,灵敏度为 67.83%,特异度为 80.12%,曲线下面积为 0.739。ROC 分析曲线见图 1。

3 讨论

临床上，未足月胎膜早破通常是指产妇在妊娠不满 37 周时其胎膜在产前发生破裂的一种症状 [12]。对于此种症状的治疗,如患者孕周低于 34 周,则可选择期待治疗以相应地延长其孕周,并提升早产儿的存活率[13,14]。然而,在治疗过程当中,患者可能会由于胎膜早破时间的延长而引发感染[15]。其中最为常见的一类并发症即为 HCA，据数据统计,HCA 在早产儿群体中的发病率甚至高达 50%,且危害极大[16,17]。有报道显示[18,19],未足月胎膜早破合并 HCA 通常会导致母儿感染，增大了母婴在围生期的风险。因此,对此种合并症实施科学而详细的研究显得十分重要。

本研究结果发现,未足月胎膜早破组及足月胎膜早破组的血清 SAA 和 PAF 水平均明显高于正常组,且未足月胎膜早破组又高于足月胎膜早破组($P<0.05$),这提示了未足月胎膜早破组血清 SAA 和 PAF 水平异常升高。分析原因，主要可能是因为 SAA 和 PAF 均参与到了胎膜早破等症状的发病机制中[20,21]。具体而言,PAF 属于内源性的可发挥广泛型生物学活性的一种磷脂介质,发生胎膜早破后机体在有关干扰素及感染等因素的刺激作用下,使得 PAF 水平明显上升[22,23]。而 SAA 是急性时相反应性蛋白,其在机体正常条件下的含量较少,当发生胎膜早破后,由于受到感染性病原体的刺激,患者的肝脏细胞可分泌出大量 SAA 并进入血液,使 SAA 水平在短期内迅速升高[24-26]。同时,本研究发现,未足月胎膜早破组 80 例患者中 HCA 发生率、血清 SAA 和 PAF 水平明显高于足月胎膜早破组($P<0.05$),合并 HCA 的未足月胎膜早破患者血清 SAA 和 PAF 水平高于未合并 HCA 的未足月胎膜早破患者($P<0.05$)。原因主要可能是因为合并有 HCA 的未足月胎膜早破患者通常感染症状相对更加严重,致使其血清 SAA 和 PAF 水平升高地更快[27]。梁辉标[28]等人报道指出,胎膜早破合并 HCA 较易导致机体产生轻微炎症反应，并使患者表现出亚临床感染的状态，从而使 SAA 水平逐渐上升。此外,本研究根据 ROC 曲线分析可知,血清 PAF 对未足月胎膜早破是否合并 HCA 的诊断临界值为 22.72 pg/mL,灵敏度为 67.83%,特异度为 80.12%,曲线下面积为 0.739。而 SAA 对未足月胎膜早破是否合并 HCA 的诊断临界值为 17.56 mg/L,灵敏度为 63.57%,特异度为 75.03%,曲线下面积为 0.704。这也再次证实了 SAA 及 PAF 对于未足月胎膜早破是否合并 HCA 的诊断价值较高。临床上可通过将 SAA 及 PAF 进行综合监测，从而有助于早期快速地作出更加科学地诊断[29,30]。需要强调的是,本次研究也存在着一定的局限性,比如研究样本量仍然较少,且无其他医疗机构的支撑或共同参与研究,今后可从上述局限性方面着手,适当扩大样本量,并进行协同性的研究,从而能够得到更加精准的研究结论。此外,下一步将分析和讨论 SAA 及 PAF 与血象、C 反应蛋白以及降钙素原等指标的相关性,同时,由于这两种因子对于哺乳动物的炎症反应的影响具有一定意义，今后将设计动物实验进行深入探索。

综上所述,未足月胎膜早破合并 HCA 孕妇的血清 SAA 和 PAF 水平均明显升高,对这两个指标进行监测有助于评估患者的实际病情。

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