血清CA125,STIP1和IGF-Ⅰ联合检测对卵巢癌的早期诊断价值研究*

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摘 要:目的 探讨血清糖类抗原125(carbohydrate antigen 125,CA125),磷酸化应激诱导蛋白1(stress-induced phosphoprotein 1,STIP1)和胰岛素样生长因子-Ⅰ(insulinlike growth factor-Ⅰ,IGF-Ⅰ)联合检测对卵巢癌的早期诊断价值。**方法** 枣庄矿业集团中心医院于2015年11月~2017年11月期间收治的经手术病理证实的90例卵巢癌患者作为卵巢癌组,同期该院收治的40例良性卵巢肿瘤患者作为卵巢良性肿瘤组,同期来该院体检的40例健康妇女作为健康组,检测血清CA125,STIP1和IGF-Ⅰ水平,对比三者单独及联合诊断卵巢癌的效果。**结果** 卵巢癌组、卵巢良性肿瘤组、健康组血清CA125水平分别为680.2±96.5,20.4±2.9和11.4±1.9 U/ml,血清STIP1水平为5.06±1.07,2.02±1.05和1.03±0.92 ng/ml,血清IGF-Ⅰ为120.4±32.4,215.4±34.3和190.3±45.6 ng/ml,经多个均数之间两两比较的q检验比较,卵巢癌组血清CA125,STIP1和IGF-Ⅰ水平与卵巢良性肿瘤组、健康组间差异具有统计学意义(q=14.319~70.632,均P<0.001);血清CA125,STIP1和IGF-Ⅰ单独检测诊断卵巢癌的ROC曲线下面积分别为0.715,0.748和0.781,最佳诊断临界值为35 U/ml,3.2 ng/ml和174.5 ng/ml,三者单独检测诊断卵巢癌的敏感度为78.9%,86.7%和75.6%,特异度为72.5%,57.5%和63,8%,准确度为75.9%,72.9%和70.0%,卡方检验显示差异无统计学意义(χ^2=2.345~3.971,均P>0.05);CA125+STIP1,CA125+STIP1+IGF-I平行联合诊断卵巢癌的ROC曲线下面积为0.812和0.854,诊断敏感度为90.0%和96.7%,特异度为60.0%和67.5%,准确度为75.9%和82.9%,卡方检验显示差异无统计学意义(χ^2=0.974,3.073,P>0.05);CA125+STIP1,CA125+STIP1+IGF-I系列联合检测诊断卵巢癌的ROC曲线下面积为0.834和0.921,诊断特异度为81.3%和92.5%,准确度为75.9%和87.1%,组间比较差异具有统计学意义(χ^2=4.440,7.033,P<0.05);CA125+STIP1+IGF-I系列联合检测诊断的特异度和准确度显著高于单独检测CA125,STIP1和IGF-Ⅰ(χ^2=2.475~12.135,P<0.05)。**结论** 血清CA125,STIP1和IGF-Ⅰ单独诊断卵巢癌敏感度和特异度较低,三者平行联合检测可提高诊断准确度,系列联合检测可提高特异度和准确度,有助于卵巢癌早期筛查和诊断。

关键词: 卵巢癌;早期诊断;糖类抗原125;磷酸化应激诱导蛋白1;胰岛素样生长因子-Ⅰ
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Clinical Value of Combined Detection of Serum CA125,STIP1 and IGF-I Levels in Early Diagnosis of Ovarian Cancer

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Abstract:Objective To explore the diagnostic value of combined detection of serum carbohydrate antigen 125 (CA125), stress-induced phosphoprotein 1 (STIP1) and insulinlike growth factor-Ⅰ (IGF-I) in early diagnosis of ovarian cancer. **Methods** 90 patients with ovarian cancer confirmed by pathology admitted from November 2015 to November 2017 were treated as ovarian cancerobservation group,40 patients with benign ovarian tumors admitted in the same periods were as ovarian benign tumor group 1,40 healthy women examined in the same periods were as healthy. To measure the serum CA125,STIP1 and IGF-I level,and compared the diagnosis efficacy of all indexes alone and jointly to diagnose ovarian cancer. **Results** The serum CA125 levels in ovarian cancerobservation group,varian benign tumor control,and healthy were 680.2±96.5,20.4±2.9 and 11.4±1.9 U/ml,and the serum STIP1 level was 5.06±1.07,2.02±1.05 and 1.03±0.92 ng/ml,serum IGF-I was 120.4±32.4,215.4±34.3 and 190.3±45.6 ng/ml,respectively. The q test of the comparison of multiple mean comparisons showed that there was a statistically significant difference between observation group and the ovarian benign tumor group and healthy group (q=14.319~70.632,P<0.001). The areas under ROC curve of serum CA125,STIP1 and IGF-I alone in the diagnosis of ovarian cancer were 0.715,0.748 and 0.781 respectively. The best diagnostic thresholds were 35 U/ml,3.2 ng/ml and 174.5 ng/ml. The sensitivity of the cancer was 78.9%,86.7% and 75.6%, the specificity was 72.5%,57.5% and 63.8%,the accuracy was 75.9%,72.9% and 70.0%. The chi-square test showed no

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statistically significant difference ($\chi^2=2.345\sim3.971$, all $P>0.05$). The area under the ROC curve of CA125+STIP1, CA125+STIP1+IGF-I parallel diagnosis of ovarian cancer was 0.812 and 0.854, the diagnostic sensitivity was 90.0% and 96.7%, the specificity was 60.0% and 67.5%, the accuracy was 75.9% and 82.9%, Chi-square test showed no significant difference ($\chi^2=0.974, 3.073$, $P>0.05$). CA125+STIP1, CA125+STIP1+IGF-I series of ovarian cancer under the ROC curve of the area of 0.834 and 0.921, thediagnostic specificity of 81.3% and 92.5%. The accuracy was 75.9% and 87.1%. The difference between the two groups was statistically significant ($\chi^2=4.440, 7.033$, all $P<0.05$). The specificity and accuracy of the combined diagnosis of CA125+STIP1+IGF-I were significantly higher than those of the two groups. Diagnosis of CA125, STIP1 and IGF-I ($\chi^2=2.475\sim12.135$, all $P<0.05$). **Conclusion** Serum CA125, STIP1 and IGF-I alone in diagnosis ovarian cancer had low sensitivity and specificity, the parallel diagnosis could improve diagnostic accuracy, the series diagnosis could improve diagnostic specificity and accuracy. It could help early screening and diagnosis for ovarian cancer.

Keywords: ovarian cancer; early diagnosis; carbohydrate antigen 125; stress-induced phosphoprotein 1; insulinlike growth factor-Ⅰ

卵巢癌是死亡率最高的妇科恶性肿瘤，其早期和晚期患者治疗5年生存率相差约60%[1]，因此，卵巢癌的早发现、早治疗尤为重要。由于卵巢癌临床症状隐匿，70%的患者确诊时已错过了最佳手术时机[2]，因此，卵巢癌的早期筛查已成为临床研究的重点。近年来，大量关于卵巢癌诊断的血清标志物得以发现并用于该病诊断，但单独诊断效果有限[3]。肿瘤标志物的联合检测已成为卵巢癌早期诊断研究的新方向[7~9]。糖类抗原CA125[4]（carbohydrate antigen 125，CA125）是卵巢癌的特异性标志物，但诊断灵敏度低；磷酸化应激诱导蛋白1[5]（stress-induced phosphoprotein 1，STIP1）是与热休克蛋白70、热休克蛋白90结合发挥转录、翻译、蛋白折叠等生物学效应的热休克蛋白，可促进卵巢癌细胞增殖；胰岛素样生长因子-Ⅰ[6]（insulinlike growth factor-Ⅰ，IGF-Ⅰ）是具有强有丝分裂效应的多肽类生长因子，以内分泌或自分泌的方式促进肿瘤进展。本研究拟联合检测血清CA125，STIP1和IGF-Ⅰ水平，探讨肿瘤标志物联合检测在卵巢癌早期诊断中的价值。

1 材料与方法

1.1 研究对象 本研究获得我院伦理委员会批准。纳入我院2015年11月～2017年11月期间收治的90例卵巢癌患者作为观察组，年龄22～55岁，平均年龄44.3±3.5岁，TNM分期Ⅰ期56例，Ⅱ期34例，组织学分类显示，27例子宫内膜样癌，15例低分化腺癌，22例浆液性囊腺癌，26例黏液性囊腺癌。纳入我院同期收治的40例良性卵巢肿瘤患者作为卵巢良性肿瘤组，年龄22～55岁，平均年龄45.7±3.8岁，组织学分类显示，15例浆液性囊腺瘤，13例成熟畸胎瘤，2例卵巢纤维瘤，10例黏液性囊腺瘤。纳入同期来我院体检的40例健康妇女作为健康组，年龄22～55岁，平均年龄44.1±3.2岁，三组患者年龄差异无统计学意义（$P>0.05$），具有可比性。

卵巢癌纳入标准：①经术后病理证实；②首次发现“卵巢肿物”；③无良恶性肿瘤史；④无肿瘤家族史；⑤未进行手术、放疗或化疗治疗；⑥自愿参与本研究，并签署知情同意书。排除标准：①肝肾功能严重紊乱；②合并心脑血管疾病；③并发精神性疾病；④使用激素类药物6月以上；⑤并发恶性疾病及其并发症者；⑥妊娠期妇女。

1.2 试剂和仪器 试剂：CA125试剂盒（德国罗氏公司），STIP1试剂盒（上海沪震实业有限公司），IGF-Ⅰ试剂盒（DRG公司）。仪器：UniCel Dxl 800型化学发光仪（Beckman Coulter公司）。

1.3 方法 所有患者入院后，取空腹肘静脉血，3 000 r/min离心10 min，取上层血清，采用化学发光法检测CA125水平，ELISA法检测STIP1和IGF-Ⅰ水平。

对比观察组、卵巢良性肿瘤组和健康组血清CA125，STIP1和IGF-Ⅰ水平，采用ROC曲线分析三者单独检测诊断卵巢癌的诊断效果，并获得最佳临界诊断值，并采用CA125+STIP1，CA125+STIP1+IGF-I平行或系列联合诊断卵巢癌，平行联合诊断时，三者中任何一项检测出现阳性，结果则判断为阳性；系列联合诊断时，三者均诊断为阳性时，结果判定为阳性。

1.4 统计学分析 本研究的数据分析采用spss19.0进行，计数资料以率表示，采用χ^2检验比较，计量资料以均数±标准差（$\bar{x}\pm s$）表示，采用ANOVA比较，组间两两比较采用q检验，诊断效果评价采用ROC曲线分析，统计结果以$P<0.05$为差异具有统计学意义。

2 结果

2.1 三组患者血清各指标比较 见表1。经多个均数之间两两比较的q检验比较，卵巢癌组血清CA125，STIP1和IGF-Ⅰ水平与卵巢良性肿瘤组、健康组间比较差异均具有统计学意义（$q=14.319\sim70.632$，均$P<0.05$）。

表 1　三组患者血清 CA125，STIP1，IGF-Ⅰ水平比较（$\bar{x}\pm s$）

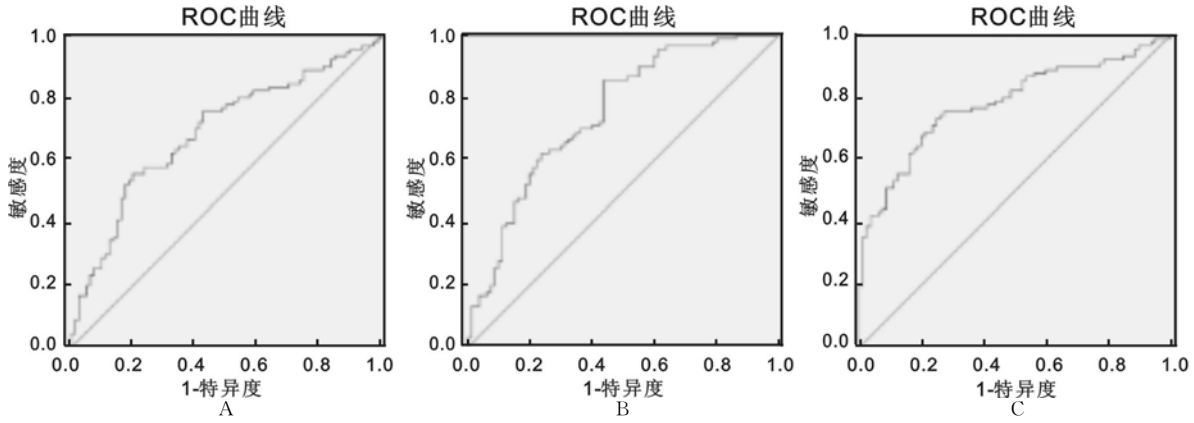
项　目	卵巢癌组（n=90）	卵巢良性肿瘤组（n=40）	健康组（n=40）	F	$q^{①}$	$q^{②}$	$q^{③}$
CA125（U/ml）	680.2±96.5	20.4±2.9	11.4±1.9	1 453.419*	69.682*	70.632*	0.808#
STIP1（ng/ml）	5.06±1.07	2.02±1.05	1.03±0.92	16.945*	21.920*	29.058*	6.066*
IGF-Ⅰ（ng/ml）	120.4±32.4	215.4±34.3	190.3±45.6	353.483*	19.461*	14.319*	4.370*

注：统计学比较，* P<0.05，# P>0.05。$q^{①}$ 卵巢癌组与卵巢良性肿瘤组比较；$q^{②}$ 卵巢癌组与健康组比较；$q^{③}$ 卵巢良性肿瘤组与健康组比较。

2.2　血清 CA125，STIP1 和 IGF-Ⅰ单独诊断卵巢癌的 ROC 曲线分析　见图 1。血清 CA125，STIP1 和 IGF-Ⅰ单独诊断卵巢癌的 ROC 曲线下面积分别为 0.715，0.748 和 0.781，最佳诊断临界值为 35 U/ml，3.2 ng/ml 和 174.5 ng/ml，经卡方检验，单独检测诊断卵巢癌的敏感度、特异度和准确度差异无统计学意义（χ^2=2.345～3.971，均 P>0.05），见表 2。

表 2　血清 CA125，STIP1，IGF-Ⅰ单独诊断卵巢癌特异度和敏感度分析[%（n/n）]

指　标	CA125	STIP1	IGF-Ⅰ	χ^2	P
敏感度	78.9(71/90)	86.7(78/90)	75.6(68/90)	3.709	0.157
特异度	72.5(58/80)	57.5(46/80)	63.8(51/80)	3.971	0.137
准确度	75.9(129/170)	72.9(124/170)	70.0(119/170)	1.49	0.475
阳性预测值	76.3(71/93)	69.6(78/112)	70.1(68/97)	1.345	0.511
阴性预测值	75.3(58/77)	79.3(46/56)	69.9(51/73)	2.566	0.277



A(CA125)，B(STIP1)，C(IGF-Ⅰ)

图 1　血清 CA125，STIP1 和 IGF-Ⅰ单独诊断卵巢癌的 ROC 曲线

2.3　血清 CA125，STIP1 和 IGF-Ⅰ平行联合诊断卵巢癌的 ROC 曲线分析　见表 3 和图 2。CA125＋STIP1，CA125＋STIP1＋IGF-I 平行联合诊断卵巢癌的 ROC 曲线下面积为 0.812，0.854，经卡方检验，诊断的敏感度、特异度和准确度差异无统计学意义（χ^2=0.974，3.073，均 P>0.05），但 CA125＋STIP1＋IGF-I 联合检测与 CA125，STIP1，IGF-Ⅰ单独检测的敏感度差异具有统计学意义（χ^2=2.475～12.135，均 P<0.05）。

表 3　血清 CA125，STIP1，IGF-I 平行联合检测诊断卵巢癌特异度和敏感度分析[%（n/n）]

指　标	CA125+STIP1	CA125+STIP1+IGF-I	χ^2	P
敏感度	90.0(81/90)	96.7(87/90)*	3.214	0.073
特异度	60.0(48/80)	67.5(54/80)	0.974	0.324
准确度	75.9(129/170)	82.9(142/170)	3.073	0.08
阳性预测值	71.7(81/113)	77.0(87/113)	0.835	0.361
阴性预测值	84.2(48/57)	94.7(54/57)	3.353	0.067

注：与血清 CA125，STIP1 和 IGF-I 单独检测诊断相比* P<0.05。

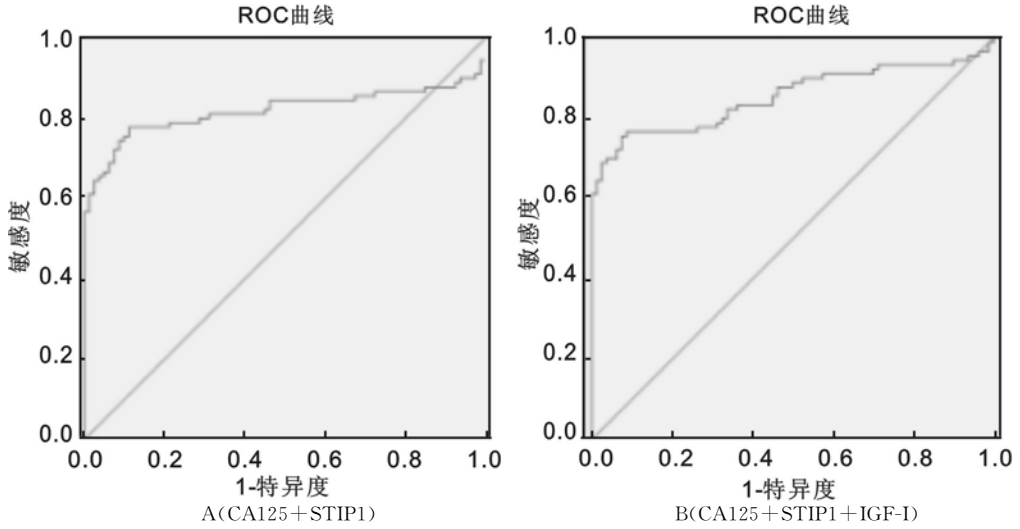


图2 CA125+STIP1+IGF-I平行联合检测诊断卵巢癌的ROC曲线

2.4 血清CA125,STIP1和IGF-Ⅰ系列联合诊断卵巢癌的ROC曲线分析 见表4和图3。CA125+STIP1,CA125+STIP1+IGF-I系列联合诊断卵巢癌的ROC曲线下面积为0.834,0.921,经卡方检验,CA125+STIP1+IGF-I联合检测与CA125,STIP1,IGF-Ⅰ单独检测诊断的特异度和准确度差异具有统计学意义(χ^2=4.440,7.033,均P<0.05)。

表4 血清CA125,STIP1,IGF-I平行联合检测诊断卵巢癌特异度和敏感度分析[%(n/n)]

指 标	CA125+STIP1	CA125+STIP1+IGF-I	χ^2	P
敏感度	71.1(64/90)	82.2(74/90)	3.106	0.078
特异度	81.3(65/80)	92.5(74/80)*	4.440	0.035
准确度	75.9(129/170)	87.1(148/170)*	7.033	0.008
阳性预测值	81.0(64/79)	92.5(74/80)	4.576	0.032
阴性预测值	71.4(65/91)	82.2(74/80)	12.427	0

注:与血清CA125,STIP1,IGF-I单独检测相比,* P<0.05。

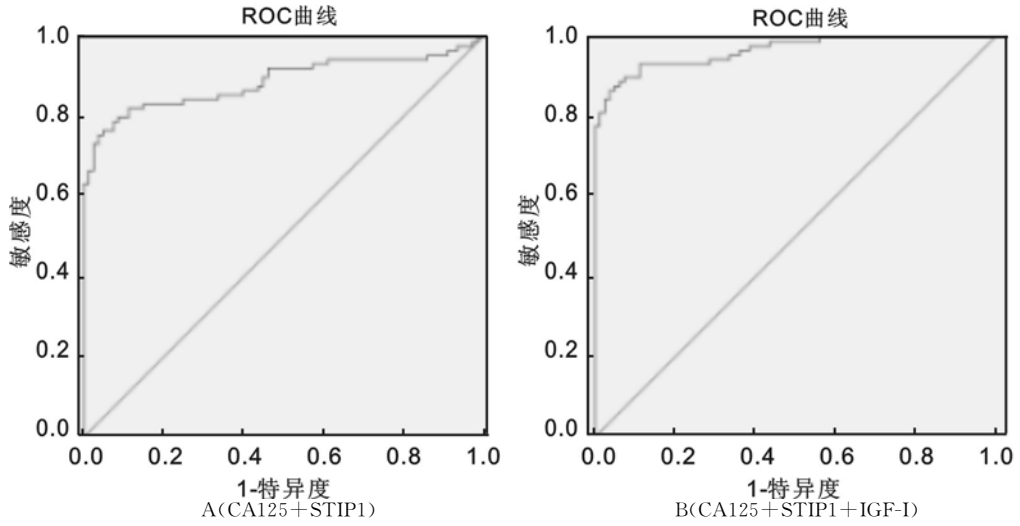


图3 CA125+STIP1+IGF-I系列联合检测诊断卵巢癌的ROC曲线

3 讨论 全球每年卵巢癌发病约20万,因缺乏敏感的早期诊断方法,死亡率较高,预计每年死亡12万左右[10]。卵巢癌的早期筛查对于提高生存率、延长患者寿命、改善预后具有重要意义。除影像学之外,肿瘤标志物是无症状早期卵巢癌筛查的有效工具[11]。该法操作简单、创伤小、结果可靠,在卵巢癌早期诊断中发展迅速。截止目前,血清CA125、甲胎蛋白、癌胚抗原等标志物已在临床广泛应用[12]。然而,由于卵巢癌组织来源多样,单一的肿瘤标志物敏感度和特异度较低,难以满足临床需要。因此,本研究选择CA125,STIP1和IGF-Ⅰ联合检测,探讨三者联用在卵巢癌早期诊断中的价

值。

3.1 CA125,STIP1和IGF-Ⅰ单独诊断卵巢癌效果分析 CA125是在恶性肿瘤组织中高表达的一种糖蛋白,可进入血液循环导致血清水平升高[4]。研究显示,CA125与卵巢癌分期显著相关,但敏感度和特异度均较差,早期卵巢癌的检出率也较低[13]。据报道[14],CA125诊断卵巢癌的敏感度、特异度和准确度分别为79.3%,72.8%和76.1%。本研究中显示单独的CA125诊断卵巢癌的准确度较差。临床资料[15]显示,子宫肌瘤、子宫内膜异位症、慢性盆腔炎、卵巢良性上皮肿瘤等患者血清CA125水平有不同程度的上升,因此,对于早期卵巢癌患者,CA125诊断价值有限。

STIP1是人卵巢癌细胞分泌的热休克蛋白,通过结合ALK2和活化SMAD-ID3信号通路促进肿瘤细胞增殖;也可与微管蛋白相互错用调节细胞极化和迁移来促进肿瘤血管生成[5]。据报道,STIP1与肿瘤分期及患者生存期相关[16],有助于预测预后。据Chao等[17]报道,对于血清CA125较低的患者,检测STIP1蛋白有助于判断人类卵巢癌的入侵。本研究发现单独用STIP1诊断卵巢癌的敏感度适宜,但特异度较差。IGF-Ⅰ是有丝分裂效应较强的多肽类生长因子,通过结合IGF-Ⅰ启动MAPK信号通路和PI13/Akt来发挥生物学活性,在正常细胞和肿瘤细胞中均表达,但肿瘤细胞表达量降低[18]。一般来说,癌细胞通过自分泌或旁分泌表达IGF-Ⅰ,导致血清水平升高。然而,本研究中,卵巢癌患者血清IGF-Ⅰ水平较低,可能与其运输蛋白IGFBP水平降低有关[19]。ROC曲线研究表明,单独的IGF-Ⅰ诊断卵巢癌的敏感度、特异度和准确度均较低,诊断效果欠佳。

3.2 CA125,STIP1和IGF-Ⅰ联合诊断卵巢癌效果分析 单独的血清肿瘤标志物诊断卵巢癌的敏感度和特异度均欠佳,而肿瘤标志物的联合检测为提高卵巢癌早期诊断的敏感度和特异度提供了新的方案。据报道[20],卵巢癌属于单项肿瘤标志物阳性比例低的肿瘤,多种标志物的联合检测有助于卵巢癌的准确诊断和预测。王静等联合血清胸苷激酶1和CA125诊断卵巢癌,诊断敏感度、特异度显著提高。本研究中,CA125,STIP1和IGF-I分别反映卵巢癌发病机制的不同方面,但尚无文献报道将三者联合用于诊断卵巢癌。本研究发现,CA125,STIP1,IGF-I平行联合检测有助于提高卵巢癌早期诊断的敏感度,有助于健康人群体检时的卵巢癌早期筛查,三者系列联合检测有助于提高卵巢癌诊断的特异度和准确度,有助于卵巢癌的准确诊断。一般来说,肿瘤标志物的联合检测并不是标志物越多,效果越好,而是尽可能地合理优化联合检测。本研究中,CA125,STIP1,IGF-I三者联合检测较单独或CA125+STIP1联合检测效果更好,这是因为三种标志物反映了卵巢癌不同的方面,故在改善敏感度和特异度方面效果显著。

当然本研究属于回访研究,而且受样本量限制,结果还有待于扩大化的前瞻性试验进行证实。

总之,CA125,STIP1和IGF-I三者平行联合检测有助于提高卵巢癌诊断的敏感度,系列联合检测有助于提高卵巢癌诊断的特异度和准确度,对于卵巢癌早期诊断具有重要价值。

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