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血清 PAEs、CA125 及 RBP-4 与卵巢囊肿患者卵巢储备功能的相关性及其诊断价值分析*

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摘要 目的:探讨血清酞酸酯类化学物(PAEs)、糖类抗原 125(CA125)及视黄醇结合蛋白-4(RBP-4)与卵巢囊肿患者卵巢储备功能的相关性及其诊断价值。**方法:**选取我院 2020 年 1 月到 2022 年 12 月收治的 150 例卵巢囊肿患者,为观察组,另选取同期体检的 150 名健康志愿者作为对照组。对比两组受检者血清 PAEs{邻苯二甲酸二乙酯(DEP)、邻苯二甲酸二丁酯(DBP)、邻苯二甲酸(2-乙基己基)酯 [di-(2-ethylhexyl)](DEHP)}、CA125、RBP-4 及卵巢储备功能相关指标表达水平,采用 Pearson 检验分析血清 PAEs、CA125 及 RBP-4 与卵巢囊肿患者卵巢储备功能的相关性,并建立受试者工作特征(ROC)曲线分析血清 PAEs、CA125 及 RBP-4 对卵巢囊肿的诊断价值。**结果:**观察组血清 PAEs、CA125 及 DEP、DBP、DEHP 和 PAEs 总水平明显高于对照组($P<0.05$);观察组卵巢储备功能相关指标卵泡刺激素(FSH)、黄体生成素(LH)水平明显高于对照组,雌二醇(E_2)水平明显低于对照组($P<0.05$);PAEs、CA125 及 RBP-4 分别与 FSH、LH 呈正相关,与 E_2 呈负相关($P<0.05$);曲线下面积(AUC)从高到低依次为联合诊断(0.864)、RBP-4(0.721)、CA125(0.698)、PAEs(0.641)。PAEs、CA125 及 RBP-4 三者联合对卵巢囊肿的诊断灵敏度、特异度高于三者单一诊断。**结论:**血清 PAEs、CA125 及 RBP-4 与卵巢囊肿患者卵巢储备功能具有显著关系,三者水平越高代表卵巢囊肿患者卵巢储备功能越差,另外 PAEs、CA125 及 RBP-4 联合对于卵巢囊肿具有较高的诊断灵敏度与特异性,可为卵巢囊肿的临床诊断及病情判断提供可靠依据。

关键词:酞酸酯类化学物;糖类抗原 125;视黄醇结合蛋白-4;卵巢囊肿;卵巢储备功能;诊断价值

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Correlation and Diagnostic Value Analysis of Serum PAEs, CA125, and RBP-4 with Ovarian Reserve Function in Patients with Ovarian Cysts*

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ABSTRACT Objective: To explore the correlation and diagnostic value of serum phthalate ester chemicals (PAEs), carbohydrate antigen 125 (CA125), and retinol binding protein-4 (RBP-4) with ovarian reserve function in patients with ovarian cysts. **Methods:** A total of 150 ovarian cyst patients admitted to our hospital from January 2020 to December 2022 were selected as the observation group, and another 150 healthy volunteers with physical examination in the same period were selected as the matched group. Compare the expression levels of serum PAEs {diethyl phthalate (DEP), dibutyl phthalate (DBP), and 2-ethylhexyl phthalate (di-(2-ethylhexyl)) (Di-(2-ethylhexyl) phthalate (DEHP)), CA125, RBP-4, and ovarian function related indicators between two groups of subjects. Use Pearson's test to analyze the expression levels of serum PAEs. The correlation between CA125 and RBP-4 and ovarian reserve function in patients with ovarian cysts, and the establishment of receiver operating characteristic (ROC) curves to analyze the diagnostic value of serum PAEs, CA125, and RBP-4 for ovarian cysts. **Result:** The total levels of serum PAEs, CA125, DEP, DBP, DEHP, and PAEs in the observation group were higher than those in the matched group ($P<0.05$); The levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the observation group were higher than those in the matched group, while the levels of estradiol (E_2) were lower than those in the matched group ($P<0.05$); PAEs, CA125, and RBP-4 were positively correlated with FSH and LH, and negatively correlated with E_2 ($P<0.05$); The area under the curve (AUC) from high to low is joint diagnosis (0.864), RBP-4 (0.721), CA125 (0.698), and PAEs (0.641). The combination of PAEs, CA125, and RBP-4 has higher diagnostic sensitivity and specificity for ovarian cysts compared to a single diagnosis of the three. **Conclusion:** There is a significant relationship between serum PAEs, CA125, and RBP-4 levels and ovarian reserve function in patients with ovarian cysts. The higher the levels of these three, the worse the ovarian reserve function in patients with ovarian cysts. In addition, the combination of PAEs, CA125, and RBP-4 has high diagnostic sensitivity and specificity for ovarian cysts, which

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can provide reliable basis for clinical diagnosis and disease judgment of ovarian cysts.

Key words: Phthalate ester chemicals; Carbohydrate antigen 125; Retinol binding protein-4; Ovarian cyst; Ovarian reserve function; Diagnostic value

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前言

卵巢囊肿为妇科常见良性疾病之一,不同年龄段均可发生,多以20~40岁育龄期女性常见^[1]。研究发现^[2],随着卵巢肿瘤的发生发展,多数患者会出现卵巢储备功能下降情况,严重影响卵巢的功能与形态,甚至出现卵巢早衰,影响女性生育功能。因此,及时判断卵巢肿瘤患者卵巢储备功能,并早期诊断与治疗对提升卵巢囊肿患者生活质量具有重要意义。当前临床上针对卵巢囊肿多采取查体、症状、超声检查等综合方式进行诊断,缺乏方便、特异性高、耗时短的诊断方式^[3]。随着临床上对卵巢囊肿研究加深,越来越多学者推荐采取血液指标对卵巢囊肿进行诊断,并评价其卵巢储备功能。血清酞酸酯类化学物(Phthalate ester chemicals, PAEs)作为一类暴露在环境中的拟激素类物质,其中主要包括邻苯二甲酸二乙酯(Diethyl Phthalate, DEP)、邻苯二甲酸二丁酯(dibutyl phthalate, DBP)、邻苯二甲酸(2-乙基己基)酯[di-(2-ethylhexyl)](Di-(2-ethylhexyl) phthalate, DEHP)三种^[4]。大量学者研究发现^[5],PAEs属于环境内分泌干扰物,对于女性生殖健康存在不利影响。随着临床上对妇科疾病环境拟激素类物质的污染研究加深,逐渐引起临床广泛关注^[6]。糖类抗原125(carbohydrate antigen 125, CA125)作为血清肿瘤标志物,已被广泛应用于各种妇科肿瘤的诊断与鉴别,然而是否可评价卵巢囊肿患者的卵巢储备功能尚无确切定论^[7]。视黄醇结合蛋白-4(RBP-4)参与糖脂代谢过程,且与动脉粥样硬化的发生与发展密切相关^[8],但其与卵巢囊肿的相关研究较少。因此,本研究探讨血清PAEs、CA125及RBP-4与卵巢囊肿患者卵巢储备功能的相关性及其诊断价值。

1 资料与方法

1.1 一般资料

选取我院2020年1月到2022年12月收治的150例卵巢囊肿患者,为观察组,另选取同期体检的150名健康志愿者作为对照组。对照组:年龄最小24岁,最大47岁,平均(35.76±4.63)

岁;BMI最小20.43 kg/m²,最大26.73 kg/m²,平均(22.42±1.25) kg/m²。观察组:均年龄最小23岁,最大45岁,平均(35.36±4.58)岁;BMI最小20.22 kg/m²,最大26.59 kg/m²,平均(22.31±1.20)kg/m²。两组受检者一般资料对比无明显差异($P>0.05$),可对比。本研究经我院伦理委员会批准。

1.2 纳排标准

纳入标准:符合卵巢囊肿诊断标准^[9];年龄≥18岁;对本研究知情同意;临床资料完整;生理周期正常;治疗依从性较好。

排除标准:合并卵巢癌、其他类型卵巢肿瘤者;有卵巢手术史者;合并恶性肿瘤者;合并重要脏器相关功能障碍者;全子宫切除手术史者;近1个月内有激素类药物应用史者;合并内分泌疾病者;合并凝血功能障碍者。

1.3 方法

血清PAEs、CA125及RBP-4检测方法:抽取所有患者入院后次日与健康志愿者清晨空腹静脉血5 mL,采取3000 r/min的速度及8 cm的离心半径离心5 min,取上层清液。应用电化学发光免疫分析仪(生产企业:罗氏生物科技公司;型号:E601)及期配套设备检测CA125表达水平,依照试剂盒说明书实施酶联免疫吸附试验法检测PAEs及RBP-4表达水平。

卵巢储备功能相关指标检测方法:取上述血清采用电化学发光免疫法检测卵泡雌激素(FSH)、黄体生成素(LH)、雌二醇(Estradiol, E₂)表达水平来评价患者卵巢储备功能。

1.4 统计学方法

采取SPSS 23.0,计数资料以(n/%)表示, χ^2 检验;计量资料用($\bar{x}\pm s$)表示,t检验;采用Pearson检验进行相关性分析;以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 血清PAEs、CA125及RBP-4水平对比分析

观察组血清PAEs、CA125及DEP、DBP、DEHP和PAEs总水平较对照组高($P<0.05$),见表1。

表1 血清PAEs、CA125及RBP-4水平对比分析($\bar{x}\pm s$)

Table 1 Comparative analysis of serum PAEs, CA125, and RBP-4 levels($\bar{x}\pm s$)

Groups	n	RBP-4(μ g/mL)	CA125(U/mL)	PAEs(mg/L)			
				DEP	DBP	DEHP	Summation
Observation group	150	30.14± 4.32	131.53± 15.47	0.13± 0.03	0.42± 0.07	0.30± 0.05	0.85± 0.11
Matched group	150	21.27± 3.08	24.75± 5.34	0.04± 0.01	0.13± 0.02	0.18± 0.04	0.35± 0.07
t	-	18.356	6.493	17.788	15.287	13.536	10.522
P	-	0.001	0.001	0.001	0.001	0.001	0.001

2.2 卵巢储备功能相关指标对比

观察组卵巢储备功能相关指标FSH、LH水平明显高于对

对照组,E₂水平明显低于对照组($P<0.05$),见表2。

表 2 卵巢储备功能相关指标对比($\bar{x} \pm s$, pmol/mL)

Table 2 Comparison of ovarian reserve function related indicators($\bar{x} \pm s$, pmol/mL)

Groups	n	FSH	LH	E ₂
Observation group	150	5.65± 1.27	8.54± 2.31	41.46± 8.53
Matched group	150	4.11± 1.06	5.33± 1.24	56.25± 11.42
t	-	5.356	8.487	7.379
P	-	0.001	0.001	0.001

2.3 PAEs、CA125 及 RBP-4 与卵巢储备功能的相关性 呈负相关($P < 0.05$), 见表 3。
PAEs、CA125 及 RBP-4 分别与 FSH、LH 呈正相关, 与 E₂

表 3 PAEs、CA125 及 RBP-4 与卵巢储备功能的相关性

Table 3 Correlation between PAEs, CA125, and RBP-4 with ovarian reserve function

Index	FSH		LH		E ₂	
	r	P	r	P	r	P
RBP-4	0.396	<0.01	0.471	<0.01	-0.473	<0.01
CA125	0.451	<0.01	0.512	<0.01	-0.432	<0.01
PAEs	0.298	<0.01	0.391	<0.01	-0.324	<0.01

2.4 PAEs、CA125 及 RBP-4 对卵巢囊肿的诊断价值分析 (AUC)从高到低依次为联合诊断(0.864)、RBP-4(0.721)、CA125 (0.698)、PAEs(0.641)。PAEs、CA125 及 RBP-4 三者联合对卵巢囊肿的诊断灵敏度、特异度高于三者单一诊断。见表 5、图 1。

表 4 PAEs、CA125 及 RBP-4 对卵巢囊肿的诊断价值

Table 4 Diagnostic value of PAEs, CA125, and RBP-4 for ovarian cysts

Project	Optimal threshold	Sensitivity(%)	Specificity(%)	AUC	95%CI
CA125	71.68 U/mL	72.67	82.54	0.698	0.512-0.835
RBP-4	23.27 μg/mL	73.25	78.56	0.721	0.721-0.887
PAEs	0.53 mg/L	69.57	72.67	0.641	0.541-0.735
Combined diagnosis	-	93.54	85.45	0.897	0.798-0.935

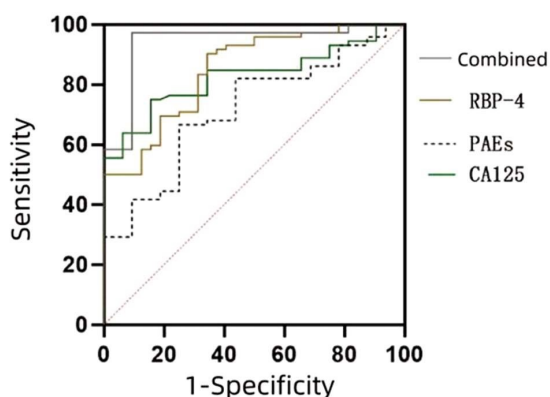


图 1 PAEs、CA125 及 RBP-4 对卵巢囊肿的诊断 ROC 曲线

Fig.1 ROC curves of PAEs, CA125, and RBP-4 in the diagnosis of ovarian cysts

3 讨论

卵巢作为女性重要生殖器官之一, 若卵巢功能遭受损伤, 不仅会导致女性月经不调, 严重影响女性生育功能^[10]。卵巢囊

肿患者会逐渐出现月经周期紊乱、下腹部不适、坠胀、疼痛等症状, 严重者可能会出现蒂扭转、囊肿破裂, 引发感染与继发性病变, 引起更严重的症状, 为卵巢储备功能造成不可逆转伤害^[11,12]。因此, 早期判断卵巢囊肿患者的卵巢储备功能, 并准确诊断, 对于制定综合性治疗措施, 早期治疗, 具有重要价值^[13]。因此, 本研究以血清 PAEs、CA125 及 PAEs 为相关血液标志物, 判断其与卵巢囊肿患者卵巢储备功能的相关性, 并分析其对卵巢囊肿的诊断价值, 以期临床提供参考意见。

本研究表明, 观察组血清 RBP-4、CA125 及 DEP、DBP、DEHP 和 PAEs 总水平较对照组高($P < 0.05$), 与 Zhang Y 等^[14]、Qing X 等^[15]、Mousavi SN 等^[16]研究结果相似。Zhang Y 等研究显示, 在卵巢囊肿、子宫肌瘤等妇科疾病女性血清中, PAEs 相关物质水平含量明显升高。另外研究显示^[17], 居住在塑料厂附近孕妇尿液中 PAEs 含量明显升高, 且与妊娠期并发症具有明显关系。分析原因为, PAEs 作为拟雌性激素类物质, 与环境污染具有重要关系, 人体 PAEs 相关物质水平升高, 可能预示 PAEs 相关污染物对患者机体造成一定损伤^[18]。另外研究显示^[19], DEHP 在聚乙烯类塑料生产过程中作为增塑剂被广泛

使用,而聚乙烯塑料类物质被广泛应用于装饰材料、食品包装、医疗设备以及地板材料的生活物质中。DBP 与 DEHP 作为溶剂被应用于个人护理用品与油漆等物质生产中,逐渐被人体吸收,导致 PAEs 相关物质水平升高^[20]。而卵巢肿瘤患者在疾病发生与发展过程中可能与 PAEs 进入血液循环,造成污染相关。Qing X 等研究显示,CA125 对于卵巢肿瘤等妇科肿瘤疾病具有较高诊断价值,且妇科肿瘤患者血清 CA125 水平显著高于健康者。分析原因为,CA125 作为肿瘤血清标志物,已经得到共识^[21]。近年来研究显示^[22],CA125 在卵巢癌的诊断及预后预测中具有重要价值,然而其是否与卵巢囊肿具有关系尚无确切定论。当肿瘤细胞增殖或恶性病变发生后,CA125 水平呈明显升高状态^[23]。Mousavi SN 等研究显示,卵巢囊肿患者血清 RBP-4 水平会呈现升高状态。分析原因为,RBP-4 可作用于血管内皮细胞,使其造成通透性损伤,并损伤血管屏障。研究发现^[24],RBP-4 水平与机体 IL-6 等促炎因子水平具有明显相关性。而卵巢囊肿的发生过程中与炎症反应密不可分,因此可能导致 RBP-4 水平升高,但其具体机制还需进一步研究分析。本研究结果表明,观察组卵巢储备功能相关指标 FSH、LH 水平明显高于对照组,E₂ 水平明显低于对照组($P<0.05$),证明卵巢囊肿的发生会对于患者卵巢储备功能造成一定影响,与 Milanetto AC 等^[25]研究结果相符。Milanetto AC 等研究表明,FSH、LH、E₂ 作为性激素相关指标与卵巢功能具有重要关系,当卵巢功能出现损伤时,血清 E₂ 水平会明显降低,FSH、LH 水平会明显升高。而卵巢囊肿在发生后,随着囊肿逐渐增大,压迫卵巢组织,造成卵巢功能损伤,影响其储备功能的同时,从而导致 FSH、LH、E₂ 相关性激素出现异常表达状态^[26,27]。本研究进一步分析发现,PAEs、CA125 及 RBP-4 分别与 FSH、LH 呈正相关,与 E₂ 呈负相关($P<0.05$),证明可采取 PAEs、CA125 及 RBP-4 来评价卵巢囊肿患者卵巢储备功能,并分析患者激素代谢异常情况。最后本研究结果表明,PAEs、CA125 及 RBP-4 三者联合对卵巢囊肿的诊断灵敏度、特异度高于三者单一诊断。分析原因为,PAEs 主要是针对女性日常生活中的污染源情况,间接判断污染源对卵巢造成的损伤,从而诊断卵巢囊肿;CA125 作为肿瘤标志物,以肿瘤相关组织生成及发展对卵巢囊肿进行诊断^[28];RBP-4 则是通过与卵巢囊肿发生后的炎症反应进行特异性诊断。三者均从不同角度来诊断卵巢囊肿的发生,进而提升其诊断灵敏度与特异度。

综上所述,血清 PAEs、CA125 及 RBP-4 与卵巢囊肿患者卵巢储备功能具有显著关系,三者水平越高代表卵巢囊肿患者卵巢储备功能越差,另外 PAEs、CA125 及 RBP-4 联合对于卵巢囊肿具有较高的诊断灵敏度与特异性,可为卵巢囊肿的临床诊断及病情判断提供可靠依据。

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