

# 基于液相色谱-串联质谱的激素测定平台 助力多囊卵巢综合征的精准诊疗

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**【摘要】目的** 建立基于液相色谱-串联质谱(liquid chromatography-tandem mass spectrometry, LC-MS/MS)的激素测定平台,并与化学发光免疫分析(chemiluminescence immunoassay, CLIA)测定的血清睾酮(T)、硫酸脱氢表雄酮(DHEA-S)、孕酮(P4)和雌二醇(E2)水平进行对比,明确该LC-MS/MS平台诊断高雄激素血症和多囊卵巢综合征(polycystic ovary syndrome, PCOS)的临床价值。**方法** 纳入PCOS患者35例(PCOS组),正常对照组33例,LC-MS/MS测定血清T、雄烯二酮(A4)、DHEA-S、双氢睾酮(DHT)、脱氢表雄酮(DHEA)、P4、E2、雌酮(E1)、雌三醇(E3)、17-羟孕酮(17-OHP)、皮质醇和可的松水平,并与CLIA测定的血清T、DHEA-S、P4和E2水平进行比较,ROC曲线分析LC-MS/MS测定的血清T、A4和E1水平诊断PCOS的曲线下面积、灵敏度、特异度和约登指数、阳性预测值和阴性预测值。**结果** LC-MS/MS测定的血清T、DHEA-S、P4和E2水平均低于CLIA,差异有统计学意义( $P < 0.05$ )。LC-MS/MS联合检测T、A4、DHEA-S、DHT和DHEA可以提高高雄激素血症的检出率( $P < 0.05$ )。PCOS患者的血清T、A4和E1水平均高于正常对照组,差异有统计学意义( $P < 0.05$ ),ROC曲线亦提示LC-MS/MS测定血清T、A4和E1水平诊断PCOS有临床价值( $P < 0.05$ )。**结论** LC-MS/MS激素测定平台检测多项雄激素能提高高雄激素血症的检出率,较CLIA能更好的识别PCOS患者。

**【关键词】** 多囊卵巢综合征;液相色谱-串联质谱法;化学发光免疫分析法;高雄激素血症;睾酮;双氢睾酮

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## Liquid chromatography-tandem mass spectrometry-based hormone measurement platform facilitates accurate diagnosis and treatment of polycystic ovary syndrome

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**【Abstract】Objective** A hormone determination platform based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) was established to compare the levels of serum testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), progesterone (P4), and estradiol (E2) with those measured by CLIA. This comparison clarified the clinical value of the LC-MS/MS platform for the diagnosis of hyperandrogenism and polycystic ovary syndrome (PCOS). **Methods** 35 patients with PCOS and 33 normal controls were included. Serum levels of testosterone (T), 4-androstenedione (A4), dehydroepiandrosterone sulfate (DHEA-S), dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), progesterone (P4), estradiol (E2), estrone (E1), estriol (E3), 17-hydroxyprogesterone (17-OHP), cortisol, and cortisone were measured by LC-MS/MS and compared with CLIA-measured levels of serum T, DHEA-S, P4, and E2. The area under the curve, sensitivity, specificity, and Jordan's index, as well as the positive predictive value and negative predictive value of ROC curves, were analyzed to diagnose PCOS using serum T, A4, and E1 levels measured by LC-MS/MS. **Results** The levels of serum T, DHEA-S, P4 and E2 measured by LC-MS/MS were lower than those of CLIA, the differences were statistically significant ( $P < 0.05$ ). The detection rate of hyperandrogenism could be improved by the combined detection of T, A4, DHEA-S, DHT and DHEA by LC-MS/MS ( $P < 0.05$ ). The serum levels of T, A4 and E1 in patients with PCOS were higher than that of the normal controls ( $P < 0.05$ ). The ROC curves also suggested that the determination of serum T, A4 and E1 levels by LC-MS/MS were valuable for the diagnosis of PCOS ( $P < 0.05$ ). **Conclusions** The LC-MS/MS hormone assay platform could improve the detection rate of multiple androgens, enhancing the diagnosis of hyperandrogenemia and better identifying PCOS patients compared to CLIA.

**【Key words】** Polycystic Ovary Syndrome; Liquid Chromatography-Tandem Mass Spectrometry; Chemiluminescence Immunoassay; Hyperandrogenism; Testosterone; Dihydrotestosterone

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多囊卵巢综合征(polycystic ovary syndrome, PCOS)是以月经异常、多毛、痤疮、肥胖、卵巢多囊样改变及糖、脂代谢紊乱为主要特征的生殖内分泌代谢性疾病。我国育龄期女性的PCOS患病率为5.6%<sup>[1-2]</sup>。高雄激素血症是PCOS的主要病理生理改变<sup>[3]</sup>。PCOS的诊断标准有鹿特丹标准<sup>[4]</sup>、美国雄激素学会标准<sup>[5]</sup>和中国标准<sup>[6]</sup>等,均把高雄激素的临床表现或高雄激素血症作为评价标准之一。文献报道,25%~35%的PCOS患者无多毛、痤疮、脱发等高雄激素体征<sup>[7]</sup>,且其判断易受评价者主观性的影响,故准确测定雄激素水平对于PCOS的诊治至关重要。2023年欧洲人类生殖与胚胎学会发布的《多囊卵巢综合征的评估和管理国际循证指南》<sup>[8]</sup>,推荐使用液相色谱-串联质谱分析(liquid chromatography-tandem mass spectrometry, LC-MS/MS)测定血清睾酮(testosterone, T)和游离睾酮水平或计算游离雄激素指数。若前述指标正常,可测量4-雄烯二酮(4-androstenedione, A4)和硫酸脱氢表雄酮(dehydroepiandrosterone sulfate, DHEA-S)水平。双氢睾酮(dihydrotestosterone, DHT)与T相比,与雄激素受体结合的亲和力更高,是活性最强的雄激素,是导致多毛、痤疮等高雄性体征的主要雄激素<sup>[9]</sup>。研究表明部分PCOS患者的脱氢表雄酮(dehydroepiandrosterone, DHEA)水平也会升高<sup>[10]</sup>。然而,目前尚不清楚同时检测DHT和DHEA能否提高PCOS高雄激素血症的检出率。此外,检测17-羟孕酮(17-hydroxyprogesterone, 17-OHP)、皮质醇和可的松有利于PCOS与非经典型先天性肾上腺皮质增生、库欣综合征的鉴别诊断,而雌激素和孕酮(progesterone, P4)水平测定是PCOS等生殖内分泌疾病的常规检查项目。鉴于LC-MS/MS是性激素检测的金标准且具有多通道同时检测的优势,能够对单个样本中的多种类固醇激素进行分析,同时评估多种类固醇激素的代谢特征<sup>[11]</sup>。本研究建立能同时测定血清T、A4、DHEA-S、DHT、P4、雌二醇(estradiol, E2)等12项PCOS诊治相关激素的LC-MS/MS平台,与目前临床普遍应用的化学发光免疫分析(chemiluminescence immunoassay, CLIA)测定的激素水平进行比较,并评价LC-MS/MS平台对高雄激素血症和PCOS的诊断价值。

## 1 资料与方法

### 1.1 一般资料

本研究纳入2023年3月~2023年4月在本院妇产科门诊就诊的PCOS患者35例,PCOS诊断按照2018年发布的《多囊卵巢综合征中国诊疗指南》的诊断标准<sup>[6]</sup>。纳入子宫肌瘤等妇科良性疾病的33例非PCOS患者作为对照组。高雄激素血症的判断标准为LC-MS/MS测定血清T $\geq$ 0.55 ng/mL或A4 $\geq$ 2.3 ng/mL或DHEA-S高于相应年龄的正常参考值(18~30岁、31~40岁的

正常值上限分别是3 770 ng/mL、2 950 ng/mL)或DHEA $\geq$ 7.01 ng/mL或DHT $>$ 0.3 ng/mL。排除标准:①年龄 $<$ 18岁或 $>$ 40岁;②处于妊娠期或哺乳期;③近3月使用性激素类药物者(例如炔雌醇丙环孕酮片、雌二醇地屈孕酮片、屈螺酮炔雌醇片等药物)。本研究获得重庆医科大学附属第二医院伦理委员会批准(批号:2021年科伦审第145号),所有研究对象均签署知情同意书。

### 1.2 仪器与试剂

采用Agilent 6495 LC-MS/MS三重四极杆液质联用仪(Agilent公司,美国)和12项类固醇激素试剂(苏州颐坤生物科技有限公司,中国),按照实际说明书测定血清T、A4、DHEA-S、DHT、DHEA、P4、E2、雌酮(estrone, E1)、雌三醇(estriol, E3)、17-OHP、皮质醇和可的松水平。采用Roche Cobas e602全自动电化学发光分析仪和配套试剂(Roche公司,德国),按照规定要求操作测定血清T、DHEA-S、P4和E2水平。

### 1.3 方法

**1.3.1 资料采集** 采集PCOS患者及对照组的人口学信息、病史、身高和体重指数等基本临床资料。

**1.3.2 血液采集** 采集PCOS患者及对照组的早卵泡期(月经第2~4 d,空腹)肘正中静脉血于肝素钠抗凝真空采血管内,快速转运至实验室,常温下以3000 rpm/min离心5~10 min,取上层血浆在2 h内完成检测,剩余血浆保存于-80 °C冰箱。

**1.3.3 激素检测** LC-MS/MS测定PCOS患者及对照组的血清T、A4、DHEA-S、DHT、DHEA、P4、E2、E1、E3、17-OHP、皮质醇和可的松水平;CLIA测定PCOS患者及对照组的血清T、DHEA-S、P4和E2水平。

### 1.4 统计学处理

全部数据资料录入Excel数据库,采用IBM SPSS Statistics 26.0软件进行统计学处理。Shapiro-Wilk检验连续变量是否符合正态分布,若符合正态分布,变量以均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示,两组间比较采用 $t$ 检验;若符合非正态分布,变量以中位数和四分位数间距M( $P_{25}, P_{75}$ )表示,两组间比较采用 $Z$ 检验。采用MedCalc软件进行受试者工作特征曲线(receiver operator characteristic curve, ROC)分析LC-MS/MS测定的血清T、A4和E1水平诊断PCOS的曲线下面积(the area under the ROC curve, AUC)、灵敏度、特异度和约登指数。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 LC-MS/MS与CLIA测定值的比较

LC-MS/MS测定的血清T、DHEA-S、P4和E2水平均显著低于CLIA( $P < 0.05$ ,见表1)。LC-MS/MS测定的血清T水平比CLIA低18%( $T_{LC-MS/MS}/T_{CLIA} = 0.82$ ),血

清 DHEA-S 水平比 CLIA 低 20% ( $DHEA-S_{LC-MS/MS}/DHEA-S_{CLIA}=0.80$ ), 血清 P4 水平比 CLIA 低 40% ( $P4_{LC-MS/MS}/P4_{CLIA}=0.60$ ), 血清 E2 水平比 CLIA 低 60% ( $E2_{LC-MS/MS}/E2_{CLIA}=0.40$ )。

表1 LC-MS/MS和CLIA测定的血清T、DHEA-S、P4和E2水平  
Table 1 Serum T, DHEA-S, P4 and E2 levels measured by LC-MS/MS and CLIA

指标	LC-MS/MS (n = 68)	CLIA(n = 68)	t/Z	P
T(ng/mL)	0.32 ± 0.16	0.39 ± 0.20	2.41	< 0.05
DHEA-S(ng/mL)	2 298.28 ± 1 017.98	2 856.85 ± 1 152.39	3.15	< 0.05
P4(ng/mL)	0.09(0.08,0.11)	0.15(0.11,0.23)	3.37	< 0.05
E2(ng/mL)	0.02(0.02,0.04)	0.05(0.04,0.06)	3.47	< 0.05

## 2.2 LC-MS/MS 单项与多项雄激素的高雄激素血症检出率

共68例患者中,LC-MS/MS仅测定血清T水平检出5例高雄激素血症,检出率7.35% (5/68);联合检测血清T、A4和DHEA-S水平,检出11例高雄激素血症,检出率16.18% (11/68);联合检测血清T、A4、DHEA-S、DHT和DHEA水平,检出19例高雄激素血症,检出率提高至27.94% (19/68)。由此可见,该LC-MS/MS平台测定多项雄激素可提高高雄激素血症的检出率(图1)。

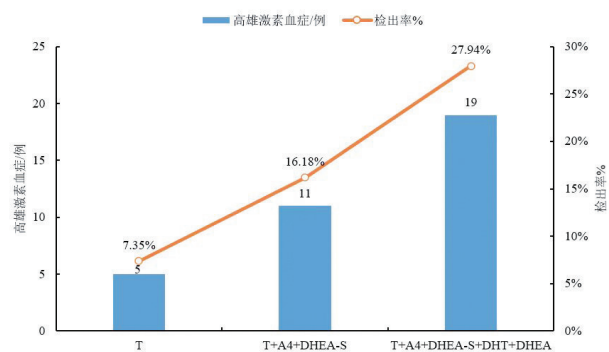


图1 LC-MS/MS测定多项雄激素的高雄激素血症检出率  
Figure 1 The detection rate of hyperandrogenemia by measuring multiple androgens using LC-MS/MS

## 2.3 PCOS 患者与对照组的血清激素水平对比

LC-MS/MS测定的PCOS患者血清T水平、A4水平和E1水平显著高于对照组(表2)。CLIA测定的PCOS患者血清T水平和E2水平显著高于对照组(表3)。

## 2.4 LC-MS/MS 测定血清T、A4和E1水平诊断PCOS的ROC分析

LC-MS/MS测定血清T水平诊断PCOS的AUC为0.75(0.64,0.87),灵敏度80%,特异度64%,约登指数1.44;LC-MS/MS测定血清A4水平诊断PCOS的AUC为0.77(0.65,0.89),灵敏度86%,特异度70%,约登指数1.55;LC-MS/MS测定血清E1水平诊断PCOS的AUC为0.75(0.64,0.87)与T相当,灵敏度71%,特异度76%,约登指数1.47。联合3项指标诊断PCOS的AUC为0.77(0.65,0.87),灵敏度83%,特异度64%,约登指数

1.47;CLIA测定血清T水平诊断PCOS的AUC为0.71(0.60,0.84),灵敏度53%,特异度85%,约登指数1.38。LC-MS/MS检测T、A4和E1诊断PCOS均有临床价值( $P < 0.05$ ,表4),AUC均高于CLIA检测T诊断PCOS的AUC(图2)。

表2 LC-MS/MS测定的PCOS与对照组的血清激素水平  
Table 2 The results of serum hormone levels between PCOS and Control detected by LC-MS/MS

指标	PCOS组(n = 35)	对照组(n = 33)	t/Z	P
T(ng/mL)	0.39 ± 0.18	0.25 ± 0.11	3.94	< 0.05
A4(ng/mL)	1.46 ± 0.46	1.04 ± 0.55	3.41	< 0.05
DHEA-S(ng/mL)	2 148.71 ± 878.51	2001.64 ± 1017.46	0.48	0.63
DHT(ng/mL)	0.09 ± 0.15	0.08 ± 0.07	0.39	0.69
DHEA(ng/mL)	4.67 ± 2.05	4.38 ± 2.52	0.51	0.61
P4(ng/mL)	0.09(0.08,0.11)	0.10(0.08,0.14)	0.18	0.85
E2(ng/mL)	0.03(0.02,0.44)	0.02(0.01,0.03)	0.74	0.46
E1(ng/mL)	0.05 ± 0.02	0.03 ± 0.02	2.56	< 0.05
E3(ng/mL)	0.020 ± 0.00	0.02 ± 0.01	0.77	0.43
17-OHP(ng/mL)	0.60 ± 0.45	0.47 ± 1.15	0.61	0.55
皮质醇(ng/mL)	91.99 ± 48.19	75.36 ± 33.89	1.65	0.10
可的松(ng/mL)	24.05 ± 5.94	22.76 ± 6.74	0.84	0.40

表3 CLIA测定的PCOS与正常对照的血清激素水平  
Table 3 The results of serum hormone levels between PCOS and Control detected by CLIA

指标	PCOS组(n = 35)	对照组(n = 33)	t/Z	P
T(ng/mL)	0.47 ± 0.20	0.33 ± 0.16	3.22	< 0.05
DHEA-S(ng/mL)	2 720.17 ± 1 106.51	2 540.83 ± 1 072.06	0.89	0.39
P4(ng/mL)	0.15(0.11,0.22)	0.17(0.12,0.27)	1.38	0.70
E2(ng/mL)	0.05(0.04,0.07)	0.04(0.04,0.06)	2.26	< 0.05

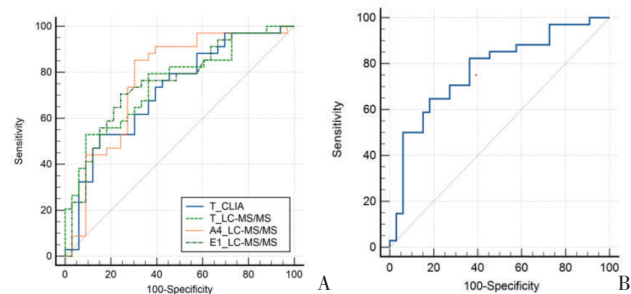


图2 LC-MS/MS测定血清T、A4和E1水平诊断PCOS的ROC曲线  
Figure 2 ROC curve for the diagnosis of PCOS by LC-MS/MS measurement of serum T, A4 and E1 levels

注:A图为血清T、A4和E1单指标诊断PCOS的ROC曲线;B图为LC-MS/MS联合检测T、A4和E1诊断PCOS的ROC曲线。

## 3 讨论

PCOS是女性常见的生殖内分泌代谢性疾病,高雄激素血症是PCOS的病理生理核心,专家建议优先测定血清T和DHEA-S水平或计算游离雄激素水平诊断高雄激素血症。由于计算游离雄激素指数的准确性易受性激素结合球蛋白影响,目前临床上仍以CLIA测定血清T水平识别高雄激素血症。LC-MS/MS是性激素检

表4 ROC分析血清T、A4和E1水平诊断PCOS的价值  
Table 4 ROC analysing the value of serum T, A4 and E1 levels for the diagnosis of PCOS

指标	T <sub>LC-MS/MS</sub>	A4 <sub>LC-MS/MS</sub>	E1 <sub>LC-MS/MS</sub>	T+A4+E1	T <sub>CLIA</sub>
AUC(95% CI)	0.75 (0.64, 0.87)	0.77 (0.65, 0.89)	0.75 (0.64, 0.87)	0.77 (0.65, 0.87)	0.71 (0.60, 0.84)
Z	4.40	4.40	4.13	4.61	3.47
P	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
敏感度	80%	86%	71%	83%	53%
特异度	64%	70%	76%	64%	85%
阳性预测值 (95% CI)	74.82% (68.70% ~ 79.89%)	80.63% (72.80% ~ 89.44%)	73.01% (65.80% ~ 82.44%)	74.58% (64.5% ~ 82.6%)	78.62% (69.60% ~ 89.80%)
阴性预测值 (95% CI)	57.46% (41.70% ~ 68.33%)	65.27% (52.34% ~ 72.76%)	61.57% (54.70% ~ 73.05%)	74.73% (57.7% ~ 86.5%)	63.47% (54.12% ~ 71.90%)

测的金标准,本研究建立了同时测定PCOS患者多种激素的LC-MS/MS平台,并与传统CLIA测定的激素水平比较。结果表明与CLIA相比,LC-MS/MS测定性激素水平普遍偏低,LC-MS/MS联合测定T、A4、DHEA-S、DHT和DHEA能提高高雄激素血症的检出率,该研究建立的LC-MS/MS平台比CLIA能更好的识别PCOS患者。

本研究中CLIA测定血清T、DHEA-S、P4和E2水平均显著高于LC-MS/MS,这与MÜNZKER、XU<sup>[12-13]</sup>等研究结果相似。尽管CLIA广泛应用,但CLIA在检测激素过程中难以避免类固醇激素之间结构类似物或同分异构体的交叉反应,造成抗体与激素结合特异性的降低。女性的雄激素水平相比男性低,更容易因激素丰度低受上述因素影响,导致结果出现假阳性<sup>[14]</sup>。LC-MS/MS可克服这些缺点,在加入稳定同位素内标的基础上,通过液相色谱将结构类似物或同分异构体分离避免交叉反应,再利用质谱仪对其特定的分子量进行检测<sup>[14]</sup>,即使低水平激素检测时仍比CLIA具有更好的灵敏度与特异度<sup>[15-16]</sup>。

高雄激素血症是PCOS的主要病理生理改变,通常会加重PCOS患者的糖脂代谢异常紊乱程度,是诊治PCOS的重要内容。T作为卵巢来源性的主要雄激素,是识别高雄激素血症和诊断PCOS的主要指标。但只测定血清T水平并不能完全地准确识别高雄激素血症<sup>[17]</sup>。传统CLIA测定血清T水平的参考范围是依据男性雄激素水平建立,尽管部分PCOS患者的血清T水平较非PCOS患者升高,在实验室中CLIA仍无法灵敏特异的测定女性血清T水平。本研究建立的LC-MS/MS激素测定平台在检测血清T和DHEA-S水平的基础上加测血清DHT、A4和DHEA水平,结果表明DHT、A4和DHEA能提高高雄激素血症的检出率。T本身可以进一步代谢为其他雄激素,其中DHT由T在5- $\alpha$ 还原酶的作用下转化形成。T和DHT都可以与雄激素受体结合,DHT在血液循环中的含量较少,但是DHT的作用持续时间比T长,是活性最强的雄激素。在T水平正常

的PCOS患者中,DHT水平可能出现异常。有研究表明DHT水平升高与PCOS患者的肥胖、胰岛素抵抗或代谢综合征等存在正相关性<sup>[18]</sup>。DHEA主要是通过脱氢表雄酮磺酸转移酶转化为DHEA-S进入血液循环,两者可在一定条件下相互转化,血液循环的DHEA-S水平受脱氢表雄酮磺酸转移酶水平影响<sup>[10]</sup>,DHEA水平并不受此酶影响,仅5%的PCOS患者的存在DHEA-S这1种雄激素水平升高<sup>[19]</sup>。在PCOS伴多毛症的患者中类固醇生成酶存在过度表达,特别是增强DHEA产生的酶<sup>[20]</sup>,已有荟萃分析证明PCOS患者体内血清DHEA水平相比健康对照人群升高<sup>[21]</sup>。DHEA也可诱导血清T水平提高,引起PCOS患者体内产生慢性炎症与氧化应激<sup>[22]</sup>。因此,检测DHT和DHEA不仅能提高高雄激素血症的检出率,或许还能作为评估PCOS患者代谢情况指标,这需要更多的研究进一步证明。

A4是T的前体物质,与T通常作为评价卵巢来源性雄激素的指标,本研究表明PCOS患者血清T和A4水平均显著高于正常对照,ROC曲线分析提示A4诊断PCOS的AUC比T高。此前已有研究证明,检测雄激素时若联合A4,可以提高PCOS的检出率<sup>[23]</sup>。与T相比,A4在血液循环中与白蛋白结合较疏松,处于游离状态的A4更多,其生物学效应更明显,血清A4水平升高可引起更严重的糖脂代谢紊乱<sup>[24]</sup>。研究证明1型糖尿病合并PCOS患者的血清A4是评估高雄激素血症的敏感指标<sup>[25]</sup>。此外,我们还发现PCOS患者E1水平显著高于正常对照人群,诊断PCOS的AUC与T相当,但是将T、A4和E1联合后,诊断PCOS的AUC虽然比T高,但是相比A4诊断PCOS的AUC并没有变化,我们推测可能因为PCOS患者垂体分泌促黄体生成素增加,引起卵泡膜细胞分泌更多的A4,A4在卵巢颗粒细胞中由芳香酶催化转化为E1<sup>[26]</sup>。

## 4 结论

高雄激素血症的准确检出对诊断PCOS至关重要。因LC-MS/MS是性激素检测的金标准,本研究建立了

同时检测血清 T、A4、DHEA-S、DHT、DHEA、P4、E2、E1、E3、17-OHP、可的松和皮质醇水平的 LC-MS/MS 激素测定平台。该平台能提高高雄激素血症的检出率,有助于 PCOS 与其他内分泌疾病的鉴别诊断,为临床精准诊疗 PCOS 提供了新的科学检测方法。

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