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血清抗苗勒管激素对多囊卵巢综合征临床诊断和促排卵疗效的评估价值

温晶，郑梅

(海口市妇幼保健院生殖医学中心，海口 570203)

[摘　要]　**目的：**探讨血清抗苗勒管激素(anti-Mullerian hormone，AMH)对多囊卵巢综合征(polycystic ovarian syndrome，PCOS)临床诊断和促排卵效果的评估价值。**方法：**选取2020年1月至2021年9月海口市妇幼保健院生殖医学中心收治的85例PCOS患者以及同期来院体检的40例健康同龄女性，分别记为PCOS组与健康组，检测两组血清AMH水平。PCOS组接受促排卵药物治疗，并依据促排卵疗效不同，分成排卵组(n=67)与无排卵组(n=18)，检测两组治疗前后血清AMH水平并计算AMH下降率。分析PCOS患者血清AMH水平与促卵泡激素(follicle stimulating hormone，FSH)、黄体生成素(luteinizing hormone，LH)、雌二醇(estradiol，E_2)和睾酮(testosterone，T)的相关性，并绘制受试者工作特征(receiver operating characteristic，ROC)曲线分析血清AMH在PCOS临床诊断和促排卵疗效中的应用价值。**结果：**PCOS组血清AMH和LH、T水平均高于健康组(均P<0.05)，且血清AMH与LH、T呈正相关(分别r=0.692、0.516，均P<0.05)。血清AMH诊断PCOS的曲线下面积(area under curve，AUC)为0.814，最佳截断值为6.83 ng/mL，敏感度、特异度和准确度分别为84.71%、72.50%、80.80%。PCOS组促排卵治疗后血清AMH明显低于治疗前(P<0.05)，排卵组治疗前后血清AMH水平均低于无排卵组，血清AMH下降率高于无排卵组(P<0.05)。血清AMH下降率评估PCOS患者促排卵疗效的AUC为0.877，明显大于血清AMH基线值的0.793(P<0.05)，血清AMH下降率评估促排卵疗效的最佳截断值29.32%，敏感度、特异度和准确度分别为83.58%、83.33%、83.53%。**结论：**PCOS患者血清AMH表达异常升高，促排卵治疗后明显下降，血清AMH可为PCOS临床诊断和促排卵疗效评估提供重要依据。

[关键词]　多囊卵巢综合征；抗苗勒管激素；促排卵药物；AMH下降率

Value of serum anti-Mullerian hormone in clinical diagnosis of polycystic ovary syndrome and evaluation of the efficacy of ovulation induction

WEN Jing, ZHENG Mei

(Reproductive Medicine Center, Haikou Maternal and Child Health Hospital, Haikou 570203, China)

Abstract　**Objective:** To investigate the value of serum anti-Mullerian hormone (AMH) in the clinical diagnosis of

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通信作者 (Corresponding author)：温晶，Email: zhengzuowu@163.com

polycystic ovary syndrome (PCOS) and evaluation of the efficacy of ovulation induction. **Methods:** Eighty-five patients with PCOS treated in the Reproductive Medicine Center of Haikou Maternal and Child Health Hospital from January 2020 to September 2021 and 40 healthy women of the same age who came to the hospital for physical examination in the same period were recorded as a PCOS group and a healthy group, respectively, and the serum AMH level of the 2 groups were detected. The PCOS group received ovulation induction drug treatment, and according to the different effects of ovulation induction, they were divided into an ovulation group (n=67) and an anovulation group (n=18). The serum AMH level of the 2 groups before and after the treatment was detected and the decline rate of AMH was calculated. The correlations between serum AMH level and follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), or testosterone (T) in patients with PCOS were analyzed. Receiver operating characteristic (ROC) curve was drawn to analyze the application value of serum AMH detection in the clinical diagnosis of PCOS and the efficacy of ovulation induction. **Results:** The levels of serum AMH, LH, and T in the PCOS group were higher than those in the healthy group (all P<0.05), and serum AMH was positively correlated with LH and T (r=0.692, 0.516, respectively, both P<0.05). The area under curve (AUC) of serum AMH in the diagnosis of PCOS was 0.814, the best cut-off value was 6.83 ng/mL, the sensitivity, specificity, and accuracy were 84.71%, 72.50%, and 80.80%, respectively. The serum AMH level in the PCOS group was significantly lower than that before the treatment (P<0.05), the serum AMH level in the ovulation group was lower than that in anovulation group before and after the treatment, and the decline rate of serum AMH was higher than that in the anovulation group (P<0.05). The AUC of the decrease rate of serum AMH in evaluating the effect of ovulation induction in PCOS patients was 0.877, which was significantly higher than the baseline value of serum AMH (P<0.05). The best cut-off value of the decrease rate of serum AMH in evaluating the effect of ovulation induction was 29.32%, and the sensitivity, specificity, and accuracy were 83.58%, 83.33%, and 83.53%, respectively. **Conclusion:** The expression of serum AMH in patients with PCOS increases abnormally and decreases significantly after ovulation induction treatment. The detection of serum AMH can provide an important basis for the clinical diagnosis of PCOS and the evaluation of ovulation induction efficacy.

Keywords polycystic ovarian syndrome; anti-Mullerian hormone; ovulation inducing drugs; AMH decline rate

多囊卵巢综合征(polycystic ovarian syndrome，PCOS)是妇科常见生殖系统疾病，好发于育龄期女性，患病率长期居高不下，为5%~10%[1]，临床主要表现为月经失调、排卵障碍所致不孕、多毛、痤疮和肥胖等，对身心健康和家庭婚姻生活产生诸多负面影响。PCOS发病因素复杂，至今尚未完全明确，且临床表型存在异质性，给临床诊断带来一定难度。PCOS所致排卵障碍是育龄期女性不孕的常见病因，目前促排卵药物是临床治疗PCOS不孕的常用手段，但个体促排卵疗效的差异较大，部分患者对促排卵的反应性较差[2]。血清抗苗勒管激素(anti-Mullerian hormone，AMH)是近些年在妇科生殖疾病领域备受重视的苗勒氏管抑制物，既往报道[3]证实血清AMH与卵泡生长发育以及内分泌激素水平有紧密关联，但AMH下降率在PCOS患者促排卵疗效评估方面的应用报道偏少，其应用价值有待进一步研究。

1 对象与方法

1.1 对象

将2020年1月至2021年9月在海口市妇幼保健院生殖医学中心就诊的85例PCOS患者作为研究对象，记为PCOS组。入选标准：1)满足PCOS的鹿特丹诊断标准[4]；2)年龄≥20且<40岁，对本研究知情且同意，签署知情同意书；3)PCOS继发不孕，患者有生育需求，拟接受促排卵药物治疗，且无使用药物相关禁忌。排除下列情形者：库欣综合征、高催乳素血症、卵巢肿瘤、子宫内膜异位症、甲状腺功能异常或卵泡膜细胞增殖症等疾病者。脱落标准：中途失访或主动退出研究；研究期间未能谨遵医嘱接受促排卵治疗和复查。另选取同期体检的40例同龄健康女性，记为健康组。本组女性月经规律，无生殖系统疾病，近1个月未使用过影响内分泌的相关药物，均同意配合相关检测。本研究获海口市妇幼保健院伦理委

员会批准。

1.2 方法

1.2.1 血清AMH检测方法

PCOS组和健康组均于月经周期第2至4天抽取晨起空腹肘静脉血5 mL，置于无抗凝干燥试管，室温条件下静置约1 h。常规3 000 r/min离心10 min，离心半径15 cm，提取血清样本，−20 ℃冰箱冷存，取样后24 h内完成检测。除促卵泡激素(follicle stimulating hormone，FSH)、黄体生成素(luteinizing hormone，LH)、雌二醇(estradiol，E_2)和睾酮(testosterone，T)常规激素指标外，血清AMH水平采用化学发光免疫分析法检测，仪器为美国Beckman公司UniCel Dxl 800型全自动免疫分析仪及配套试剂，严格按说明书完成测定。正常年轻女性的血清AMH参考范围为2.2~6.8 ng/mL。

1.2.2 PCOS促排卵治疗和分组

PCOS患者谨遵医嘱于月经周期第4至5天接受促排卵药物治疗，其中38例使用氯米芬(塞浦路斯Medochemie Ltd.生产；50 mg×10 s)促排卵，口服50 mg/d，每天1次，持续5 d。另外47例使用来曲唑(江苏恒瑞医药；2.5 mg×10片)促排卵，2.5 mg/d，每天1次，持续5 d。治疗后间隔2 d复查AMH和采用阴道彩色超声监测卵泡发育情况，当卵泡成熟(直径≥18 mm)或尿LH检测试纸监测提示LH出现峰值时，肌注人绒毛膜促性腺激素(human chorionic gonadotropin，HCG)10 000 U诱发排卵。排卵标准[5]：B超检查提示正常排卵，血清孕酮(progesterone，P)>5 ng/mL。依据促排卵药物治疗的反应性，将PCOS组分成排卵组与无排卵组。

1.3 观察指标

主要比较PCOS组(促排卵治疗前)与健康组血清AMH水平；比较排卵组与无排卵组促排卵治疗前后血清AMH水平。AMH下降率=(治疗前AMH−治疗后AMH)/治疗前AMH×100%。

1.4 统计学处理

邀请专业统计人员采用SPSS 21.0进行统计分析，计量资料经Levene法和Kolmogorov-Smirnov法检验，均符合正态分布和方差齐性，以均数±标准差($\bar{x}\pm s$)表示，两组间比较采用独立t检验，组内治疗前后采用配对t检验。计数资料用例(%)表示，组间比较用χ^2检验。两个连续变量的相关性采用Pearson法分析。PCOS患者血清AMH水平对PCOS临床诊断和促排卵疗效的诊断评估效能采用受试者工作特征(receiver operating characteristic，ROC)曲线分析。P<0.05为差异有统计学意义。

2 结果

2.1 PCOS组和健康组血清AMH水平和相关指标比较

PCOS组肥胖比重和血清AMH、LH、T水平明显均高于健康组(均P<0.05)，组间年龄、FSH、E_2比较差异均无统计学意义(均P>0.05，表1)。

2.2 PCOS组血清AMH与4项激素指标的相关性

PCOS组血清AMH与FSH、E_2无相关性(P>0.05)，与LH、T均呈正相关(分别r=0.692、0.516，均P<0.05)。

2.3 血清AMH对PCOS的诊断价值

ROC曲线分析结果显示：血清AMH诊断PCOS的曲线下面积(area under curve，AUC)为0.814[95%CI：0.704~0.925]，最佳截断值为6.83 ng/mL，敏感度为84.71%，特异度为72.50%，准确度为80.80%(图1)。

表1 PCOS组和健康组血清AMH水平和相关指标比较

Table 1 Comparison of serum AMH level and related indexes between PCOS group and healthy group

组别	n	年龄/岁	肥胖/[例(%)]	AMH/(ng·mL^{-1})	FSH/(mU·mL^{-1})	LH/(mU·mL^{-1})	E_2/(pg·mL^{-1})	T/(nmol·mL^{-1})
健康组	40	27.96 ± 4.02	6 (15.00)	4.52 ± 1.07	5.92 ± 1.14	4.74 ± 1.36	39.57 ± 8.53	1.42 ± 0.38
PCOS组	85	28.04 ± 3.79	42 (49.41)	7.56 ± 1.18	5.57 ± 1.18	8.35 ± 2.01	42.06 ± 9.79	1.67 ± 0.42
χ^2/t		0.108	13.617	13.832	1.564	10.293	1.380	3.198
P		0.914	<0.001	<0.001	0.121	<0.001	0.170	0.002

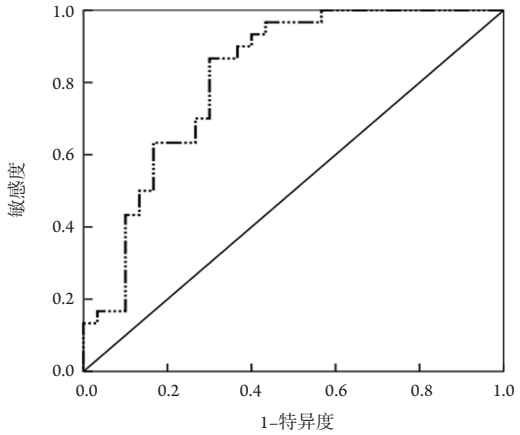

图1 血清AMH对PCOS的诊断效能

Figure 1 Diagnostic efficacy of serum AMH for PCOS

2.4 PCOS 组促排卵疗效及亚组血清 AMH 水平比较

PCOS组促排卵治疗后血清AMH明显低于治疗前[(5.20±1.06) ng/mL vs (7.56±1.18) ng/mL]，差异有统计学意义(t=13.717，P<0.05)。PCOS组治疗后排卵者67例，排卵率为78.82%，其中使用氯米芬促排卵29例，排卵率76.32%，使用来曲唑促排卵38例，排卵率84.44%。两种促排卵方案的排卵率比较无明显差异(χ^2=0.259，P>0.05)。排卵组治疗前后血清AMH均低于无排卵组，治疗后血清AMH下降率高于无排卵组，差异有统计学意义(P<0.05，表2)。

表2 排卵组与无排卵组治疗前后血清AMH比较

Table 2 Comparison of serum AMH between ovulation group and anovulation group before and after the treatment

组别	n	AMH		
		治疗前/($ng\cdot mL^{-1}$)	治疗后/($ng\cdot mL^{-1}$)	下降率/%
排卵组	67	7.31 ± 1.04	4.87 ± 1.10	33.38 ± 5.41
无排卵组	18	8.49 ± 1.35	6.43 ± 1.06	24.26 ± 4.80
t		4.512	5.381	6.252
P		<0.001	<0.001	<0.001

2.5 血清 AMH 对 PCOS 患者促排卵疗效的评估价值

绘制血清AMH基线值和AMH下降率评估PCOS患者促排卵疗效的ROC曲线(排卵=1，无排卵=0)，结果显示：血清AMH下降率、血清AMH基线值评估促排卵疗效的AUC分别为0.877(95%CI：0.789~0.964)、0.793(95%CI：0.670~0.916)，二者AUC经秩和检验，差异有统计学意义(Z=2.732，P<0.05)。血清AMH下降率评估促排卵疗效的最佳截断值为29.32%，敏感度为83.58%，特异度为83.33%，准确度为83.53%(图2)。

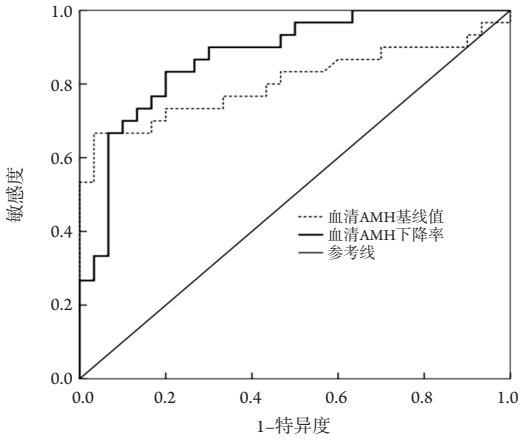

图2 血清AMH对促排卵疗效的评估价值

Figure 2 Value of serum AMH in evaluating the efficacy of ovulation induction

3 讨论

近些年AMH与卵泡生长发育和内分泌激素的关系引起关注，成为生殖内分泌疾病临床诊断和治疗评估研究的重要指标[6]，深入挖掘AMH辅助临床诊断PCOS以及AMH下降率评估促排卵疗效的价值具有重要意义。

AMH是转化生长因子β(transforming growth factor-β，TGF-β)超家族成员之一，由早期卵泡颗粒细胞分泌，其作用主要是抑制原始卵泡的募集，调低生长卵泡对FSH的敏感度，在卵泡生长发育过程中扮演重要角色。Foroozanfard等[7]报道指出，AMH作为女性卵泡募集的重要调节因子，积极参与卵泡发育和生殖激素的合成分泌，不仅可作为卵巢储备功能的评估指标，还在预测卵巢对超排卵的反应性方面有积极作用。本研究显示：PCOS组血清AMH明显高于健康组，AMH与LH、T呈正相关，与陈颖等[8]和Makolle等[9]报道相符。本研究ROC曲线分析显示：AMH诊断PCOS的AUC为0.814，敏感度、特异度分别为84.71%、72.50%，最佳截断值为6.83 ng/mL。这与唐婕等[10]报道的6.739 ng/mL接近，表明血清AMH可作为临床诊断PCOS的重要生化指标。早期窦状卵泡数量是影响AMH水平的主要原因，PCOS患者血清AMH受窦状卵泡数量明显增多影响而显著

很高[11]。有报道[12]指出，超声检查下可见PCOS患者≤4 mm的小窦状卵泡数量异常增多，是正常同龄女性的2~3倍，且血清AMH高表达者上述超声征象表现更为突出。AMH与LH、T的相关性表明AMH与PCOS患者高雄激素血症(hyperandrogenemia，HA)密切相关，AMH升高可能进一步加重PCOS局部高雄激素环境和内分泌激素分泌紊乱，也增加了促排卵治疗的难度[13-14]。

目前血清AMH与PCOS患者促排卵疗效的关系有待深入证实。本研究发现PCOS组治疗后血清AMH水平明显下降，本研究所用氯米芬和来曲唑均为常用一线促排卵药物，二者促排卵的效果接近，不同药物方案对促排卵疗效的影响可忽略不计。本研究显示：排卵组治疗前后血清AMH水平均明显低于无排卵组，AMH下降率(33.38±5.41)%，也显著低于无排卵组的(24.26±4.80)%，提示AMH较高者或治疗后AMH下降不明显者的反应性可能较差。有报道[15]依据AMH的四分位数对216例PCOS患者进行分组，发现AMH基础水平越高，排卵率和临床妊娠率越低。但该报道同时发现，血清AMH基础水平预测促排卵疗效的AUC仅为0.620，表明血清AMH基础水平对PCOS患者促排卵疗效的预测评估价值有限。AMH下降率与促排卵疗效的关系鲜有报道，本研究创新性应用血清AMH下降率评估促排卵疗效，具有一定新颖性，ROC曲线显示AMH下降率评估促排卵反应性的AUC为0.877，明显高于血清AMH基线值的0.793，表明计算治疗前后AMH下降率更能准确评估PCOS患者促排卵的反应性，AMH下降不明显者可考虑增加药物用量、延长治疗周期或更换促排卵药物种类等处理，提高排卵率和临床妊娠率[16]。

综上可知，血清AMH可为PCOS临床诊断和促排卵疗效评估提供可靠依据，而且AMH具有检测方便、敏感性好等优点。本研究为PCOS临床诊断和促排卵疗效提供了AMH的参考界值，但也存在样本量偏少、未能统计临床妊娠等不足，后续有待优化和深入探讨。

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