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多囊卵巢综合征患者血清抗苗勒管激素与肥胖、胰岛素抵抗程度的相关性分析*

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摘要 目的:探讨多囊卵巢综合征(polycystic ovary syndrome, PCOS)患者血清抗苗勒管激素(anti-Müllerian hormone, AMH)水平与肥胖、胰岛素抵抗(insulin resistance, IR)程度的相关性。**方法:**选择在我院生殖中心就诊的 139 名 PCOS 患者为研究组,并以月经周期正常、因输卵管因素或男性因素导致不孕者 48 名作为对照组。检测和比较 PCOS 患者的血清 AMH、性激素水平及代谢指标,分析血清 AMH 水平与 PCOS 患者肥胖、胰岛素抵抗程度的关系。**结果:**PCOS 组患者体质量指数(body mass index, BMI)、黄体生成素(luteinizing hormone, LH)、睾酮(testosterone, T)、垂体泌乳素(pituitary prolactin PRL)、空腹血糖(fasting plasma glucose, FPG)、空腹胰岛素(fasting insulin, FINS)、稳态模型胰岛素抵抗指数(homeostasis models assessment-insulin resistance index, HOMA-IR)的水平均显著高于对照组($P<0.05$),PCOS 组和对照组年龄、卵泡刺激素(follicle stimulating hormone, FSH)比较差异无统计学意义($P>0.05$)。PCOS 各表型组的血清 AMH 浓度、LH/FSH 比值均明显高于对照组 ($P<0.05$)。肥胖组患者的 AMH 浓度低于正常体重组, BMI、FPG、FINS、HOMA-IR、甘油三酯(triglycerides, TG)水平均高于正常体重组, LH、LH/FSH、高密度脂蛋白(high density lipoprotein, HDL-C)水平均低于正常体重组($P<0.05$)。高 HOMA-IR 组患者的血清 AMH 浓度、LH、LH/FSH 水平均明显低于低 HOMA-IR 组, BMI、T、FPG、FINS、TG、低密度脂蛋白(low density lipoprotein, LDL-C)水平均高于低 HOMA-IR 组($P<0.05$)。PCOS 患者血清 AMH 浓度和 BMI 及 HOMA-IR 均存在显著负相关。**结论:**PCOS 患者血清的 AMH 水平较对照组明显升高,与其肥胖、胰岛素抵抗(IR)程度呈显著负相关。

关键词:多囊卵巢综合征;抗苗勒管激素;肥胖;胰岛素抵抗

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Analysis of the Relationship between Serum Anti-Müllerian Hormone Level and Obesity and Insulin Resistance in Patients with Polycystic Ovary Syndrome*

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ABSTRACT Objective: To investigate the correlation of anti-müllerian hormone (AMH) level with the severity of obesity, insulin resistance (IR) in polycystic ovary syndrome (PCOS). **Methods:** 139 cases of PCOS patients who admitted in the reproductive center of our hospital were selected as the study group, and the patients with normal menstrual cycle, fallopian tube factor or male factors were selected as the control group. The serum AMH, sex hormone levels and metabolic index of PCOS patients were detected and compared, and the relationship between serum AMH level and the severity of obesity and insulin resistance in patients with PCOS were analyzed. **Results:** The body mass index (BMI) of study group (body mass index, BMI), luteinizing hormone, luteinizing hormone, LH), testosterone (testosterone, T), pituitary prolactin (pituitary prolactin PRL), fasting glucose, fasting plasma glucose, FPG), fasting insulin, fasting insulin and FINS), steady-state model of insulin resistance index (homeostasis models assessment - insulin to hold the index, HOMA - IR) levels were significantly higher than those of the control group ($P<0.05$), and the age, FSH (follicle stimulating hormone, FSH) showed no statistically significant difference between two groups ($P>0.05$). The serum AMH concentration and LH/FSH ratio of each phenotype group were significantly higher than those in the control group ($P<0.05$). The AMH concentration was lower in the obese patients than those patients with normal body weight, while the BMI, FPG, FINS, HOMA-IR, triglycerides (triglycerides, TG) levels were higher than in the normal weight group, the LH, LH/FSH, high-density lipoprotein cholesterol (HDL-C) levels were lower than those of the normal weight group ($P<0.05$). The serum AMH concentration, LH, and FSH levels of patients with high HOMA-IR group were significantly lower than those with lower HOMA-IR, and the levels of BMI, T, FPG, FINS, TG, and low-density lipoprotein (LDL-C) were

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all higher than those with lower HOMA-IR($P<0.05$). There was significantly negative correlation of serum AMH concentration with BMI and HOMA-IR of PCOS patients. **Conclusion:** The serum AMH level of PCOS patients was significantly upregulated, and it was significantly negatively correlated with the degree of obesity and IR.

Key words: Polycystic ovary syndrome; Anti-Müllerian hormone; Obesity; Insulin resistance

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前言

多囊卵巢综合征(PCOS)是女性最常见的内分泌紊乱性疾病,其主要表现为多因子、多源性和多系统内分泌失调,是导致无排卵性不孕的常见病因。目前,不同国家地区的育龄女性PCOS的患病率不同,据报道^[1]为5%-20%,临床表现以月经紊乱、排卵稀发、高雄性激素血症的临床或生物化学征象、卵巢多囊形态改变为特征,常伴有肥胖和胰岛素抵抗。近年来,人们对于这种疾病的认识越来越多,对这种疾病的长期联系有了更深入的了解,包括代谢综合征及其远期并发症,以及患有多囊卵巢综合征女性的子宫内膜癌和胰岛素抵抗型糖尿病等特定疾病的风险。

抗苗勒管激素(AMH)由颗粒细胞分泌,在直径小于4 mm的小窦状卵泡中表达最强。PCOS患者血清AMH浓度较正常女性高出2-3倍,高浓度的AMH可能为引起PCOS患者不排卵的主要原因^[2]。研究表明^[3]血清AMH浓度可评估PCOS患者的严重程度和预后。目前,PCOS患者AMH浓度、内分泌及代谢水平的关系已经成为临床研究的热点问题。由于肥胖女性较正常体重相比,更容易发生排卵障碍、异常子宫出血、不孕症、流产、妊娠期高血压疾病等^[4,5]。关于肥胖与正常体重的PCOS患者血清AMH水平变化间是否存在差异结论尚未统一。因此,本研究通过探讨PCOS患者AMH水平与BMI及HOMA-IR指数的关系,旨在评估PCOS患者血清AMH水平与肥胖及胰岛素抵抗的相关性,为今后的临床诊疗提供参考依据。

1 资料和方法

1.1 研究对象

选取2017年4月至2017年10月在我院生殖中心就诊的139例PCOS患者,年龄18-35岁,平均年龄(25.39 ± 4.33)岁。根据2003年PCOS鹿特丹^[6]诊断标准:①排卵稀发或无排卵(OA);②高雄激素血症(HA)或高雄性激素临床表现(如多毛、痤疮等);③卵巢多囊样改变(PCO),盆腔超声显示一侧或双侧卵巢2~9 mm的小卵泡 ≥ 12 个,和(或)卵巢体积 $\geq 10\text{ cm}^3$;只要具备以上3项中2项作为纳入标准。排除标准:①既往盆腔手术史;②I型、II型糖尿病、Cushing综合征、分泌雄激素的肿瘤和甲状腺功能异常;③合并严重的心血管、肝肾功系统原发性疾病;④入组前3月均未接受过任何药物治疗。对照组根据促卵泡激素(FSH)和雌二醇(E2)水平排除卵巢储备能力低下者。所有患者均充分知情并同意参加本次研究。

1.2 分组

研究组:将139名PCOS患者分为3组:①PCO+OA+HA(组1):67例;②OA+HA(组2):30例;③OA+PCO(组3):42例,比较各组间AMH与激素及代谢指标的差异。

将PCOS患者按BMI分为肥胖组($\text{BMI}\geq 25\text{ Kg/m}^2$)49例、非肥胖组($\text{BMI}<25\text{ Kg/m}^2$)90例,用于研究不同BMI指数PCOS患者临床指标的差异。

将PCOS患者按HOMA-IR指数的中位数分组,高HOMA-IR指数组($\text{HOMA-IR}\geq 2.62$)70例,低HOMA-IR指数组($\text{HOMA-IR}<2.62$)69例,用于研究不同HOMA-IR的PCOS患者临床指标。

对照组:纳入月经周期正常、因输卵管因素或男方因素导致不孕者48名作为对照组。

1.3 测量指标

①基本病史:年龄、身高、体质量、体质量指数(BMI)、有无抽烟酗酒史、家族遗传史、患不孕症年限、生育史及月经史。 $\text{BMI}=\text{体质量(Kg)}/\text{身高}(\text{m}^2)$ 。②性激素指标:抗苗勒管激素(AMH)、卵泡刺激素(FSH)、黄体生成素(LH)、睾酮(T)、垂体泌乳素(PRL)。所有人组均清晨空腹,于月经周期第2-3天或黄体酮撤退出血后2-3天,无规律月经或闭经者采取任意时间,静脉采血,分离血清,罗氏化学发光法检测性激素。采用酶联免疫吸附试验(ELISA)测定血清AMH水平(美国RD公司)。③血糖测定:空腹血糖(FPG)和空腹胰岛素(FINS), $\text{HOMA-IR}=\text{FPG}\times\text{FINS}/22.5$ 。④血脂测定:总胆固醇(CHOL)、甘油三酯(TG)、高密度脂蛋白(HDL-C)、低密度脂蛋白(LDL-C)(化学发光法)。

1.4 统计学分析

采用SPSS 21.0软件进行统计分析,计量资料采用均数 $\pm$ 标准差($\text{mean}\pm\text{SD}$)表示,组间比较采用t检验或非参数检验。血清AMH水平与各临床指标间关系采用Pearson相关分析, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组间测量指标的比较

PCOS组患者BMI、LH、T、PRL、FPG、FINS、HOMA-IR的水平均显著高于对照组($P<0.05$),PCOS组和对照组年龄、FSH比较差异无统计学意义($P>0.05$)。PCOS各表型组的血清AMH浓度、LH/FSH比值均明显高于对照组($P<0.05$)。见表1、表2。

2.2 不同BMI指数PCOS患者临床指标的比较

肥胖组PCOS患者的血清AMH浓度明显低于非肥胖组($P<0.05$),BMI、FPG、FINS、HOMA-IR、TG水平均高于非肥胖组($P<0.05$)。肥胖组患者LH、LH/FSH、HDL-C水平均低于正常体重组($P<0.05$)。两组患者的年龄、FSH、T、PRL、CHOL、LDL-C比较差异无统计学意义($P>0.05$)。见表3。

2.3 不同HOMA-IR的PCOS患者临床指标的比较

139例PCOS患者的HOMA-IR指数为0.96-31.76,中位数为2.62。高HOMA-IR组患者的AMH浓度、LH、LH/FSH水平均低于低HOMA-IR组($P<0.05$),BMI、T、FPG、FINS、TG、

LDL-C 水平均高于低 HOMA-IR 组(P<0.05)。两组患者的年龄、 FSH、PRL、CHOL、HDL-C 差异无统计学意义(P>0.05)。见表 4。

表 1 各组一般情况的比较
Table 1 Comparison of the general situation among different groups

Indicators	All patients(n=188)	PCOS(n=139)	Controls(n=49)
Age	25.76± 4.40	25.19± 4.31	26.23± 4.01
BMI	22.19± 2.11	23.61± 4.44	21.92± 1.89
Family history	5.85(11)	6.47(9)	4.08(2)
Smoking	1.06(2)	1.06(2)	0
Characteristic/Duration of infertility			
>2-4 years	81.91(154)	82.73(115)	79.59(39)
5 or more years	18.09(34)	17.27(24)	20.41(10)

表 2 PCOS 各种表型和对照组间血清 AMH 水平及其他指标比较

Table 2 Comparison of the serum AMH levels and other indicators between the various phenotypes of PCOS patients and control group

Indicators	Group 1	Group 2	Group 3	Control group	P
N	67	30	42	49	
Age	25.50± 4.40	25.12± 4.00	25.40± 4.51	26.23± 4.01	0.537
BMI/(Kg/m ²)	23.65± 4.33 ^d	24.73± 5.09 ^d	23.03± 3.87	21.92± 1.89 ^{ab}	0.002
AMH/(ng/mL)	8.80± 3.55 ^{bcd}	7.07± 3.86 ^{acd}	8.74± 3.14 ^{abd}	1.96± 0.92 ^{abc}	0.000
FSH/(mIU/mL)	5.47± 1.85	5.93± 2.20	6.25± 1.56	6.93± 3.86	0.129
LH/(mIU/mL)	14.77± 6.99 ^{bd}	12.29± 6.51 ^{ab}	14.38± 7.62 ^d	7.04± 5.41 ^{abc}	0.000
LH/FSH	2.78± 1.72 ^{bcd}	2.26± 1.26 ^{acd}	2.29± 0.99 ^{abd}	1.09± 0.66 ^{abc}	0.000
T/(ng/mL)	0.72± 0.36 ^{cd}	0.71± 0.36 ^{cd}	0.38± 0.09 ^{ab}	0.26± 0.11 ^{ab}	0.000
RPL/(ng/mL)	19.01± 18.52 ^d	18.40± 12.20	16.60± 7.76 ^d	12.72± 6.36 ^{ac}	0.011
FPG/(mmol/mL)	5.26± 0.61 ^d	5.37± 0.64 ^d	5.25± 0.52 ^d	4.95± 0.57 ^{abc}	0.006
FINS/(mIU/L)	16.79± 15.72 ^d	18.91± 17.76 ^{cd}	12.05± 7.53 ^b	10.30± 2.59 ^{ab}	0.000
HOMA-IR	4.10± 4.36 ^d	4.76± 5.17 ^d	2.88± 2.04	2.29± 0.75 ^{ab}	0.000

Note: ^aP<0.05 vs group 1, ^bP<0.05 vs group 2, ^cP<0.05 vs group 3, ^dP<0.05 vs Controls; Group 1: PCO+OA+HA; Group 2: OA+HA; Group 3: PCO+OA.

表 3 不同 BMI 指数 PCOS 患者临床指标的比较

Table 3 Comparison of the clinical indicators between PCOS patients with different BMI

Indicators	Obese group	Normal weight group	p
N	49	90	
Age	26.31± 4.36	24.87± 4.24	0.062
BMI/(Kg/m ²)	28.73± 2.98	21.02± 2.30	0.000
AMH/(ng/mL)	7.10± 3.16	9.20± 3.52	0.001
FSH/(mIU/mL)	5.51± 1.51	5.97± 1.96	0.175
LH/(mIU/mL)	10.25± 5.50	16.34± 6.70	0.000
LH/FSH	1.94± 0.95	2.85± 1.13	0.000
T/(ng/mL)	0.59± 0.18	0.63± 0.40	0.521
PRL/(ng/mL)	17.53± 10.99	18.49± 16.46	0.936
FPG/(mmol/mL)	5.57± 0.61	5.12± 0.51	0.000
FINS/(mIU/L)	25.93± 20.00	10.09± 3.18	0.000
HOMA-IR	6.61± 5.71	2.33± 0.86	0.000
CHOL/(mmol/mL)	4.22± 0.76	4.10± 0.73	0.318
TG/(mmol/mL)	1.83± 1.15	1.31± 0.76	0.005
HDL-C/(mmol/mL)	1.29± 0.45	1.47± 0.35	0.015
LDL-C/(mmol/mL)	2.40± 0.80	2.17± 0.74	0.087

表 4 不同 HOMA-IR 的 PCOS 患者临床指标的比较

Table 4 Comparison of the clinical indicators between PCOS patients with different HOMA-IR

Indicators	High-HOMA-IR	Low-HOMA-IR	p
N	70	70	
HOMA-IR	5.74± 4.92	1.90± 0.42	0.000
Age	25.58± 4.23	25.12± 4.40	0.532
BMI/(Kg/m ²)	26.44± 4.31	21.04± 2.66	0.000
AMH/(ng/mL)	7.49± 3.11	9.32± 3.71	0.002
FSH/(mIU/mL)	5.40± 1.65	6.15± 1.93	0.065
LH/(mIU/mL)	11.50± 5.44	16.69± 7.69	0.000
LH/FSH	2.48± 1.10	2.81± 1.17	0.004
T/(ng/mL)	0.68± 0.44	0.54± 0.16	0.019
PRL/(ng/mL)	18.57± 12.82	16.21± 7.54	0.192
FPG/(mmol/mL)	5.52± 0.57	5.01± 0.49	0.000
FINS/(mIU/L)	22.80± 11.30	8.50± 1.66	0.000
CHOL/(mmol/mL)	4.22± 0.74	4.06± 0.73	0.214
TG/(mmol/mL)	1.80± 1.07	1.18± 0.65	0.000
HDL-C/(mmol/mL)	1.35± 0.42	1.46± 0.36	0.090
LDL-C/(mmol/mL)	2.39± 0.79	2.11± 0.71	0.027

2.4 PCOS 患者血清 AMH 浓度与 BMI、HOMA-IR 的相关性

将 PCOS 患者的血清 AMH 和 BMI、HOMA-IR 行 Pearson 相关分析,并做散点图(见图 1,2),结果显示 PCOS 患者血清 AMH 浓度和 BMI 存在显著负相关($r=-0.284$, $P=0.001$),直线回

归分析显示两者间有直线关系 ($R^2=0.088$)。血清 AMH 浓度和 HOMA-IR 亦存在明显负相关($r=-0.281$, $P=0.001$),直线回归分析显示两者间有直线关系($R^2=0.088$)。

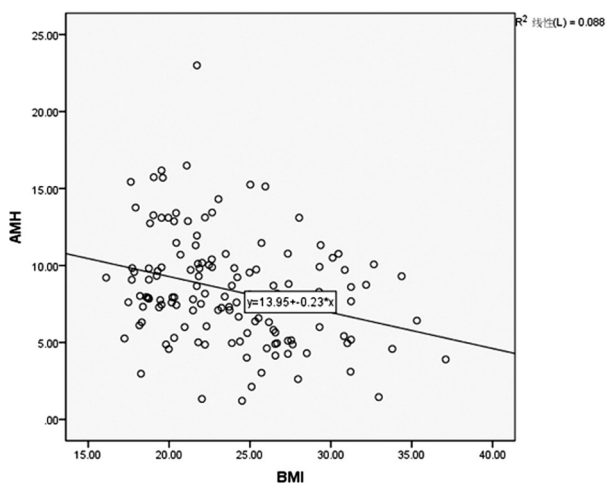


图 1 PCOS 患者血清 AMH 与 BMI 间的直线相关散点图

Fig. 1 Linear correlation scatter diagram of serum AMH and BMI of PCOS patients

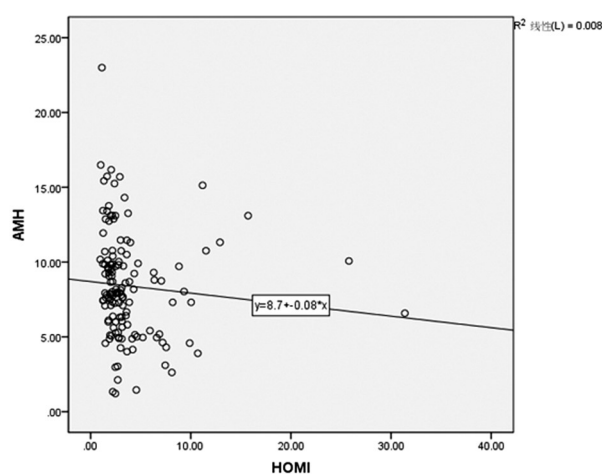


图 2 PCOS 患者血清 AMH 与 HOMA-IR 间的直线相关散点图

Fig.2 Linear correlation scatter diagram of serum AMH and HOMA-IR of PCOS patients

3 讨论

本研究首先根据多囊卵巢综合征及对照组 AMH 水平特点进行组间比较,结果显示血清 AMH 水平最高的是组 1 (PCO+OA+HA),这与 Budi 等^[7]研究结果一致。总 PCOS 患者的血清 AMH 水平较对照组高 3 倍($P=0.000$),提示 AMH 与窦卵泡数显著增多相关。血清 AMH 浓度可作为 PCOS 良好的诊断指标,并且在 IVF 助孕技术中起到举足轻重的作用^[8]。在本研究的 PCOS 患者分组中,组 1 的血清 AMH 水平最高,组 2 的

AMH 水平最低,这两组的区别是组 2 中没有 PCO 征,这也说明了 PCO 征对 AMH 水平的影响最大,即验证了 AMH 在始基卵泡中无表达,而初级卵泡的颗粒细胞能微量表达,在直径小于 4 mm 的小窦状卵泡中表达最强,在直径 4-9 mm 的窦卵泡中表达逐渐降低,在直径大于 9 mm 的卵泡中几乎无表达。这也与目前大量研究相符^[9,10],PCOS 患者血清 AMH 水平较正常女性高,这不仅是因为 PCOS 患者较正常女性的窦卵泡数增多,更为重要的因素是每个卵泡生成会增加颗粒细胞的数量,故血清 AMH 表达量也随之升高。

多囊卵巢综合征患者除排卵障碍、高雄激素血症外,代谢功能障碍也是其主要特征,主要表现为肥胖、胰岛素抵抗(IR),维生素D缺乏、心血管疾病等,同时造成远期并发症。肥胖会导致和加重HPO轴功能紊乱和胰岛素抵抗、高胰岛素血症。高胰岛素与LH协同作用,增加泡膜细胞雄激素的生成;低生长激素状态又抑制了肥胖者脂肪溶解,更加重了肥胖。PCOS患者的血清AMH水平升高是否与体重指数(BMI)有关还存在很大争议。Moamar等^[11]认为肥胖可能对促性腺激素的释放有抑制作用,从而抑制LH和卵泡发展,导致AMH水平增高,并且减肥成功者AMH水平下降更明显,提示PCOS患者的血清AMH水平与BMI呈明显正相关。2017年, Kim等^[12]最新报道通过测定46名肥胖的PCOS女性和43名肥胖的非PCOS女性血清AMH水平,发现肥胖PCOS女性AMH水平明显高于肥胖非PCOS女性。但有根据PCOS患者的横断面研究显示AMH水平与BMI呈负相关^[13,14]。同时,也有报道提出两者间无相关性^[15]。本研究分析了总PCOS患者血清AMH浓度与BMI、胰岛素抵抗(HOMA-IR),结果显示两者均呈负相关。同时,PCOS组患者肥胖组血清AMH水平显著低于正常体重组,这与Vicky^[16]等研究结果一致。有研究显示^[17,18]LH可以使PCOS患者颗粒细胞中分泌更多的AMH,LH升高和LH/FSH比值的异常改变会诱使卵泡膜细胞活性增强,从而导致卵泡细胞合成雄激素增多,窦卵泡募集亢进,最终卵泡成熟障碍和闭锁。也有一些研究表明^[19]抑制素B的分泌的变化可能导致FSH水平的相对不足,LH的过度产生。LH/FSH比值升高多见于正常体重患者,肥胖患者因瘦素、脂联素等因素对中枢LH的抑制作用,导致LH/FSH比值可能处于正常标准或降低。本研究显示总PCOS患者的LH、LH/FSH升高,肥胖组LH、LH/FSH明显低于非肥胖组,与上述研究结果一致。因此,LH是使PCOS患者AMH水平升高的一个因素,肥胖组LH相对较低,导致AMH水平低于正常体重组。

胰岛素抵抗(IR)和高胰岛素血症是慢性高雄激素性不排卵女性的重要特征,显著的胰岛素抵抗与高雄激素和黑棘皮病有关,并在多囊卵巢综合征中独立发生肥胖,尤其是腹型肥胖^[20]。有研究显示^[21,22]AMH基因多态性与PCOS患者胰岛素抵抗与雄激素水平有关。胰岛素能抑制性激素结合球蛋白的肝脏合成,这是与睾酮结合的关键循环蛋白,从而增加了雄激素指数的比例。肥胖的患者多有IR或高胰岛素血症,同时可发生血管内皮功能障碍,代谢性疾病和心血管风险将明显增加^[23]。几项研究表明^[24,25]多达60%-90%的PCOS女性会出现胰岛素抵抗(IR),伴随着腹部脂肪的增加,会加重IR。2017年,Wiweko等^[26]研究证明用胰岛素增敏剂和二甲双胍治疗PCOS患者能够有效的降低胰岛素水平,同时可降低PCOS患者血清中AMH浓度。2015年,Avin等^[27]通过对PCOS患者不同表型的胰岛素抵抗的代谢综合症的病例对照观察研究提出AMH水平与IR呈正相关。但2014年Pinola等^[28]研究发现AMH水平与IR呈负相关。高胰岛素血症的PCOS患者胰岛素刺激类固醇产生,同时损害颗粒细胞中糖代谢,这就可能解释AMH浓度与雄激素水平呈正相关,但与IR呈负相关^[29]。在本研究中,PCOS患者AMH浓度与HOMA-IR呈负相关,高HOMA-IR组PCOS患

者血清AMH水平显著低于低HOMA-IR组,肥胖组的空腹胰岛素水平及HOMA-IR显著高于正常体重组,与上述研究相同。本次研究数据显示胰岛素抵抗可使AMH水平降低是由于肥胖使AMH下降的结果,研究前后一致。

综上所述,PCOS患者血清的AMH水平较对照组明显升高,PCO征是影响AMH水平最显著的因素。PCOS患者血清AMH水平与肥胖、胰岛素抵抗(IR)呈负相关,肥胖组患者AMH水平显著低于非肥胖组,高HOMA-IR组AMH水平明显低于低HOMA-IR组。肥胖和IR可能与PCOS患者AMH水平下降有关。因此,临床医生在解决不孕不育方面的同时,也需关注解决肥胖和IR的问题。目前,血清AMH水平与PCOS患者各指标间关系的研究结果仍不尽相同,之间存在差异可能与PCOS患者存在高度异质性,不同国家及地区、不同种族PCOS患者的临床表现、内分泌指标及代谢水平都存在较大差异,这可能与不同种族的遗传差异、营养、环境等因素有关^[30]。因此,还需要大量的研究用来更全面的阐明其基因水平的关系。

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