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GONADAL PHYSIOLOGY AND DISEASE

Different diagnostic power of anti-Mullerian hormone in evaluating women with polycystic ovaries with and without hyperandrogenism

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Abstract
Purpose The aim of this study is to compare the secretory profiles and diagnostic power of anti-Mullerian hormone (AMH) for the PCOS patient with and without hyperandrogenism.
Methods One hundred and thirty-one PCOS patients with oligomenorrhea or amenorrhea were recruited into the study. Sixty-two and sixty-nine patients had and did not have hyperandrogenism (HA+) hyperandrogenism (HA−), respectively. Sera were collected for determining the levels of AMH, basal sexual hormones, glucose and lipid metabolic indicators.
Results The AMH serum levels of PCOS patients were significantly higher than the control group, with the highest AMH serum level in the HA+ group. The cut-off value for predicting PCOS patients of all types was 3.92 ng/mL, with a sensitivity of 65 %, and specificity of 62 %. The cut-off value for predicting PCOS patients in the HA+ group was 4.23 ng/mL, with a sensitivity of 82 %, and specificity of 64 %. The cut-off value for predicting PCOS patients in the HA− group was 3.76 ng/mL, with a sensitivity of 64 %, and specificity of 62 %. In the HA+ group, AMH was negatively associated with FSH and positively associated with LH. In the HA− group, AMH was negatively associated with HDL and positively associated with BMI, fasting glucose and LDL.
Conclusions AMH is only suitable for predicting the PCOS patients with hyperandrogenism. The diagnostic power of AMH is limited when used to predict patients without hyperandrogenism. It reflects the differences in pathophysiology and severity of disrupted folliculogenesis between the two subtypes.

Keywords Anti-Mullerian hormone · Polycystic ovary syndrome · Hyperandrogenism · Folliculogenesis

Capsule AMH is suitable for predicting the PCOS patients with hyperandrogenism and not suitable for the patients without hyperandrogenism, thus reflecting the differences in pathophysiology between the two subtypes.

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common gynecologic endocrine diseases. According to the Rotterdam diagnostic criteria established in 2003, patients can be diagnosed with PCOS if at least two of three conditions are met, as follows: 1) oligomenorrhea or amenorrhea; 2) clinical and/or biological hyperandrogenism; 3) polycystic ovaries and/or an ovarian volume >10 ml [26]. PCOS consists of multiple clinical subtypes based on the diagnostic criteria. In addition, PCOS can be caused by complex factors especially hyperandrogensim [21]. Therefore, the various etiologies of PCOS also result in the heterogeneity of the disease [3, 5, 6].

The dimeric glycoprotein anti-Mullerian hormone (AMH) is a member of the transforming growth factor-β superfamily [9]. In males, AMH is produced by Sertoli cells and induces Mullerian duct degeneration. In females, AMH is produced by granulosa cells from preantal and small antral follicles. AMH plays an important role in inhibiting initial and selective follicular growth [31]. The serum level of AMH can be used as a sensitive marker for evaluating ovarian reserve due to its close association with the number of antral follicles [14, 30].

The AMH level is significantly enhanced in the sera of women with PCOS because of the increased number of

antral follicles and excessive production of granulosa cells [15, 22, 27]. Thus, AMH has been recommended as a diagnostic marker for PCOS in recent years [4]. Pigny et al. [24] suggested AMH to be a good marker for the diagnosis of PCOS. According to Pigny et al. [24], the diagnostic specificity reached 92 % and the sensitivity reached 67 % if a serum level of 60 pmol/L was set as the cut-off value. However, Li et al. [17] reported that the diagnostic specificity was only 70 % and the sensitivity was only 61.7 % when AMH was used for the diagnosis of PCOS patients. Hart et al. [13] reported that the specificity of AMH in predicting PCOS in adolescent patients was <70 % and the sensitivity was only 50 %.

Actually, the heterogeneity of the disease is considered to be the primary basis for inconsistencies when AMH was used as a diagnostic marker for PCOS. Hyperandrogenism has been confirmed in previous studies as the primary etiology of PCOS. In many cases, women with PCOS are often differentiated as subtypes with or without hyperandrogenism [1, 2]. The purpose of the current study was to compare the AMH secretory profiles and diagnostic power between the two main PCOS subtypes.

Materials and methods

One hundred and thirty-one women diagnosed with PCOS according to the Rotterdam consensus were recruited into the study. All of the patients had oligomenorrhea or amenorrhea, and at least 12 follicles 2–9 mm in diameter per ovary. Sixty-two of the patients had hyperandrogenism, as defined by a modified Ferriman and Gallwey score >6, severe acne/seborrhea, a testosterone level >0.7 ng/ml, corresponding to the mean +2 SD control subjects, and designated as PCOS patients with hyperandrogenism (HA+). Sixty-nine patients had normal androgen levels and no clinical hyperandrogenism, and designated as PCOS patients without hyperandrogenism (HA−).

Sixty-one women were recruited into the control group with fallopian tube or male factor infertility. The exclusion criteria for this group were as follows: history of menstrual disturbances (cycle length <25 days or >35 days); ovarian volume >10 ml and at least 12 follicles 2–9 mm in diameter per ovary; a modified Ferriman and Gallwey score >6; severe acne/seborrhea; a testosterone level >0.7 ng/ml.

Biochemical parameter assay

Sera were collected from the recruited subjects and separated for biochemical parameter assays in the first 2–3 days of the natural menstrual cycle or progesterone-induced vaginal bleeding. The samples were stored at −20^{O}C until use in the assays. The serum levels of AMH were determined by enzyme-linked immunosorbent assay (ELISA; DSL Inc., Webster, TX, USA), and the intra- and inter-assay variation coefficients were <5 % and 10 %, respectively. Basal sexual hormones, such as FSH, LH, E_2, T, and PRL were measured by an Axsym chemiluminescence detection system (Axsym; Abbott Laboratories, Rungis, France). Fasting blood glucose and insulin levels were determined by the Axsym chemiluminescence detection system. Fasting blood glucose and insulin levels were converted for homeostasis model assessment of insulin resistance (HOMA-IR), and the conversion formula was as follows: fasting glucose × fasting insulin/22.5. Lipid metabolic indicators levels, such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A (Apo-A), and apolipoprotein B (Apo-B) were determined by the Axsym chemiluminescence detection system.

Statistical methods

The data were presented as mean ± sd. One-way analysis of variance of the least significant difference was performed for multiple comparisons of the data between the groups. Receiver operating characteristic (ROC) curves were constructed to examine the diagnostic performance of the AMH serum level to discriminate PCOS patients with or without hyperandrogenism and controls. The area under the curve (AUC) represents the probability of correctly identifying the PCOS subtypes and controls. Sensitivity (Y-axis) against 1-specificity (X-axis) was plotted at each threshold level. Significant relationships between AMH and the various parameters were evaluated by Spearman correlation. All statistical analyses were performed using SPSS11.5 (SPSS, Inc., Chicago, IL, USA), with $P<0.05$ considered as the significant level.

Results

The basal clinical parameters of the subjects are summarized in Table 1. Patient age was not significantly different between the groups. The levels of LH, E_2, and T in the PCOS groups were significantly higher than the control group, with the highest levels in the HA+ group ($P<0.05$). The BMI, fasting glucose and insulin levels, and HOMA-IR in the HA− group were significantly higher than the other groups ($P<0.05$). There were no significant differences in lipid metabolic indicators, such as TG, TC, HDL, LDL, Apo-A, and Apo-B, between the groups.

The AMH levels in the PCOS groups were significantly higher than the control group, with the highest level in the HA+ group ($P<0.05$). The diagnostic power of AMH for different PCOS subtypes is summarized in Table 2. The area under the ROC curve for diagnosing PCOS of all types was 0.68 (0.60–0.76), with a cut-off value of 3.92 ng/mL,

Table 1 Comparison of basal parameters between different groups

Basal parameters	HA+	HA−	Control
N	62	69	61
Age (year)	29.95±4.13	29.22±4.07	30.31±3.83
BMI (kg/m^2)	20.1±5.76^{ab}	23.35±5.22^{c}	20.52±1.58
AMH (ng/ml)	8.41±4.57^{ab}	5.81±3.85^{c}	3.74±2.25
FSH (IU/L)	5.42±1.68	5.17±1.40	5.72±1.52
LH (IU/L)	18.21±5.46^{ab}	7.9±34.00^{c}	4.20±2.02
E_2 (ng/mL)	50.30±27.6^{ab}	41.28±17.07	35.80±12.83
T (nmol/L)	0.93±0.30^{ab}	0.55±0.22	0.51±0.21
PRL (μg/L)	21.50±12.58	18.85±9.32	18.73±10.72
Fasting glucose (mmol/L)	4.80±0.37	5.11±1.23^{c}	4.49±0.59
Fasting insulin (IU/mL)	9.38±4.38^{a}	12.17±6.78	10.53±4.83
HOMA-IR	2.02±0.95^{a}	2.87±2.04^{c}	2.11±1.08
TG (mmol/L)	1.00±0.57	1.26±0.79	1.07±0.71
HDL (mmol/L)	1.59±0.37	1.47±0.36	1.52±0.21
LDL (mmol/L)	2.81±0.59	3.11±0.93	3.05±0.61
TC (mmol/L)	4.63±0.53	4.89±0.96	4.73±0.64
APO-A (g/L)	1.60±0.30	1.54±0.32	1.66±0.27
APO-B (g/L)	0.72±0.17	0.80±0.19	0.78±0.17

HA+: PCOS patient with hyperandrogenism, HA−: PCOS patient without hyperandrogenism

[a] $P<0.05$, when the HA+ group was compared with the HA− group

[b] $P<0.05$, when the HA+ group was compared with the control group

[c] $P<0.05$, when the HA− group was compared with the control group

sensitivity of 65 %, and specificity of 62 %. The area under the ROC curve for diagnosing HA+ PCOS was 0.82 (0.72–0.92), with a cut-off value of 4.23 ng/mL, sensitivity of 82 %, and specificity of 64 %. The area under the ROC curve for diagnosing HA− PCOS was 0.66 (0.56–0.75), with a cut-off value of 3.76 ng/mL, sensitivity of 64 %, and specificity of 62 %.

The correlations between AMH and other clinical parameters in the PCOS groups are shown in Table 3. In HA+ PCOS patients, AMH was negatively associated with FSH ($r=-0.42$, $P<0.05$) and positively associated with LH($r=0.46$, $P<0.05$).

Table 2 Diagnostic power of AMH for PCOS patients of different subtypes

Groups	AUC	*P* value	Threshold (ng/ml)	Sensitivity	Specificity
All types	0.68 (0.60–0.76)	<0.01	3.92	65 %	62 %
HA+	0.82 (0.72–0.92)	<0.01	4.23	82 %	64 %
HA−	0.66 (0.56–0.75)	<0.01	3.76	64 %	62 %

HA+: PCOS patients with hyperandrogenism, HA−: PCOS patients without hyperandrogenism

Table 3 Correlation between serum AMH level and other clinical parameters in PCOS patients with and without hyperandrogenism

Groups	Parameters	Correlation coefficient	*P* value
HA+	FSH	−0.42	<0.05
$n=62$	LH	0.46	<0.05
HA−	BMI	0.26	<0.05
$n=69$	Fasting glucose	0.27	<0.05
	HDL	−0.28	<0.05
	LDL	0.29	<0.05

In HA− PCOS patients, AMH was negatively associated with HDL ($r=-0.28$, $P<0.05$) and positively associated with BMI ($r=0.26$, $P<0.05$), fasting glucose ($r=0.27$, $P<0.05$), and LDL ($r=0.29$, $P<0.05$).

Discussion

The complexity of the pathophysiology underlying PCOS determines the heterogeneity of the disease. PCOS patients can be categorized into various subtypes based on the Rotterdam criteria [3, 5, 6]. In like manner, there are the differences in the severity of folliculogenesis among the subtypes of PCOS.

Although the pathophysiology of PCOS is not completely uncovered, androgen undoubtedly plays an important role [1, 2]. Androgen contributes to enhance the secretion of AMH by inducing the recruitment of small follicles. The excessive secretion of AMH leads to polycystic ovaries by inhibiting follicular growth [23]. Considering the important role of androgen in PCOS, the patient can be categorized into two main clinical subtypes patients with hyperandrogenism [HA+] and patients without hyperandogenism [HA−].

In the present study, the serum AMH level in the HA+ group was significantly higher than the HA− group. The conclusion is consistent with previous studies, which indicates that hyperandrogenism is associated with an extra increase in AMH [12]. Although the DSL ELISA kits were used in the present study while the Beckman-Coulter ELISA kits used in other studies, the results are quite comparable. As a matter of fact, oligomenorrhea or amenorrhea in PCOS patients with hyperandrogenism occurs more frequently than patients without hyperandrogenism [25]. Thus, over-production of AMH in PCOS patients with hyperandrogenism may contribute to the disruption of folliculogenesis.

In recent years, AMH has been recommended for diagnosing PCOS, but in practice there are great discrepancies in the diagnostic power [17, 18, 24]. In the present study, the

diagnostic sensitivity and specificity of AMH was not satisfying, suggesting that sole use of AMH is not adequate for diagnosing PCOS because of its low accuracy. Ultrasonography, biological parameters, and clinical presentation are still needed to enhance the diagnostic accuracy of AMH. Considering the impact of the heterogeneity of PCOS on diagnostic power, PCOS patients were classified into HA+ and HA− groups. After such classification of patients, the diagnostic sensitivity of AMH for the HA+ group was enhanced to a large extent. The conclusion was confirmed by another study. AMH and/or follicle number were regarded as surrogates for the classical markers of PCOS patient with HA [7]. Thus, AMH is not suitable for diagnosing all types of PCOS, but was only applicable for a specific subtype, such as PCOS patients with hyperandrogenism.

In the HA+ group, the mechanism underling the positive relationship between LH and AMH is still under investigation. This PCOS subtype may be primarily caused by hypothalamic-pituitary dysfunction, because the increased pulse frequency of GnRH secreted by the hypothalamus in PCOS patients may induce AMH secretion and inhibit the follicular growth [10]. It was also proven by an in vitro study that the granulosa cells from PCOS patients have the amplified AMH secretion in presence of LH in the culture media [22]. The possible explanation for that was the granulosa cells from anovulatory women with PCOS may have the premature response to LH [32]. Additionally, a negative relationship between FSH and AMH was found in the present study. AMH can suppress the effect of FSH by inhibiting the activity of aromatase [8]. In our former study, FSH can also suppress the excessive production of AMH in the granulosa cells from PCOS patients [18]. However, the mechanism underling their mutual relationship was on the debate.

On the average, the incidence of obesity in the HA− group was higher than that in the other groups. Obesity often contributes to glucose metabolic disorders. Of obese PCOS patients, 40 % have impaired glucose tolerance, which causes insulin resistance and hyperinsulinemia [11, 16]. Obesity together with impaired glucose tolerance may contribute to disruption of folliculogenesis in PCOS patients. It is reported that exercise can decrease BMI and improve insulin sensitivity for the PCOS patients, subsequently suppress AMH over-production [19]. Moreover, AMH can be used for predicting menstrual response in overweight PCOS patients after weight loss. The patients with low AMH baseline level get more chances to be improved menstrual response [20]. However, another study shows that a 20-week weight loss intervention has no effect on AMH secretion [29]. Therefore, the relationship between AMH and BMI still needs to be explored. Interestingly, HDL and LDL were significantly associated with AMH in our study, which was correspondent with another study [28]. It suggests that AMH may be not only a marker of ovarian function but also a potential new marker for cardiovascular diseases.

In conclusion, our study showed that AMH is not suitable for diagnosing all types of PCOS patients, and a satisfactory diagnostic potential can be achieved by combining AMH with other clinical indicators. AMH is only suitable for the diagnosis of some specific PCOS subtypes, such as HA+ patients. The diagnostic accuracy was very limited when AMH was used to diagnose HA− PCOS patients. It reflects different severity of folliculogenesis between the two subtypes. However, more sample size and other populations should be recruited into future study before an accurate statement can be generalized.

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Disclosure statement The authors have nothing to declare.

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