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AMH

Relation of antimullerian hormone with the clinical signs of hyperandrogenism and polycystic ovary morphology

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Abstract

The relation of antimullerian hormone (AMH) levels with the clinical and biochemical markers of polycystic ovary syndrome (PCOS) could be different. A total of 463 PCOS patients were evaluated in this cross-sectional study. Groups were constructed according to polycystic ovarian morphology (PCOM) and menstrual cycle-length. The relation of serum AMH with androgenic hormones, menstrual cycle-length and clinical signs of PCOS were investigated. A powerful positive relation was found between the PCOM and AMH levels (odds ratio = 2.49). There was a negative correlation between age and AMH level ($p < 0.001$, r[correlation coefficent] = −0.155). Positive correlations were found between luteinizing hormone (LH) and AMH ($p < 0.001$, $r = 0.25$) and also between cycle length and AMH ($p < 0.01$, $r = 0.27$). We found a negative week correlation between AMH and follicle-stimulating hormone (FSH) ($p = 0.01$, $r = -0.19$). After controlling main androgenic hormones, AMH was found to be correlated with the Ferriman–Gallway score ($p = 0.03$, $r = 0.18$). There was a positive relationship between hirsutism and AMH (odds ratio = 1.43), but no correlation between AMH and other parameters of clinical hyperandrogenism like hair-loss, acne and seborrhea were identified. The strongest relation was presented between the AMH levels and PCOM. Also, cycle-length correlated well with the AMH levels. The relationship between hirsutism and AMH is found to be independent from androgenic hormones.

Keywords

AMH, hirsutism, hyperandrogenism, menstrual cycle-length, PCOS, PCOM

History

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Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder among women, characterized by a heterogeneous presentation of hyperandrogenism (HA) and ovulatory dysfunction [1]. HA is defined either clinically by hirsutism (modified Ferriman–Gallwey score >6), severe acne or seborrhoea or biologically by high serum testosterone levels.

AMH is secreted by small follicles and regulates the early follicular development. AMH levels reflect the primordial pool, and concentrations decline with age in adult women [2]. AMH inhibits the recruitment of primordial follicles into the pool of growing follicles and also decreases the responsiveness of growing follicles to follicle-stimulating hormone (FSH) [3–5]. In gynecology, AMH is known as being a reliable marker of ovarian reserve, it is also useful in the prediction of poor responders [6] and ovarian hyperstimulation syndrome (OHSS) [7].

It has been demonstrated that serum AMH levels correlate closely with early antral follicle number in both normal and PCOS women [8]. Circulating concentrations of AMH are significantly higher in women with PCOS than in age-matched controls [9,10].

AMH concentrations are strongly associated with the main phenotypic features of PCOS. Serum AMH levels in amenorrheic women with PCOS are significantly elevated compared to oligomenorrhoeic women with PCOS [8,10].

Highly elevated AMH levels are partly due to the increased production of AMH by individual follicles and not simply attributable to the increased number of small antral follicles. This suggests an intrinsic abnormality in the ovarian follicles of PCOS patients, which could contribute to altered folliculogenesis [11].

The purpose of this article is to investigate the correlations betweeen the clinical signs of HA, cycle-length, PCOM with the serum AMH levels. To the best of our knowledge, only few studies were found in literature that investigated the relationship between serum AMH and the clinical signs of HA and so far our sample size is larger than the previous studies.

Materials and methods

Between January 2008 and May 2012, 463 women who were admitted to our endocrinology department with the complaints of hirsutism and/or acne and/or seborrhea and/or alopecia and/or oligo/amenorrhea were enrolled to this study. The patients had never been treated before and they were diagnosed as PCOS for the first time at our department.

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On cycle day 3–5, we performed gynecological examination, pelvic ultrasound and a hormonal evaluation: FSH, LH, total testosterone (total T), free testosterone (free T), dehydroepiandrosterone-sulfate (DHEAS), 17-OH-progesterone (17-OHP) and AMH. Ages were recorded and body mass indexes (BMI = kg/m^2) were calculated.

PCOS is diagnosed according to the Rotterdam criteria [12]. The diagnosis was based on the association of at least two of three following criteria:

(1) Ovulatory disturbance (OA: oligomenorrhea or amenorrhea); oligomenorrhea was defined as fewer than eight cycles of menstruation during the past 12 months or menstrual interval of more than 35 d. Amenorrhea was defined as the absence of menstruation for more than 90 d.
(2) HA, as defined either clinically by hirsutism (modified Ferriman–Gallway score (FGS) >6), severe acne or seborrhoea or endocrinological (hyperandrogenemia) by a free testosterone serum level greater than 2.7 pg/ml and/or total testesterone greater than 80 ng/dl.
(3) Polycystic ovarian morphology (PCOM): more than 12 follicles of 2- to 9-mm range in each ovary on the ultrasound examination and/or an ovarian volume greater than 10 mL.

The relation of the serum androgen levels and menstrual cycle length with the serum AMH levels were investigated by correlation analysis. The correlation of hirsutism, acne, hair loss and seborrhea with the AMH were investigated by constructing subgroups according to the presence or absence of those symptoms and, also by logistic regression analysis.

The serum AMH samples were collected in a lithium heparin tube. The concentrations were measured with enzymatically amplified two-site AMH-Gen-II ELISA kit (Beckman Coulter, Immunotech, Webster, TX). The circulating levels of FSH, LH, total T, free T, DHEA-S and 17-OH-P were measured with ELISA.

None of the participants had hyperprolactinemia (galactorrhea), thyroid dysfunction or any other endocrine or systemic disease that could possibly affect reproductive physiology.

Statistical analysis was performed by SPSS 17.0 program (SPSS Inc., Chicago, IL). The group means of continuous variables were compared by Student's t test and Mann-Whitney U test. All data were presented as mean standard deviation (SD). The correlations of continuous variables with the AMH levels were evaluated by Pearson test. Partial correlation analysis was performed to investigate the relation of FGS with the AMH, independently from androgenic hormones. Logistic regression analysis was used to investigate the relation of nominal variables with the AMH. p Value was <0.05 was considered as significant.

Results

Mean age of participants was 25.7 ± 5.5 years (15–40), mean BMI was 25.4 ± 4.5 (kg/m^2) (16–39). The mean serum AMH level was 7.7 ± 3.36 ng/ml (0.6–23.9). Other hormonal parameters were summarized in Table 1. There was a negative correlation between the age and the serum AMH level ($p < 0.001$, r[correlation coefficent] = −0.155). Positive correlations were found between LH and AMH ($p < 0.001$, $r = 0.25$) and also between cycle length and AMH ($p < 0.01$, $r = 0.27$). We found a negative week correlation between the AMH and FSH ($p = 0.01$, $r = -0.19$) (Table 2 and Figure 1a–c).

Patients were divided into two groups according to the presence or absence of polycystic ovary morphology (PCOM+ and PCOM−). AMH was significantly higher in PCOM+ group compared to PCOM− group (8.1 ± 5.3 ng/ml versus 3.4 ± 2.4, $p < 0.001$) (Table 3). Logistic regression analysis revealed a strong relation of AMH with the PCOM when AMH values are above the mean level of our study population (odds ratio = 2.49, $p < 0.001$).

Table 1. Hormonal and demographic features of participants.

	Mean	SD	Range
Age (year)	25.79	5.51	15–40
BMI (kg/m^2)	25.40	4.58	16.4–39.7
FSH (mIU/l)	5.19	1.66	1.2–12.6
LH (mIU/l)	5.71	3.71	1.5–25.9
E2 (ng/ml)	40.94	22.65	5–210
PRL (ng/ml)	18.67	8.75	0.6–29.5
TSH (IU/l)	1.82	0.97	0.5–5.0
17-OHP (ng/ml)	1.34	0.89	0.13–5.9
DHEAS (mg/dl)	335.45	152.06	2.55–854
Free testosterone (pg/ml)	2.61	2.97	0.11–17.9
Total testosterone (ng/dl)	94.72	52.48	0.22–454
Ferriman–Gallwey score	10.13	5.04	0–30
Cycle-length (day)	62.05	31.22	15–180
AMH (ng/ml)	7.79	3.36	0.6–23.9

Table 2. Correlation between AMH and FSH, LH, free T, total T, 17-OHP, DHEAS.

	FSH	LH	Free T	Total T	17-OHP	DHEAS
AMH (ng/ml)	−0.19	0.26	0.04	0.01	0.06	0.01
p	0.00*	0.00*	0.51	0.83	0.37	0.07

*Pearson correlation analysis (statistically significant).

No correlations between AMH and androgenic hormones were identified (total T, free T, DHEA-S, 17-OH-P) (Table 2). After discarding the effects of listed androgenic hormones, the effect of BMI and LH on the FGS was measured by partial correlation analysis and a positive correlation between AMH and FGS was found ($p = 0.034$, $r = 0.18$).

For the evaluation of serum AMH with the clinical HA symptoms, patients were grouped according to the presence or absence of acne. The logistic regression analysis revealed no difference between two groups in terms of AMH values. Similar results were found for the correlation of the hair loss and seborrhea with the AMH, respectively.

AMH levels were significantly higher in hirsutism group, compared to non-hirsute group (8.5 ± 6.7 ng/ml versus 7.0 ± 4.8 ng/ml, $p = 0.04$). Logistic regression analysis confirmed that when the serum AMH value is above the mean value of our PCOS population, prevalance of hirsutism is significantly increased (odds ratio = 1.43, $p = 0.01$).

Comments

It is well established by many studies that women with PCOM have higher serum AMH levels compared to the women with normal ovarian morphology [8,13]. We also demonstrated a three-fold increase in serum AMH level in PCOS patients compared to non-PCOS women [13]. Most of the studies about the relation of AMH with PCOS were usually constructed with limited number of patients, our study covered the largest population among those. We divided 463 PCOS patients into two groups according to the presence of PCOM and cycle length. We found that AMH was significantly higher in PCOM group. After having investigated several different parameters of PCOS, correlation between AMH and ovarian morphology was the strongest one. The cause of the increased AMH production in PCOS is unknown; however, increase in AMH concentration is largely attributed to the increase in the production of AMH by each follicle and not just a consequence of an increased follicle number [14,15].

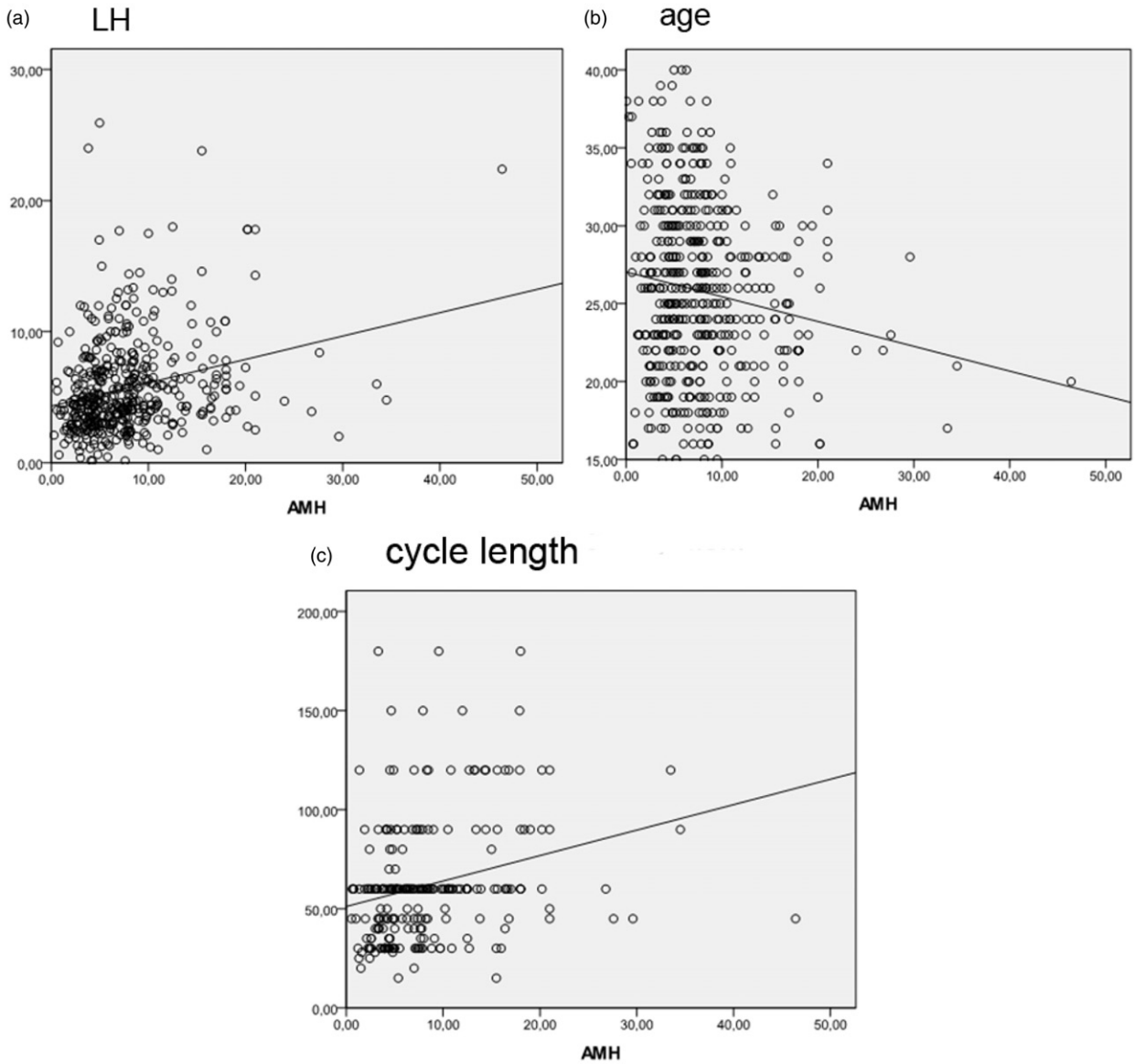

Figure 1. Graphical presentation of linear relation of AMH (ng/ml) with (a) LH (mIU/l), (b) age (years), (c) cycle-length (days). O: observed, ___: linear.

Table 3. Grouping of patients according to the presence or abscence of PCOM.

	Age (year)	BMI (kg/m^2)	AMH (ng/ml)	LH (mIU/l)	Total T (ng/dl)	FGS	Acne (%)	Seborrhea (%)	Hair loss (%)
PCOM+	25.92	25.36	8.09*	5.77	94.83	10.11	28.97	37.98	25.86*
PCOM−	24.19	26.46	3.44*	4.73	94.72	10.35	36.36	35.00	12.5*
<35 d	25.77	25.67	5.86*	5.35	94.74	9.45	31.37	36.00	27.27
>35 d	24.68	25.61	9.26*	6.19	95.87	10.21	28.57	36.25	27.97

Grouping of patients according to the presence of oligo/amenorrhea (cycle-length >35 d). Percentage of the hyperandrogenism symtoms (acne, seborrhea, hair loss) according to those two main groups are given in table. FGS: Ferriman–Gallway score. Mann–Whitney *U*, Student's *t* and Chi square tests (comparison of values represented as percentages).
*Significantly different ($p < 0.001$).

Consistent with our previous results, amenorrheic women with PCOS display elevated AMH compared to oligomenorrheic women with PCOS, indicating the association of AMH in the pathogenesis of PCOS-related anovulation [8,10]. We found a positive moderate correlation between the AMH and cycle-length (Figure 1c) two parameters. High serum AMH values could reflect the impaired folliculogenesis in the ovary of amenorrheic patients compared to the oligomenorrheic PCOS women [10,16]. AMH appears to have a major inhibitory role during folliculogenesis, which may contribute to anovulation in PCOS [14].

Age has been reported to be both negatively related [17] or not correlated [18] with the serum AMH. We found a negative weak correlation between age and AMH (Figure 1b). Another conflict with AMH is its relation with the prediction of pregnancy. In our previous studies we could not find AMH as a pregnancy prediction marker in both normoresponder and PCOS groups.

However, we demostrated a parallel increase between the serum AMH levels and the pregnancy rates, but this correlation was insignificant [19,20].

Relationship between PCOS and obesity is not as simple as it sounds. Some women suffer from obesity while others are lean. A negative correlation was found between AMH and BMI in a report [18], but no such relationship was reported in other studies. In our previous study, we could not find a correlation between the BMI and the serum AMH in both PCOS and healthy women [13].

Our results were consistent with the studies showing positive correlation between the serum LH and the AMH (Figure 1a) [17,18] while other reports could not identify any relationship between those two parameters [8,21].

There are several hypotheses about androgens that may play a role in the increased AMH secretion by potentiating the growth-promoting factors of oocytes which involves the androgen receptor [22]. Considerable evidence supports that anovulation concept as PCOS is a functional disorder in which anovulation is a consequence of ovarian androgen overproduction [23].

Androstenedione, testosterone or free-androgen-index have been reported to be positively correlated [17,18]. Nonetheless, we found AMH as an independent (apart from androgenic hormones) indicator of hirsutism, which is the most important component of clinical HA. In one study, a weak significant correlation was found between AMH and clinical HA [24]. We did not established any relationship between the androgenic hormones and the serum AMH, but there was a weak negative correlation between FSH and AMH levels (Table 2). AMH has an inhibitory effect on follicular sensitivity to FSH and could therefore play a role in the process of dominant follicle selection [25,26].

In another study, there was a direct correlation between AMH and androgen levels in PCOS patients and after 6 months of androgen suppression with dexamethasone the AMH concentrations remained unchanged [27]. So it looks like a different control mechanism could be presented in the ovary which is responsible for the rise of androgens in PCOS [14].

There are some limitations in our study in which the evaluation of hirsutism, acne and seborrhea are semi-quantitative and subject to significant inter-observer variability. Objective methods for the assessment of hair growth including photographic evaluations and microscopic measurements are available but those have limitations for clinical use, including a significant degree of complexity and a high cost [28]. Nowadays the most common visual scoring method for the extent of body and facial terminal hair growth is based on a modification of the method originally described by Ferriman and Gallwey. In our study, three experienced and a senior gynecologists evaluated all patients for both visual scoring and ultrasonographic examination to decrease the inter-observer variability.

Our study is unique in which we investigated the relationship between hirsutism, acne, seborrhea and the serum AMH levels seperately by logistic regression analysis and only hirsutism component of HA was found to be related with the serum AMH.

Severity of PCOS was traditionally defined by its two cardinal elements: HA and oligo/anovulation. Serum AMH level in PCOS is both closely related to the markers of HA and ovulatory disturbance [29]. We demostrated that none of the androgenic hormones were correlated with the serum AMH. We evaluated the relation of clinical HA (acne, seborrhea, hirsutism) with the AMH separately. Among clinical components of HA, hirsutism was the only parameter that was related to AMH. These results may indicate that high serum AMH levels in PCOS may be more strongly related to the presence of PCOM rather than to the full spectrum of the PCOS, as the modifications in androgens and insulin sensitivity are not followed by changes in ovarian AMH output [27,30].

In summary, a strong relationship presented between the serum AMH and PCOM. Even in the absence of either HA or oligo/anovulation, still moderate AMH elevations were recorded in PCOS patients with the typical PCOM. The cycle-length is another important factor which was correlated well with the serum AMH levels. Our findings also indicate that AMH levels are independently correlated with the hirsutism component of HA.

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Declaration of interest

The authors report no declarations of interest.

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