Correlation between Anti-Mullerian Hormone Levels and Antral Follicle Numbers in Polycystic Ovary and Metabolic Syndromes

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Research

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Abstract

Background Anti-Mullerian hormone (AMH) is expressed by granulosa cells of the pre-antral and small antral follicles in the ovary. Serum AMH levels are significantly higher in women with polycystic ovary syndrome (PCOS) due to an increased number of antral follicles and also a higher production per antral follicle. We proposed diagnostic criteria for the identification of PCOS that are based on variation in the AMH concentrations.

Methods This study explored the relationship between serum AMH levels and other hormonal markers in patients with polycystic ovary syndrome (PCOS) and metabolic syndrome. One hundred fifty patients with PCOS and normally cycling women were examined in a cohort study. Of these, some were candidates for the assisted reproductive methods. The following serum levels were measured in all patients on day 5 of the menstrual cycle: AMH, glucose, HOMA/IP, BMI, testosterone and cholesterol, lipoproteins and triglycerides.

Results In the PCOS group, a 2-fold increase in the serum AMH level was observed as compared to the controls. With AMH, the following increments were seen: testosterone (by 184%); fasting blood glucose (by 18%); fasting insulin (83.86%); HOMA/IR (by 64.23%); mean cholesterol (by 30%); mean triglycerides (by 17%); and BMI (by 26.75%). The high-density lipoprotein concentration decreased by 29.3%.

Conclusion Thus, monitoring the level of AMH allows predicting for OHSS during the ovulation induction and during the use of assistive reproductive technologies. Such a practice also allows deciding on the treatment strategy for obesity, hirsutism, type II diabetes, infertility and cardiovascular diseases.

Background

Anti-Mullerian Hormone (AMH) regulates the maturation of follicles in the ovary and prevents the premature egg production [1]. Some experts evaluate the ovarian reserve by measuring the level of AMH. It is likely that in the future, the ovarian reserve and the follicle count will be analysed specifically by examining the serum AMH levels. The follicle-stimulating hormone (FSH) and AMH are regulating the follicular growth, although many other factors besides these two hormones are involved [2]. This double-triangle model promotes the hypothesis that the secretion of AMH would be FSH-dependent until the E2 (estradiol) is synthesized. However, this hypothesis has not yet been confirmed. Finally, this model is applicable to both normal follicular growth and the excessive follicular growth, which can be observed in PCOS (polycystic ovary syndrome). Consequently, the abnormalities of folliculogenesis in PCOS would result from the exaggeration of a physiological process, rather than aberration. However, the elevated AMH can inhibit the formation of primary follicles and egg maturation, which is integral to PCOS. In this case, at least 12 primordial follicles can be found in the ovary. Measuring the AMH level is crucial in PCOS diagnosis but this method has some limitations, as the concentration of AMH tends to decrease with age. The important effect of age was shown in [3]. These findings allowed the authors to demonstrate that polycystic ovarian morphology (PCOM) could be observed both in young and older

women, suggesting that isolated PCOM did not correspond to the upper limit of follicle count in regularly cycling young women. Older women (≥ 40 [n = 444]) had significantly lower AMH compared to < 35 year old women [n = 64], with the adjusted median of 0.73 ng/ml vs 2.52 ng/ml. The AMH concentrations were significantly lower in young women at menarche (< 12 year old [n = 96] vs ≥ 14 year old [n = 200]: 0.90 ng/ml vs. 1.12 ng/ml) and in women who used oral contraceptives ([n = 27] vs those who never used them [n = 468]: 0.36 ng/ml vs 1.15 ng/ml). Variables such as race, body mass index (BMI), education, height, smoking status, parity, and the menstrual phase did not correlated with the AMH level significantly. There were no significant associations found between the AMH level and the androgen level, between the AMH level and the concentration of sex hormone-binding globulin, or between the AMH level and the blood collection factors (e.g. sample, time, season and year).

In another study [4], serum concentrations of AMH were significantly higher in the PCOS group compared to the control group during early infancy (20.4 ± 15.6 vs. 9.16 ± 8.6 pmol/liter; P = 0.024) and during childhood (14.8 ± 7.7 vs. 9.61 ± 4.4 pmol/liter; P = 0.007). The concentrations of gonadotropin and serum sex steroids were similar in both groups during the two study periods, except for FSH, which was lower in prepubertal daughters of PCOS women, suggesting that these girls showed evidence of an altered follicular development during infancy and childhood. As the ovarian reserve decreases, the level of AMH drops spontaneously. In some case, such a trend contributes to spontaneous restoration of fertility in the late reproductive age. Cases like this are often found in the medical practice [5]. The diagnostic criteria for PCOS have been grouped in various classifications that have been conflicting for many years. The Rotterdam criteria are the most used today. Although its underlying principle (two criteria required out of three) is still valid, each of its three items (oligo-anovulation (OA), hyperandrogenism (HA), and PCOM) needs to be updated [6]. According to many authors, the diagnosis of PCOS by the Rotterdam criteria should always be a diagnosis of exclusion [7, 8]. The definition of biological HA and its connection with PCOS still needs to be explored [9]. The primary goal of androgenic assays should be to exclude other states of HA. Although, hirsutism does not always seen in PCOS or metabolic syndrome. The criteria used to define OA are insufficient. The definition of PCOM proposed in 2003 is now obsolete when using the latest generation of ultrasound machines. The serum AMH assay seems increasingly to be an excellent substitute for follicular count and is likely to emerge as the official PCOM marker [10]. Monitoring AMH fluctuations is advisable when planning for in-vitro fertilization (IVF) [11] because a constantly high level of AMH (⩾14.24 ng/ml) increases the risk of ovarian hyperstimulation syndrome (OHSS). In the study assessing a relationship between the serum level of AMH and other hormonal markers through IVF, the cut-off point for AMH level according to presence or absence of pregnancy was 4.8 ng/ml but it was not statistically significant (P = 0.655). In PCOS patients with an AMH level ⩾2.7 ng/ml, the number of oocytes that have recovered (six or more) was higher than in the group with higher AMH concentrations [12]. Whereas the place of AMH as a diagnostic aid for PCOS has yet to be settled, the role of AMH in the pathophysiology of this enigmatic syndrome is a challenge for further research [6].The inverse relationship between AMH and FSH serum concentrations adds an intriguing facet to the puzzle while the positive correlation of AMH with LH has been confirmed.

The most common methods for the treatment and prevention of PCOS are the BMI correction, exposure to the corrective influence on carbohydrate and lipid metabolism, moderate physical and aerobic exercises, and the use of metformin hydrochloride and spironolactone solutions, to normalise the HOMA index and reduce the effect of androgens on the body [13].

Other authors do not indicate whether the elevated AMH is a primary cause or a result of PCOS. The previous studies define the isolated PCOM neither as an independent factor nor as a residual PCOS phenotype. The likelihood of constantly present subclinical defects in women of all ages who have PCOS was not discussed either.

Relevance of the study. This study identified the long-term health risks associated with the polycystic ovaries.

The paper aimed to establish the correlation between the levels of hormonal markers and AMH concentration, with the purpose of identifying potential metabolic and cardiovascular risks that emerge with an increase in the AMH level. With this knowledge, an appropriate PCOS treatment can be established.

Methods

Patients

This case-control study on 30 healthy middle-age women (control group), 30 female patients with PCOS, and 90 female patients with metabolic abnormalities was conducted at the Beijing Maternal and Child Health Care Hospital in 2019, during the period from February to September. All participants gave written informed consent. All procedures were performed in accordance with the ethical standards of the hospital and were approved by the ethics committee of the National Center for Radiation Research and Technology. The subjects were divided into two groups, the PCOS group consisting of 30 women with PCOS (OA + HA + PCOM phenotypes) and the control group including 30 regularly cycling women with normal ultrasound findings. Oligo-anovulation (OA) was defined as the self-reported menstrual cycles of ≥36 days or <10 cycles a year.

Diagnostic Methods

Clinical hyperandrogenism (HA) was diagnosed by scoring the presence of terminal hairs over nine body areas on the scale from 0 to 4 using the Ferriman-Gallwey scoring system. Normally, hirsutism is characterized as mild within scores up to 15, moderate from 16-25, and severe above 25. Biochemical HA was determined at the serum testosterone level >2.5 nmol/L [14]. The selection of the control group was carried out using the ultrasound method. Subjects who have undergone previous ovarian surgery, received cytotoxic drugs or pelvic irradiation, who undergone 3 months of hormone therapy before the

study, or had another endocrinological disorder were excluded. The diagnosis of PCOS was based on two of three Rotterdam criteria: (1) irregular menstrual cycles or OA (≥35 days); (2) HA, clinical (the acne presence of acne, or hirsutism) or biochemical manifestations (increase in the level of at least one circulating ovarian androgen); and (3) polycystic ovaries (PCOs) on ultrasound [14]. The existing Rotterdam guidelines suggest that PCOM is indicated by the presence of at least 12 follicles measuring 2 to 9 mm in the whole ovary or by the finding of increased ovarian size (>10 mL) [15]. The multifollicular ovarian (MFO) size threshold should be adapted to the ultrasound machine that is used [16]. Both groups underwent (1) a complete anamnesis; (2) clinical examination, to gather relevant data such as the extent and degree of hirsutism, weight and height; and (3) ultrasonography. AFC (antral follicle count) and OV (ovarian volume) were assessed with the General Electric Logiq Book XP with vaginal probe 7.5 MHz (General Electric Medical Systems, Solingen, Germany). Ovary size was measured in three dimensions, and the volume was subsequently calculated by the formula: height × width × depth × 0.5. All visible follicles of 2–9 mm in diameter in both ovaries were included in the AFC. All ultrasound examinations were performed by the same investigator.

Laboratory Methods

Blood samples were taken with a syringe; serum was separated by centrifugation after coagulation, placed in aliquots and stored at -20° C until analysis. Hormone levels were measured in both groups during the follicular phase.

Measuring the levels of all hormonal markers in irregularly cycling subjects was not always possible but the AMH concentrations does not change significantly during the menstrual cycle [17]. Hence, the serum AMH concentrations were estimated using an ELISA kit (MBS 702605, My Biosource Company, USA). Testosterone levels were measured by competitive binding immunoenzymatic assay using a Beckman Coulter Unicel DXI 800 analyzer (Beckman Coulter Diagnostics Australia, Gladesville, Australia). Fasting plasma glucose (FPG) and fasting insulin (FI), cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) were measured by the enzymatic colorimetric assay method (BIOLABO REAGENTS SA 02160, Maizy, France). FPG and FI were determined for the homeostatic model assessment of insulin resistance (HOMA-IR) [18]. The HOMA-IR was calculated as [*fasting serum insulin* (μU/mL) × *fasting blood glucose* (mmol/L)/*22.5*] [19].

Statistical analysis

The results are presented as means ± standard deviations (SD) [20]. Differences between the PCOS and control groups were determined through an independent test [21]. The connections between variables were estimated using the two-sided Pearson correlation coefficient (r) [22]. Statistical data processing was performed using SPSS 20.0 statistical software (SPSS Inc, version 20.0, Chicago, Illinois, USA), Microsoft Excel, and Statistica. The reliability and significance of statistical parameters were taken at $p < 0.05$.

Results

The results are presented in tables and figures as follows. Table 1 showed statistically significant differences between the control and PCOS groups with respect to various parameters that were measured.

[Table 1 here]

Table 2 showed the correlation between AMH levels and other factors in the PCOS group. As it turned out, the AMH level correlated directly with the antral follicle count and ovarian volume. A slight correlation (p□0.005, r <0.7) was noted between AMH, age, BMI, hirsutism, testosterone, fasting blood glucose, insulin concentration, HOMA/IR, cholesterol, HDL, and triglycerides.

[Table 2 here]

Table 3 demonstrated a direct high correlation between AMH and parameters such as testosterone, HOMA/IR, BMI, cholesterol, HDL at p=0.000 and TG in both groups.

[Table 3 here]

Table 4 provides evidence of a high direct correlation between AMH and ovarian parameters like AFC and OV at p=0.0001 in both groups.

[Table 4 here]

Table 2 showed a direct correlation between AMH, AFC, and OV but a slight correlation between AMH and all other factors.

Data in Table 4 showed a highly significant direct correlation.

Figure 1 showed a highly significant direct correlation between AMH and AFC values in the PCOS group at R^2 = 0.9977 and p <0.001. For the control group, R^2 equaled 0.79 and the asymptotic significance was presented as p <0.001.

[Figure 1 here]

Figure 2 showed a correlation between AMH and OV values in the PCOS group. Statistical findings indicated a direct significant correlation at R2 = 0.8911 and asymptotic p <0.001. For the control group, R^2 equaled 1 and the asymptotic significance was presented as p <0.001.

[Figure 2 here]

Figure 3 showed area under the ROC curve for AMH that equaled 1 while the AMH cut-off value for diagnosing PCOS is 5.80, with 100% sensitivity and 100% specificity.

[Figure 3 here]

Figure 4 presented an ultrasound image of polycystic ovaries.

[Figure 4 here]

Discussion

The polycystic ovary syndrome presents with a set of symptoms that range from mild to severe and has reproductive, endocrine, and metabolic implications [23]. PCOS is one of the leading causes for female sub-fertility and the most common endocrine disorder among the reproductive age women. Despite many decades of extensive research, the exact etiology and pathogenesis of this complex disorder remain hidden. AMH is a promising marker, as its concentration is constant throughout the menstrual cycle and is not affected by fluctuations of other reproductive hormones [23].

Although serum AMH levels are used as a predictive marker of ovarian response during IVF, there are conflicting reports of its predictive value for folliculogenesis in ovulation induction with clomiphene citrate [23]. Measurement of AMH levels allows for the further investigation of PCOS and its clinical implications. Addressing AMH values in the present study, we determined that they could distinguish between PCOM and PCOS as separate entities, adding strength to the notion that PCOM is a precursor to PCOS and suggest that PCOM is not merely a normal variation of ovarian morphology.

This study was to examine the relationship between serum AMH levels, antral follicle count, and the ovarian volume in healthy women and women having PCOS. The results confirmed that fasting blood glucose is significantly higher in the PCOS group (5.98 ± 2.1 mmol/L) than in the control group (5.05 ± 0.99 mmol/L). The fasting insulin levels are significantly higher as well (22.1 ± 5.1 μU/mL vs 12.02 ± 2.44 μU/mL).

This study confirmed that HOMA/IR is significantly higher in the PCOS group (6.1 ± 2.49) compared to that in the control group (2.4 ± 0.5). There was a highly significant direct correlation between HOMA/IR and cholesterol values. Such a result was consistent with other studies that showed a significant correlation between HOMA-IR and variables such as TG, LDL cholesterol and HDL [24]. In our study, the HOMA/IR cut-off value was ≥ 3.22 with 87.3% sensitivity and 87.3% specificity, which turned out to be consistent with the recent research [24]. The Ferriman-Gallwey (FG) score was significantly higher in the PCOS group (26.49 ± 3.6 vs 7.73 ± 1.66), with a cut-off value of ≥ 15.7 at 100% sensitivity and 100% specificity. Some authors [23, 24] conducted an extensive review of publications in which they reported a cut-off point for mFG of ≥ 11 for indigenous women in China [24]. Androgenic disorders may be present with normal body hair; therefore, the absence of hirsutism does not exclude consideration of PCOS with other symptoms of androgen excess such as the presence of acne, alopecia, infertility or menstrual dysfunction [24].

The mean cholesterol level was significantly higher in the PCOS group (218 ± 20 mg/dl vs 167.7 ± 17.19 mg/dl). There was a significant increase in the mean triglyceride level in women with PCOS (99.6 ± 10 mg/dl) as compared to healthy controls (85.00 ± 9 mg/dl). In this study, the PCOS group had a significantly lower mean concentration of HDL 39.45 ± 7.25 mg/dl vs 55.80 ± 4.53 mg/dl), indicating a high risk of developing metabolic syndrome. Such a result was consistent with the study claiming low HDL cholesterol as a criterion which best explained the high prevalence of the metabolic syndrome in PCOS subjects which, in turn, was influenced by hyperinsulinemia, rather than hyperandrogenemia [25]. In the current study, a significant increase in BMI was observed in patients with PCOS (34.78 ± 3.43 kg/m²) as compared to controls (27.44 ± 1.73 kg/m²). A direct correlation was observed between the serum AMH levels and all other parameters in all subjects under study.

We found that exercises decreased the level of AMH in overweight women with PCOS. These findings were consistent with other publications [26].

In this study, the serum AMH concentrations in women with PCOS (12.90 ± 3.3 ng/ml) were significantly higher as compared to controls (4.3 ± 0.5 ng/ml).These AMH values were in line with data in [2]. The authors found that elevated AMH (> 4.5 ng/ml) may be useful as an alternative to PCOM if the ultrasound findings are not conclusive [27]. In this study, the mean AMH level was 2.72-fold higher in patients with PCOS as compared to healthy controls. This was consistent with data from previous researchers [11]. The have reported 2- to 3-fold higher serum AMH levels in women with PCOS as compared to ovulatory women, which corresponded to an increase in the number of small follicles seen in PCOS. Normally, the serum AMH concentrations in patients with PCOS are higher than in ‘normal’ women [28]. The present study showed a diagnostic cut-off value of serum AMH for PCOS, 5.8 ng/ml, yielding a sensitivity of 100% and specificity of 100%. In contrast, Lin et al. reported an AMH cut-off value of 7.3 ng/ml (specificity, 76%; sensitivity, 70%) [29]. In addition, the measurement of serum AMH levels may also be used as an indicator of the PCOS patients’ response to therapeutic approaches, including evaluation after treatment with insulin sensitizers and monitoring after laparoscopic ovarian resection.

In this study, the mean number of follicles (26.6 ± 6) in both ovaries is significantly higher in the PCOS group than in the control group (9 ± 2). These data are coherent with [3], which confirmed ≥ 12 threshold for the follicle number per ovary in Chinese women. The 2003 Rotterdam consensus, the most common ultrasound definition employed to date, was based on the Balen’s study and on expert agreement [30]. Many authors found that PCOS cases differ from controls on transvaginal ultrasound with a threshold of ≥ 12 follicles measuring 2–9 mm in diameter (mean of both ovaries) [29].

In terms of ovarian volume, the PCOS group demonstrated significantly higher values (11.56 ± 3.1 cm^3 vs 6.23 ± 0.73 cm^3) as well as a significant correlation between AMH and OV at $r = 0.853$ and $P < 0.0001$. Without contradicting the present results, other researchers demonstrated that AMH had a statistically significant positive correlation with the ovarian volume ($r = 0.623$, $P < 0.01$) [24]. In a recent study, the ovarian volume showed the strongest positive correlation ($r = 0.62$) with the serum AMH level among related factors [3]. Here, it also demonstrated a highly significant correlation with AFC ($r = 0.861$, $P <$

0.0001). The AMH/AFC ratio was 0.46 in the PCOS group and 0.48 in the control group, indicating the concentration of AMH per follicle. Therefore, the number of follicles depends on the serum AMH level. Here, a significant correlation was observed between serum AMH levels and variations in testosterone, AFC, and OV on ultrasound [31]. A very significant correlation between AMH and AFC values among PCOS patients was in line with the results obtained by other researchers [29]. According to them, the AMH levels may be used to replace the number of follicles as a diagnostic criterion if the ultrasound cannot provide accurate.

Conclusions

The present findings confirmed a significant correlation between serum AMH levels and variations in AFC and OV. The measurement of AMH is a simple diagnostic tool for PCOS that can serve an alternative to other biochemical assays and ultrasound and can predict the morphology of PCOS, especially in virgins, given a close positive correlation between AMH, AFC and OV.

Declarations

Ethics approval and consent to participate. All procedures were performed in accordance with the ethical standards of the hospital and were approved by the ethics committee of the National Center for Radiation Research and Technology.

Consent for publication. All participants gave written informed consent.

Availability of data and materials. Data will be available on request.

Competing interests. Authors claim no conflict of interest.

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Tables

Table 1. Clinical, biochemical, hormonal and ultrasound characteristics of both groups expressed as means ± SD

	Control Group (n = 30), Mean ± σ	PCOS Group (n = 30), Mean ± σ	P-values
Age, years	28.01±2.23	27.64±2.3	-
BMI, kg/m	27.2±1.71	35.08±2. 3	<0.0001
Hirsutism, score	7.8±1.7	25.79±2.6	<0.0001
Fasting glucose, mmol/L	5.05±0.99	5.98±2.1	<0.05
Fasting insulin, µU/mL	12.02±2.44	22.1±5.1	<0.0001
HOMA/IR	2. 4± 0.5	6. 1 ± 2.49	<0.0001
Cholesterol, mg/dL	166.7±17.19	218.0±20,0	<0.0001
TG, mg/dL	85.00±9	99. 6±10.0	<0.001
HDL, mg/dL	55.80±4.53	39.45±7.25	<0.0001
Testosterone, ng/mL	0.301± 0.13	0.856± 0.30	< 0.0001
AMH. ng/mL	4.3±0.5	12.90±3. 3	< 0.0001
AFC	9±2	26±6	<0.0001
OV, mL	6.23±0.73	11.56±3.1	<0.0001

σ –dispersion

Table 2. Correlation between AMH levels and hormonal markers in PCOS group

Pearson’s correlation	Age	BMI	Hirsutism
AMH, r =	-0.017	-0.126	0.092
p =	0.972	0.507	0.629
Pearson’s correlation	AFC	OV	Testosterone
AMH, r =	0.879	0.853	0.063
p=	0.000	0.000	0.740
Pearson’s correlation	Fasting Blood Glucose	Fasting Insulin	HOMA/IR
AMH, r =	0.177	0.211	0.265
p=	0.350	0.262	0.157
Pearson’s correlation	Cholesterol	HDL	TG
AMH, r =	0.101	-0.137	-0.112
p=	0.595	0.470	0.557

Table 3. Correlation between AMH, testosterone, HOMA/IR, BMI, cholesterol, HDL and TG in both groups

	Pearson’s correlation	AMH	HOMA/IR	BMI	Testosterone	Cholesterol	HDL	TG
AMH	r=	1	0.581	0.494	0.552	0.594	-0.608-	0.286
	P=		0.000	0.001	0.000	0.000	0.000	0.050
HOMA/IR	r=	0.581	1	0.592	0.384	0.649	-0.442-	0.199
	P=	0.000		0.000	0.009	0.000	0.002	0.189
BMI	r=	0.494	0.592	1	0.578	0.631	-0.561-	0.448
	P=	0.001	0.000		0.000	0.000	0.000	0.002
Testosterone	r=	0.552	0.384	0.578	1	0.376	-0.584-	0.417
	P=	0.000	0.009	0.000		0.011	0.000	0.004
Cholesterol	r=	0.594	0.649	0.631	0.376	1	-0.494-	0.233
	P=	0.000	0.000	0.000	0.011		0.001	0.124
HDL	r=	-0.608-	-0.442-	-0.561-	-0.584-	-0.494-	1	-0.500-
	P=	0.000	0.002	0.000	0.000	0.001		0.000
TG	r=	0.286	0.199	0.448	0.417	0.233	-0.500-	1
	P=	0.050	0.189	0.002	0.004	0.124	0.000	

Table 4. Correlation between AMH, AFC and OV in both groups

Pearson’s correlation		H	AFC	OV, reference value
AMH	r =	1	0.902	0.951
	P=	-	0.000	0.000
AFC	r =	0.902	1	0.903
	P=	0.000	-	0.000
OV	r=	0.951	0.903	1
	P=	0.000	0.000	-

Figures

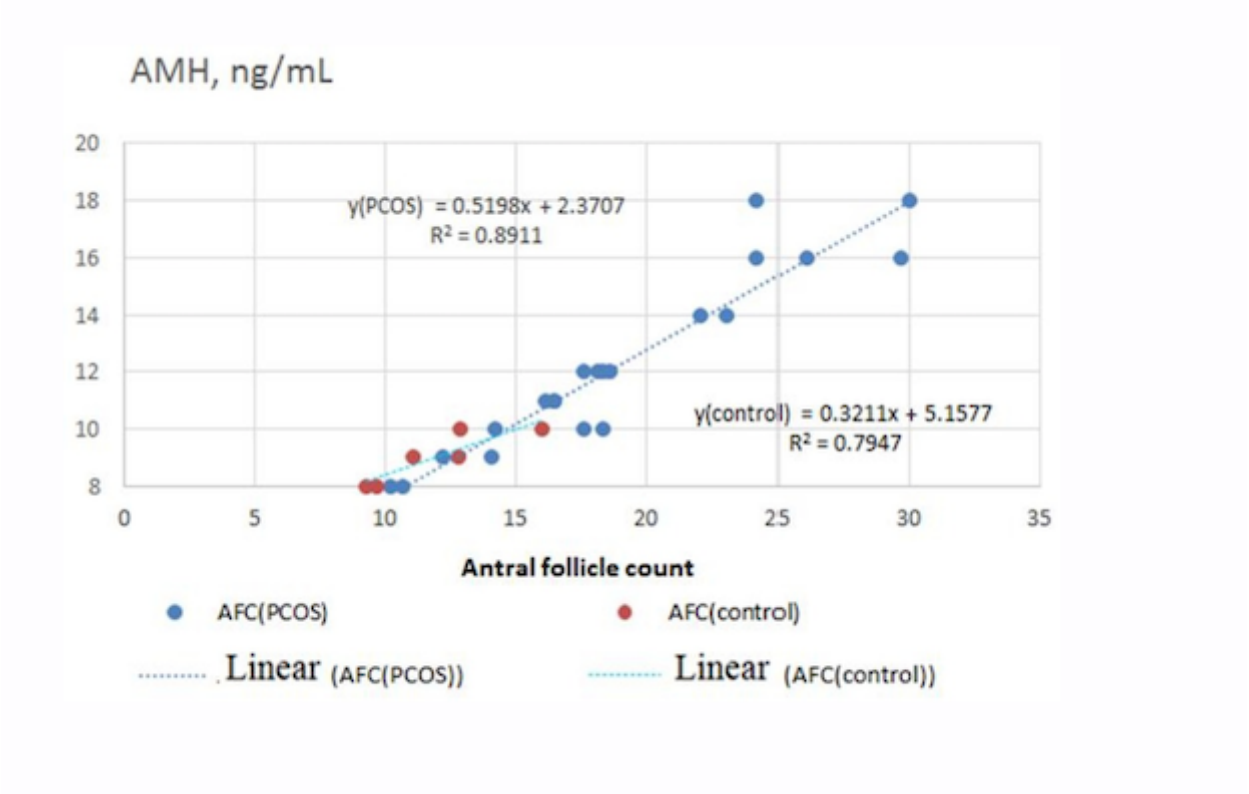

Figure 1

Correlation between AMH and AFC in PCOS group and control group.

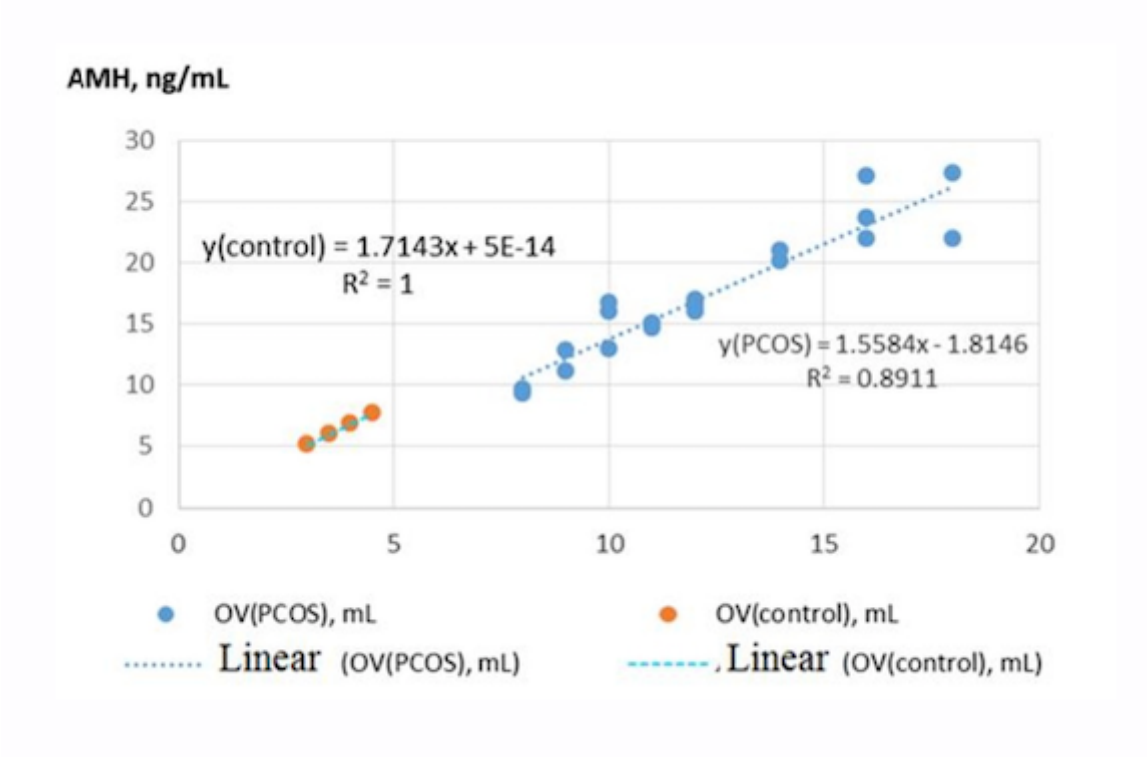

Figure 2

Correlation between AMH and OV in PCOS group and control group.

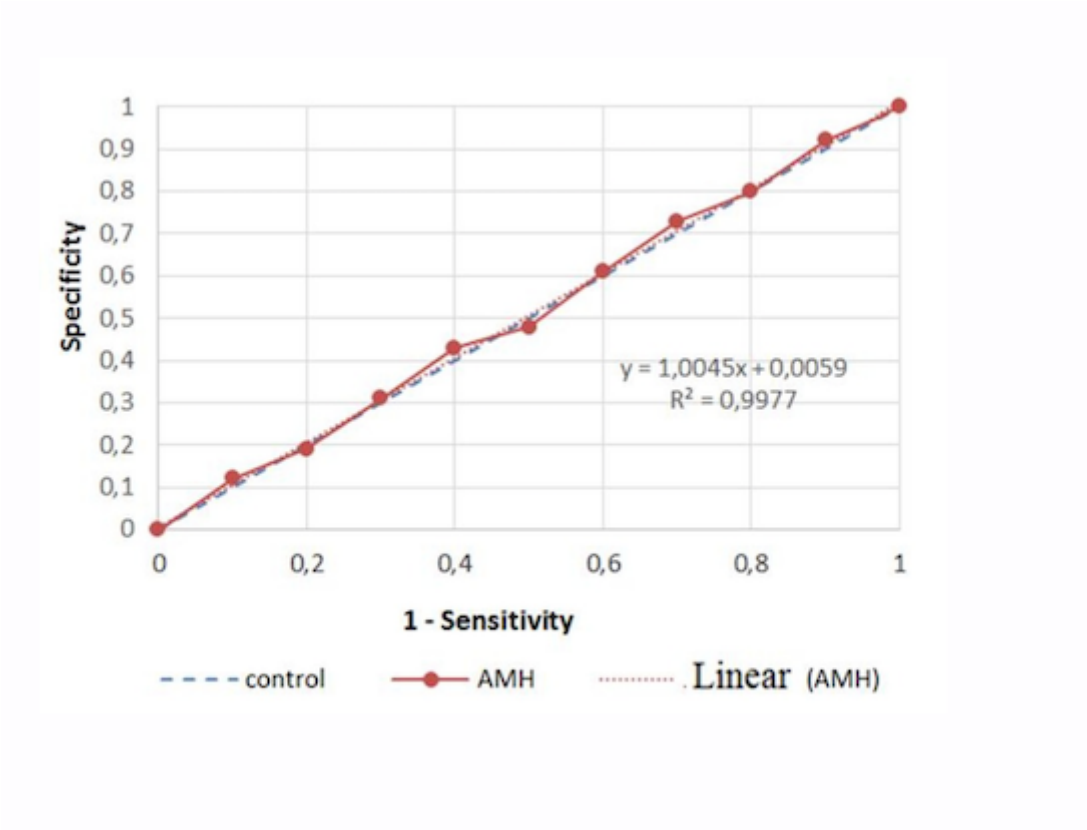

Figure 3

Receiver operating characteristic (ROC) curve for AMH levels.

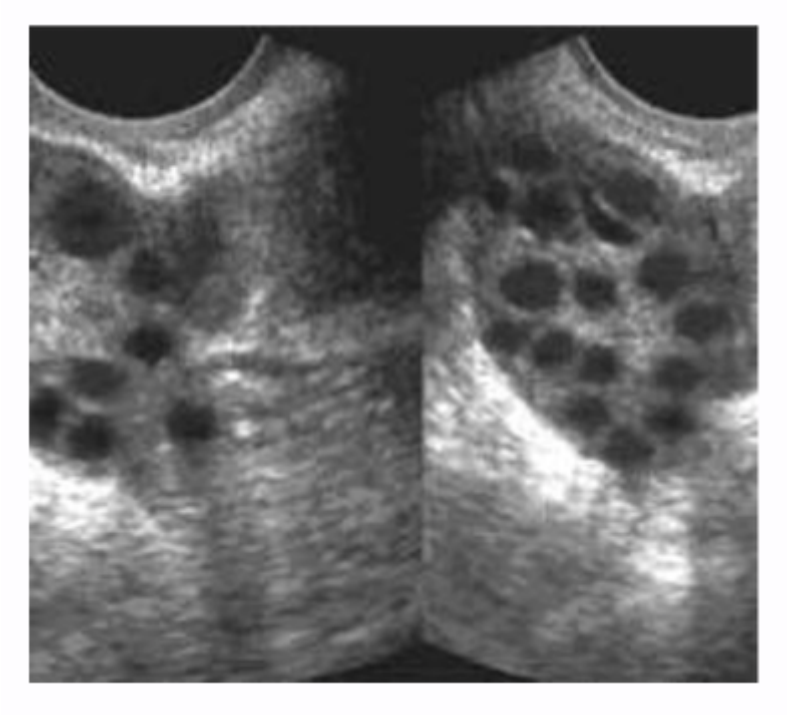

Figure 4

AMH and OV in PCOS patients, ultrasound image.