

The Relationship Between Insulin Resistance and Obesity and Serum Anti-Mullerian Hormone Level in Chinese Women with Polycystic Ovary Syndrome: A Retrospective, Single-Center Cohort Study

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Background: Anti-Mullerian hormone (AMH) is vital in the pathophysiological process of polycystic ovary syndrome (PCOS). The exact relationship between obesity and insulin resistance (IR) with AMH levels remains unclear.

Methods: A retrospective, single-center cohort study of 220 women with PCOS who underwent physical, endocrine, and metabolic assessments were performed. Patients were grouped by age, body mass indices (BMI), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and different phenotypes. Pearson correlation analysis assessed the correlation between AMH and HOMA-IR, BMI, and other PCOS indicators, and multiple linear regression analysis was performed to determine factors influencing AMH.

Results: In 220 patients with PCOS, serum AMH levels decreased with age and were significantly higher in the IR group than in the non-IR group ($P < 0.01$). AMH increased significantly in anovulatory patients with hyperandrogenemia and/or polycystic ovary, with no significant difference between obese and non-obese individuals. AMH levels correlated positively with luteinizing hormone (LH), LH/follicular stimulating hormone (FSH), testosterone, fasting insulin (FINS), and HOMA-IR levels; negatively with age and BMI levels ($P < 0.05$) and weakly with fasting plasma glucose in the classical PCOS phenotype ($r=0.148$, $P < 0.05$). Regression analysis showed that age, testosterone, FINS, LH, LH/FSH, and BMI influenced AMH levels ($P < 0.05$).

Conclusion: Chinese women with PCOS-IR showed associations with greater AMH levels. AMH levels correlated positively with HOMA-IR levels and negatively with BMI. AMH combined with BMI and HOMA-IR levels may help determine PCOS severity.

Keywords: polycystic ovary syndrome, anti-Mullerian hormone, insulin resistance, obesity, metabolic abnormality

Background

Polycystic ovary syndrome (PCOS) is a common reproductive, endocrine, and metabolic disease in women of reproductive age, with a prevalence rate of approximately 2.2–5.6% in China.^{1–3} It is mainly characterized by hyperandrogenism (HA), chronic anovulation, and polycystic ovaries and is accompanied by metabolic abnormalities such as insulin resistance (IR) and obesity.^{4,5} Since PCOS was first reported in 1935, several diagnostic criteria for PCOS have emerged, including the Rotterdam criteria, Androgen Excess Society (AES) criteria, and National Institute of Child Health and Human Development (NICHD) criteria.^{6–8} In 2018, the Chinese Endocrine Association issued Chinese guidelines for diagnosing and treating PCOS⁹ (Table 1). The critical value of ovulation disorder in diagnosing and treating PCOS was emphasized. Indeed, PCOS is the leading cause of menstrual abnormalities and infertility in Chinese women of reproductive age, and ovulation disorders and high androgen performance are the main problems first diagnosed in women with PCOS in clinical practice.^{10,11}

Table 1 PCOS Phenotypes According to Diagnostic Criteria Applied.^{5–8}

	HA+OA	HA +PCO	OA +PCO
NICHD	+	–	–
Rotterdam	+	+	+
AES	+	+	–
Chinese criteria	+	–	+

Abbreviations: PCO, polycystic ovary; HA, hyperandrogenism; OA, oligomenorrhea.

Anti-Mullerian hormone (AMH) is a transforming growth factor superfamily member. It is produced and secreted by granulosa cells in the antral and small antral follicles of the ovary and is a reliable indicator of ovarian reserve.^{12–15} AMH has an essential role in the pathophysiological process of PCOS by regulating follicular development and is closely related to the severity of PCOS.¹⁶ Furthermore, serum AMH levels are independent of the menstrual cycle and are more sensitive and specific than ultrasound.^{16–18} AMH has been reported as an independent predictor of PCOS.^{19–22} Previous studies have shown that serum AMH level in PCOS patients is 2–3 times higher than that in ordinary women of reproductive age, and women with higher AMH levels (≥ 4.45 ng/mL) are more likely to develop PCOS than those with lower AMH level.²³ Besides, high levels of AMH in women with PCOS are associated with reduced ovulation induction response and the risk of early abortion after in vitro fertilization and embryo transfer (IVF-ET) treatment.^{24,25} AMH appears to predict the response of letrozole-induced ovulation and gonadotropin-stimulated ovaries to IVF in women with PCOS,^{26,27} suggesting the importance of AMH in the diagnosis and treatment of PCOS.

however, serum AMH levels are affected by multiple factors, such as the environment and heredity.^{15,28} Previous studies have suggested that AMH levels in PCOS are related to HA levels and are affected by obesity and IR.^{23,29–31} Obesity and IR, as two underlying pathophysiological processes of PCOS, although not included in the diagnostic criteria, are closely associated with PCOS.³² Many clinical and epidemiological data show that about 70% of women with PCOS have IR, and up to 80% are overweight or obese, especially with abdominal obesity.³³ Obesity and IR may exacerbate PCOS-related ovulation disorders by enhancing follicular excess through AMH dysregulation or the HA pathway.²³ Appropriate weight management and improvement of IR can improve ovulation function in women with PCOS.³² However, the exact relationship between AMH levels and obesity and IR remains unclear. Furthermore, those relationships in different phenotypes and races are still controversial.^{34–38} Understanding the influencing factors of AMH in women with PCOS is advantageous for a better understanding of the clinical significance of AMH level fluctuations. Furthermore, it may help clinicians detect PCOS predisposition and intervene early to improve metabolic and reproductive outcomes. Therefore, we designed a retrospective, single-center cohort study to explore the relationship between serum AMH levels and IR and obesity in Chinese women with PCOS, which aimed to add to the current literature and provide insight into optimal clinical treatment.

Methods

Participants

We enrolled 220 Chinese women with PCOS aged 20–39 who visited the endocrinology clinic at Shengjing Hospital of China Medical University between January 2018 and January 2022. The inclusion criteria were (1) subjects meeting the diagnostic criteria of the 2018 Chinese PCOS Guidelines for women of reproductive age,⁹ which include the following: irregular menstrual cycle, amenorrhea, irregular uterine bleeding, or irregular menstrual volume. The diagnosis was also based on at least one of the following criteria: hyperandrogenic performance, hirsuteness, or HA; manifestations of HA, including acne and hirsutism; and biochemical indexes of HA (ie, testosterone [T] > 0.75 ng/mL) or a polycystic ovary on ultrasonography; (2) subjects aged between 18 and 40 years; and (3) subjects who had not received any prescription or non-prescription drugs that affect insulin sensitivity or ovarian function, including hormonal contraceptives, within three months before the trial.

The exclusion criteria were as follows:

1. Subjects with Cushing's syndrome and adrenal cortex hyperplasia or tumors

2. Subjects with abnormal uterine bleeding, primary amenorrhea, hypothalamic amenorrhea, pituitary amenorrhea, and uterine amenorrhea
3. Subjects with hyperprolactinemia
4. Subjects with thyroid dysfunction
5. Subjects with premature ovarian aging, functional ovarian tumors, and theca cell proliferation
6. Subjects who were pregnant or breastfeeding
7. Subjects with a 17 hydroxyprogesterone level > two ng/mL.
8. Subjects with autoimmune disease, malignant tumors, diseases of the central nervous system, or other conditions caused by HA and ovulation disorders

A complete medical history was required for all subjects. The Institutional Review Board approved this study at China Medical University (approval number: 2022PS674K), and informed consent was obtained from each patient before the study.

Assessments

This was a retrospective, single-center cohort study. After obtaining informed consent, the following data were obtained: (1) height, weight, and age; (2) menstrual cycle; and (3) medical history. The height and weight of each subject wearing light clothes were measured to the nearest 0.1 cm and 0.1 kg, respectively. The BMI was calculated as weight (kg) divided by height (m) square. Menstrual cycle disorders included oligomenorrhea and amenorrhea. Oligomenorrhea refers to patients with less than six menstrual periods within 12 months, and amenorrhea refers to patients who have stopped menstruating for more than six months. Each bleeding incidence counts as one menstrual cycle.

Venous blood levels were measured on days 2–5 of the menstrual cycle or when no dominant follicles were found on gynecological ultrasound, and the subjects fasted for 8–12 h overnight. All samples were measured in a vital laboratory in the hospital using standard laboratory techniques. Serum AMH levels were determined by enzyme-linked immunosorbent assay. Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and T were measured using an electrochemical luminescence analyzer on Beckman Coulter Unicel Dx 800. We calculated LH/FSH = LH (mIU/mL)/FSH (mIU/mL); fasting plasma glucose (FPG) and fasting insulin (FINS) levels were measured using an automatic biochemical analyzer. Glycated hemoglobin (HbA1c) levels were determined using an automatic HbA1c detector (high-pressure liquid chromatography). On the day of blood collection, the ovarian volume and number and size of ovarian follicles on each side were determined by ultrasound examination. Those who had never engaged in sexual activity underwent a transabdominal ultrasound examination, and those who had engaged in sexual activity underwent a transvaginal ultrasound examination.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) level was calculated using the following formula to evaluate IR:³⁹

$$\text{HOME} - \text{IR} = \frac{\text{FPG} \times \text{FINS}}{22.5}$$

HOMA-IR is currently the most commonly used clinical indicator to evaluate the degree of IR. China's diabetes cooperative group defines HOMA-IR ≥ 2.69 as IR, and obesity is defined as a BMI ≥ 25 kg/m² according to the World Health Organization (WHO)'s standard in Asia.^{40,41}

Based on age, participants were divided into the 20–29-year-old group (131 women) and the 30–39-year-old group (89 women). The participants were also divided into two groups according to the level of HOMA-IR: the IR group (HOMA-IR ≥ 2.69 , 126 patients) and the non-IR (NIR) group (HOMA-IR < 2.69, 94 patients). Furthermore, according to BMI, 93 women were categorized into the non-obese group (BMI < 25 kg/m²), and 127 women were categorized into the obese group (BMI ≥ 25 kg/m²). Finally, combined with the current standard classification of PCOS,⁴² we divided PCOS into three phenotypes according to our inclusion criteria, that is, the polycystic ovary (PCO) and oligomenorrhea (OA) (102 patients), OA and hyperandrogenism (HA) (34 patients), and PCO+OA+HA (84 patients) groups. Among them, the group of OA+HA and PCO+OA+HA belonged to the classic phenotype of the Rotterdam criteria, while PCO+OA was the non-hyperandrogenemia phenotype.⁴²

Statistical Analyses

SPSS (version 25.0; IBM, Armonk, NY, USA) and GraphPad Prism 8.0.1 (GraphPad Software, Chicago, IL, USA) were used to perform all statistical analyses. All data were tested for normality and homogeneity of variance. Normally distributed data are expressed as means \pm standard deviations. Independent sample *t*-tests were performed to compare two groups, and R software (version 3.5.0, MathSoftCorp, AT&T Bell Laboratories) was used to correct *P*-values. Effects in three groups were analyzed by analysis of variance, and the Bonferroni test was performed as a posthoc test to determine where the statistical differences existed. Pearson correlation analysis was performed to study the correlation between AMH and age, obesity, IR, and other indicators of PCOS, and multiple linear regression analysis was performed to determine the factors influencing AMH. Bilateral tests were performed for all statistical tests. *P* < 0.05 was considered statistically significant.

Results

Demographics

The mean age, AMH level, BMI, HOMA-IR level, and T level of our participants were 28.13 ± 4.29 years, 7.97 ± 5.10 ng/mL, 27.21 ± 4.85 kg/m², 4.31 ± 3.10 , and 0.79 ± 0.34 ng/mL, respectively. IR was present in 126 (57%) participants; 127 (57%) were obese, 110 (50%) had abnormal glucose tolerance, 167 (80%) had an LH/FSH >1, and 119 (54.1%) had HA. Combined with the current standard classification of PCOS, 102 (46.4%) had PCO+OA, 34 (15.5%) had OA+HA, and 84 (38.2%) had PCO+OA+HA (Figure 1).

Age (years)	AMH (ng/mL)	BMI (kg/m-2)	HOMA-IR	T (ng/mL)
28.13 ± 4.29	7.97 ± 5.10	27.21 ± 4.85	4.31 ± 3.10	0.79 ± 0.34

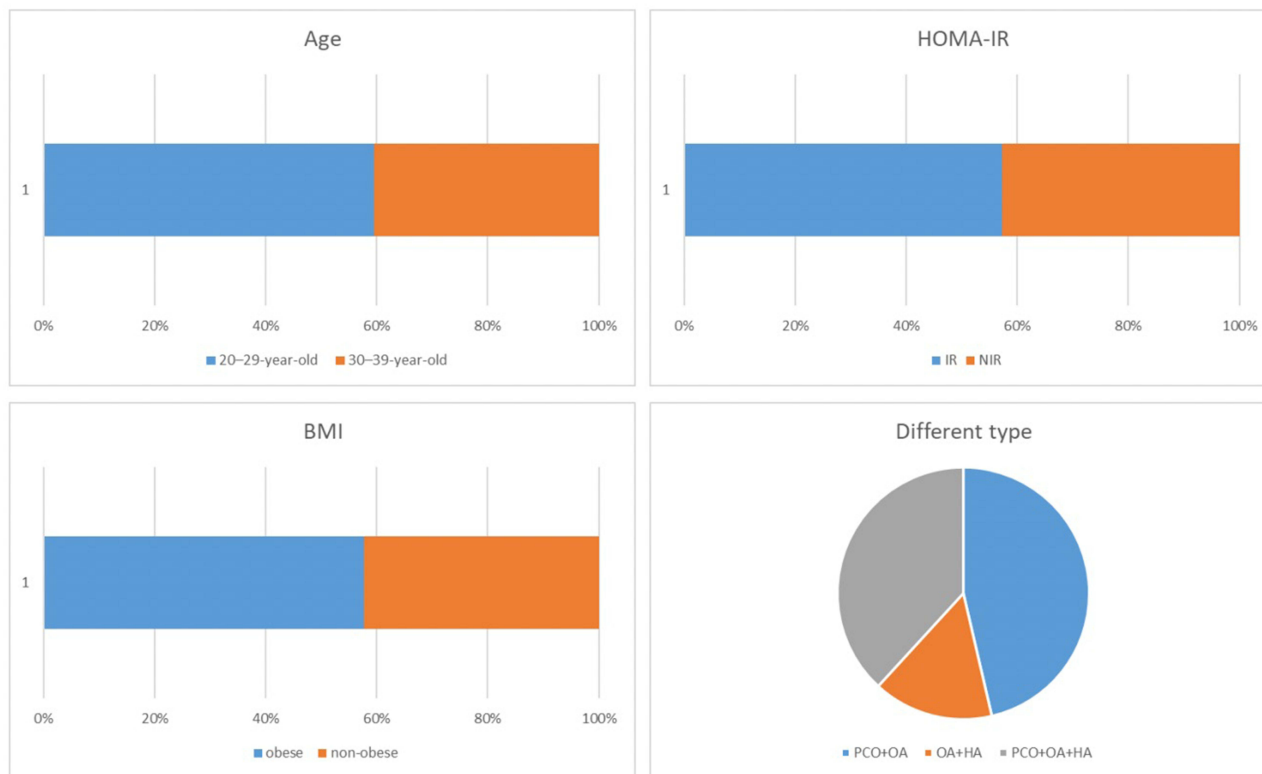


Figure 1 General characteristics and classification proportion of PCOS population.

Differences Between Age Groups

By comparing the two age groups, we found that women in the 20–29-year-old group showed significantly higher AMH, LH, T, FINS, HOMA-IR, and LH/FSH levels than women in the 30–39-year-old group. There was no significant difference in BMI and HbA1c, FPG, and FSH levels between the two age groups. Notably, AMH [(8.90±5.22) ng/mL vs (6.61±4.61) ng/mL, $P < 0.05$]; LH/FSH (1.83±0.91 vs 1.39±0.85, $P < 0.05$); LH [(11.84±6.24) mIU/mL vs (8.70±5.75) mIU/mL, $P < 0.01$]; and T [(0.99±0.29) ng/mL vs (0.50±0.14) ng/mL, $P < 0.01$] levels remained significantly different after adjusting for P values (Table 2), which suggests that these hormone levels decrease with an increase in the age of patients with PCOS.

Correlation Between AMH and Other Indicators in the HOMA-IR Groups

In comparing the IR group and the NIR group at the cut-off point of HOMA-IR 2.69, we found that the ages of the participants in the NIR group were significantly higher than those in the IR group. AMH, LH, LH/FSH, and T levels were significantly higher in the IR group than in the NIR group; a larger HOMA-IR suggests higher AMH, LH, LH/FSH, and T levels and lower age. However, only AMH [(6.03±3.74) ng/mL vs (9.39±5.48) ng/mL, $P < 0.00$] showed a significant difference after adjusting P values. There were no differences in other indicators between the two groups (Table 3).

Table 2 PCOS General Information and Comparison of PCOS General Information Among Different Age Groups

General Indicators	20 to 29 Years Old(n=131)	30 to 39 Years Old(n=89)	Age Group T	Age Group P	p.Adjust
AMH (ng/mL)	8.90±5.22	6.61±4.61	3.347	0.001 [#]	0.020*
LH/FSH	1.83±0.91	1.39±0.85	3.615	0.001 [#]	0.020*
LH (mIU/mL)	11.84±6.24	8.70±5.75	3.774	0.000 [#]	0.000 [#]
T(ng/mL)	0.99±0.29	0.50±0.14	15.111	0.000 [#]	0.000 [#]
BMI (kg m ⁻²)	26.85±4.99	27.75±4.60	-1.359	0.176	1.000
HbA1c (%)	5.93±1.28	5.78±1.09	0.599	0.550	1.000
FPG (mmol/L)	5.64±1.00	5.50±1.33	-1.090	0.277	1.000
FINS (mmol/L)	18.08±10.04	15.23±7.71	2.259	0.025*	0.500
HOMA-IR	4.67±3.33	3.78±2.66	2.110	0.036*	0.720
FSH (mIU/mL)	6.67±2.02	6.32±1.68	1.364	0.174	1.000

Note: * $P < 0.05$, [#] $P < 0.01$. SPSS were used to perform this statistical analysis. All data were tested for normality and homogeneity of variance. Normally distributed data are expressed as means ± standard deviations. Independent sample t -tests were performed to compare two groups, and R software was used to correct P -values.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone. FINS, Fasting insulin; FPG, Fasting plasma glucose.

Table 3 Comparison of AMH Levels and Other Indicators Under Different HOMA-IR Conditions

General indicators	NIR (n=94)	IR (n=126)	T	P	p.adjust
AMH (ng/mL)	6.03±3.74	9.39±5.48	-5.121	0.000 [#]	0.000 [#]
LH/FSH	1.47±0.77	1.79±0.98	-2.647	0.009 [#]	0.144
LH (mIU/mL)	9.49±5.77	11.36±6.46	-2.215	0.028*	0.448
T (ng/mL)	0.73±0.31	0.83±0.35	-2.138	0.034*	0.544
Age (years)	28.89±4.32	27.57±4.19	2.255	0.025*	0.400
HbA1c (%)	5.74±1.01	5.96±1.31	-0.905	0.368	1.000
BMI (kg m ⁻²)	27.62±4.63	26.91±4.99	1.075	0.284	1.000
FSH (mIU/mL)	6.61±2.23	6.47±1.61	0.521	0.603	1.000

Note: * $P < 0.05$, [#] $P < 0.01$. SPSS were used to perform this statistical analysis. All data were tested for normality and homogeneity of variance. Normally distributed data are expressed as means ± standard deviations. Independent sample t -tests were performed to compare two groups, and R software was used to correct P -values.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone. FINS, Fasting insulin; FPG, Fasting plasma glucose; IR, Insulin resistant; NIR, Non-insulin resistant.

Differences in BMI Groups

According to BMI, 93 women were categorized into the non-obese group (BMI < 25 kg/m²), and 127 women were categorized into the obese group (BMI ≥ 25 kg/m²). We found that HbA1c was significantly higher in the obese group than in the non-obese group. AMH, LH/FSH, and LH levels in the obese group were significantly lower than in the non-obese group. There were no differences in T, FPG, FSH, FINS, and HOMA-IR levels, as well as age between the two groups. However, we found that the previous correlation was not significant after the correction of *P* values (*P*>0.05) (Table 4).

Differences in Different PCOS Phenotypes

We divided PCOS into three phenotypes according to the diagnostic criteria and compared them between multiple groups. AMH, T, LH, LH/FSH, and age differed among different phenotypes. Compared with PCO+OA type, AMH [(6.60±4.53) ng/mL vs (9.81±5.30) ng/mL vs (8.89±5.27) ng/mL, *P* < 0.01], T [(0.53±0.15) ng/mL vs (1.02±0.28) ng/mL vs (1.02±0.29) ng/mL, *P* < 0.01], LH [(8.93±5.78) mIU/mL vs (13.16±6.91) mIU/mL vs (11.51±5.98) mIU/mL, *P* < 0.01], and LH/FSH (1.41±0.86 vs 1.94±0.94 vs 1.84±0.91, *P* < 0.01) were increased in the OA+HA group and PCO+OA+HA group, while age [(31.85±2.47) years vs (24.91±2.54) years vs (24.90±2.58) years, *P* < 0.01] decreased. There were no significant differences in other indicators. In addition, there was no significant difference between the OA+HA group and the PCO+OA+HA group (Table 5 and Figure 2).

Table 4 Comparison of AMH Level and Other Indexes Under Different BMI

General Indicators	Non-Obese Group(n=93)	Obese Group (n=127)	T	P	p.Adjust
AMH (ng/mL)	8.83±5.44	7.35±4.75	2.146	0.033*	0.660
LH/FSH	1.82±0.91	1.54±0.91	2.260	0.025*	0.500
LH (mIU/mL)	11.68±6.30	9.75±6.07	2.298	0.023*	0.460
T (ng/mL)	0.84±0.37	0.76±0.31	1.694	0.092	1.000
Age (years)	27.61±4.15	28.50±4.36	-1.528	0.128	1.000
HbA1c (%)	5.50±0.52	6.04±1.37	-2.137	0.035*	0.700
FPG (mmol/L)	5.73±1.15	5.47±1.14	1.592	0.113	1.000
FINS (mmol/L)	18.61±10.61	15.70±7.94	-0.505	0.614	1.000
HOMA-IR	4.86±3.62	3.91±2.60	-0.172	0.863	1.000
FSH (mIU/mL)	6.58±2.19	6.49±1.65	0.335	0.738	1.000

Note: **P* < 0.05. SPSS were used to perform this statistical analysis. All data were tested for normality and homogeneity of variance. Normally distributed data are expressed as means ± standard deviations. Independent sample *t*-tests were performed to compare two groups, and R software was used to correct *P*-values.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone; FINS, Fasting insulin; FPG, Fasting plasma glucose.

Table 5 Comparison of AMH Level and Other Indexes in Different PCOS Phenotypes

Indicators	PCO+OA (n=102)	OA+HA (n=34)	PCO+OA+HA (n=84)	F	P
AMH (ng/mL)	6.60±4.53	9.81±5.30	8.89±5.27	7.712	0.001 [#]
Age (years)	31.85±2.47	24.91±2.54	24.90±2.58	207.124	0.000 [#]
LH (mIU/mL)	8.93±5.78	13.16±6.91	11.51±5.98	7.930	0.000 [#]
LH/FSH	1.41±0.86	1.94±0.94	1.84±0.91	7.421	0.001 [#]
T(ng/mL)	0.53±0.15	1.02±0.28	1.02±0.29	121.996	0.000 [#]
BMI (kg m ⁻²)	27.69±4.73	26.9±5.12	26.8±4.88	0.930	0.396
HOMA-IR	3.75±2.41	4.67±1.81	4.02±2.28	2.078	0.128

(Continued)

Table 5 (Continued).

Indicators	PCO+OA (n=102)	OA+HA (n=34)	PCO+OA+HA (n=84)	F	P
FSH (mIU/mL)	6.44±1.75	6.81±1.31	6.52±2.23	0.474	0.623
FPG (mmol/L)	5.50±1.23	5.86±1.01	5.61±1.06	1.261	0.286
FINS (mmol/L)	15.12±6.75	18.01±6.82	15.93±7.11	2.237	0.109
HbA1c (%)	5.775±1.05	6.16±1.46	5.84±1.25	0.698	0.500

Note: # $P < 0.01$. SPSS were used to perform this statistical analysis. All data were tested for normality and homogeneity of variance. Normally distributed data are expressed as means \pm standard deviations. Effects in three groups were analyzed by analysis of variance, and the Bonferroni test was performed as a post-hoc test to determine where the statistical differences existed.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone. FINS, Fasting insulin; FPG, Fasting plasma glucose. PCO, polycystic ovary; HA, hyperandrogenism; OA, oligomenorrhea.

Correlation Between AMH and Other Indicators and Multiple Linear Regression Analysis Affecting AMH Levels

In Pearson correlation analysis, a significant moderate positive correlation between AMH and the following factors was noted: T ($r = 0.356$, $P < 0.01$); LH/FSH ($r = 0.311$, $P < 0.01$); FINS ($r = 0.265$, $P < 0.01$); HOMA-IR ($r = 0.223$, $P < 0.01$).

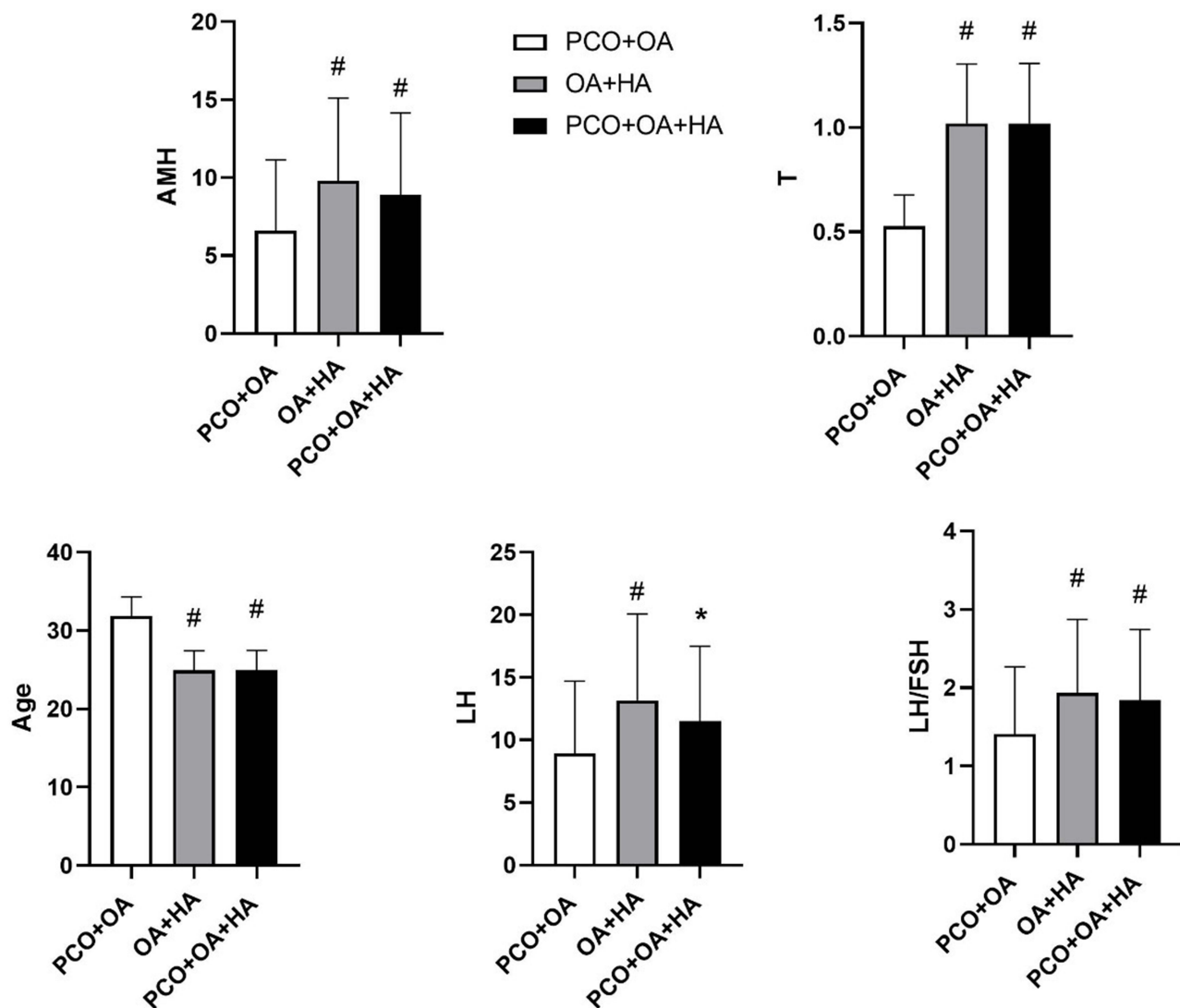


Figure 2 Indicators of significant differences in different PCOS phenotypes. * $P < 0.05$, # $P < 0.01$ vs. PCO+OA.

0.01); and LH ($r = 0.223, P < 0.01$). Conversely, AMH was negatively correlated with age ($r = -0.315, P < 0.01$) and BMI ($r = -0.208, P < 0.01$). In order of size of correlation, T showed the highest correlation, whereas BMI was the lowest ($T > \text{Age} > \text{LH/FSH} > \text{FINS} > \text{HOMA-IR} = \text{LH} > \text{BMI}$). There was no correlation between AMH and HbA1c, FPG, and FSH levels (Table 6). Multiple linear regression analysis using AMH level as the dependent variable and LH, LH/FSH, T, FINS, HOMA-IR levels, age, and BMI as independent variables revealed statistically significant results ($R^2 = 0.259, F = 10.574, P < 0.01$). We found that AMH levels could be explained in terms of T, LH/FSH, FINS, and BMI. Meanwhile, T, LH/FSH, and FINS positively affected AMH, and BMI negatively affected AMH. T has the most significant influence on the level of AMH among them. HOMA-IR was one of the independent determinants of AMH level in women with PCOS. The regression coefficients of the other variables are shown in Table 7.

Table 6 Correlation Analysis of AMH and Various Indexes

Indicators	AMH	
	R	P
BMI (kg m^{-2})	-0.208	0.002 [#]
FINS (mmol/L)	0.265	0.000 [#]
LH (mIU/mL)	0.223	0.001 [#]
LH/FSH	0.311	0.000 [#]
FSH (mIU/mL)	-0.126	0.062
HOMA-IR	0.223	0.001 [#]
T (ng/mL)	0.356	0.000 [#]
Age (years)	-0.315	0.000 [#]
HbA1c (%)	-0.011	0.915
FPG (mmol/L)	-0.053	0.439

Note: [#] $P < 0.01$. SPSS were used to perform this statistical analysis. Pearson correlation analysis was performed to study the correlation between AMH and age, obesity, IR, and other indicators of PCOS.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone; FINS, Fasting insulin; FPG, Fasting plasma glucose.

Table 7 Multiple Linear Regression Analysis of AMH Influencing Factors

Model	Nonstandardized Coefficients		Standardized Coefficients Beta	T	P
	B	Std.Error			
Constant	-2.9592.999	7.718		-0.383	0.702
T (ng/mL)	6.578	2.431	0.437	2.707	0.007 [#]
LH/FSH	2.017	0.728	0.362	2.769	0.006 [#]
FINS (mmol/L)	0.195	0.091	0.265	2.148	0.033*
BMI (kg m^{-2})	-0.179	0.064	-0.171	-2.790	0.006 [#]
LH (mIU/mL)	-0.173	0.105	-0.211	-1.643	0.102
Age (years)	0.225	0.192	0.189	1.170	0.243
HOMA-IR	-0.081	0.270	-0.036	-0.301	0.764

Note: * $P < 0.05$, [#] $P < 0.01$. SPSS were used to perform this statistical analysis. Multiple linear regression analysis was performed to determine the factors influencing AMH.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone. FINS, Fasting insulin.

Correlation and Multiple Linear Regression Analysis in Different PCOS Phenotypes

Due to the different expression of AMH between the OA+HA group and PCO+OA+HA group (classical group for short) and PCO+OA group, we further analyzed the correlation factors and independent determinants of AMH in these two groups. As shown in Table 8 and Table 9, T ($r = 0.347$, $P < 0.01$) had the highest correlation with AMH in the classical group, while LH/FSH ($r = 0.410$, $P < 0.01$) had the highest correlation in the PCO+OA group. In addition, a weak correlation between FPG ($r = 0.148$, $P < 0.05$) and AMH was observed in the classical group. Other related factors were not significantly different from the correlation analysis of AMH in general. These related factors were further incorporated into multiple linear regression analysis. Moreover, we found that T, LH/FSH, and BMI levels in the classical group were independent determinants of AMH ($R^2 = 0.262$, $F = 9.330$, $P < 0.01$), whereas only LH/FSH was the influencing factor of AMH in the PCO+OA group ($R^2 = 0.295$, $F = 5.628$, $P < 0.01$).

Table 8 Correlation Analysis of AMH and Various Indexes in Different PCOS Phenotypes

indicators	AMH(OA+HA/PCO+OA+HA) n=118		AMH(PCO+OA) n=102	
	R	P	R	P
Age (years)	-0.259	0.000 [#]	-0.212	0.033*
BMI (kg m ⁻²)	-0.227	0.001 [#]	-0.213	0.031*
HbA1c (%)	-0.055	0.613	-0.167	0.257
FPG (mmol/L)	0.148	0.040*	0.002	0.987
FINS (mmol/L)	0.204	0.004 [#]	0.343	0.000 [#]
HOMA-IR	0.245	0.001 [#]	0.234	0.018*
LH (mIU/mL)	0.143	0.046*	0.287	0.004 [#]
FSH (mIU/mL)	-0.121	0.092	-0.180	0.071
LH/FSH	0.231	0.001 [#]	0.410	0.000 [#]
T (ng/mL)	0.347	0.000 [#]	0.217	0.029*

Note: * $P < 0.05$, [#] $P < 0.01$. SPSS were used to perform this statistical analysis. Pearson correlation analysis was performed to study the correlation between AMH and various indexes in different PCOS phenotypes.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone. FINS, Fasting insulin; FPG, Fasting plasma glucose. PCO, polycystic ovary; HA, hyperandrogenism; OA, oligomenorrhea.

Table 9 Multiple Linear Regression Analysis of AMH Influencing Factors in Different PCOS Phenotypes

Model		Nonstandardized Coefficients		Standardized Coefficients	T	P
		B	Std.Error	Beta		
OA+HA/PCO+OA+HA (n=118)	Constant	3.514	9.026		0.389	0.697
	Age (years)	0.265	0.204	0.165	1.298	0.196
	BMI (kg m ⁻²)	-0.218	0.073	-0.201	-2.985	0.003 [#]
	FPG (mmol/L)	-1.145	0.892	-0.215	-1.283	0.201
	FINS (mmol/L)	-0.209	0.255	-0.269	-0.820	0.413
	HOMA-IR	1.542	1.009	0.586	1.528	0.128
	LH (mIU/mL)	-0.183	0.108	-0.218	-1.703	0.090
	LH/FSH	1.743	0.782	0.292	2.230	0.027*
	T (ng/mL)	6.878	2.024	0.434	3.398	0.001 [#]

(Continued)

Table 9 (Continued).

Model		Nonstandardized Coefficients		Standardized Coefficients	T	P
		B	Std.Error	Beta		
PCO+OA (n=102)	Constant	1.241	28.423		0.044	0.965
	Age (years)	0.059	0.712	0.032	0.082	0.934
	BMI (kg m ⁻²)	-0.137	0.088	-0.143	-1.568	0.120
	FINS (mmol/L)	0.200	0.116	0.298	1.723	0.088
	HOMA-IR	-0.072	0.311	-0.038	-0.232	0.817
	LH(mIU/mL)	-0.184	0.166	-0.235	-1.109	0.270
	LH/FSH	2.782	1.158	0.525	2.402	0.018*
	T (ng/mL)	4.304	11.803	0.142	0.365	0.716

The dependent variable: AMH

Note: * $P < 0.05$, # $P < 0.01$. SPSS were used to perform this statistical analysis. Multiple linear regression analysis was performed to determine the factors influencing AMH in different PCOS phenotypes.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-mullerian hormone; HOMA-IR, Homeostatic model assessment insulin resistant; T, Total testosterone; FINS, Fasting insulin; FPG, Fasting plasma glucose; PCO, polycystic ovary; HA, hyperandrogenism; OA, oligomenorrhea.

Discussion

Our study aimed to lay a foundation for the future exploration of ovulation and metabolic abnormalities in PCOS patients in China. We found that AMH levels in the IR group were significantly higher than in the NIR group. Although differences are insignificant after adjusting for P values, HbA1c levels were higher, and AMH, LH/FSH, and LH levels were lower in obese individuals than in non-obese individuals. The classical phenotype (PCO+OA+HA and OA+HA) had higher AMH, T, LH/FSH, and LH levels and lower ages than the phenotype of PCO+OA. Furthermore, AMH levels were positively correlated with LH, LH/FSH, T, HOMA-IR, and FINS levels and negatively correlated with age and BMI. Besides, there was also a weak correlation in FPG in the classical PCOS phenotype. Through multiple linear regression, we found that AMH levels could be explained by T, LH/FSH, FINS, and BMI. In addition, among different phenotypes, AMH has the highest correlation with T in the classical phenotype, and T, LH/FSH, and BMI are independent determinants of AMH. However, the correlation between AMH and LH/FSH was strongest in non-hyperandrogenemia PCOS, and AMH was only affected by LH/FSH levels.

Normal ovarian development is affected by the factors inside and outside the ovary. The former include growth factors, cytokines, and inhibin in the follicular fluid, and the latter includes FSH deficiency, LH hypersecretion, high androgen levels in the ovaries and adrenal gland, IR, and hyperinsulinemia.^{43,44} AMH is recognized as the primary hormonal regulator of ovarian follicular development by concurrently stimulating preantral follicle growth and inhibiting antral follicle maturation.⁴³ The above endogenous and exogenous factors could also influence serum AMH levels, which limits the accurate interpretation of AMH values in a clinical setting.⁴⁵ Previous studies have determined that AMH levels are positively correlated with HA and LH and significantly negatively correlated with age in patients with PCOS.⁴⁶ As we know, age is the most critical factor affecting the quality of the ovarian reserve.⁴⁷ AMH levels increase steadily till nine years of age, decline slightly during the pubertal ages, and peak at around 25. A gradual decline follows this by reducing the primordial follicle pool with age until it reaches undetectable levels at an average of 50–51 years of age, corresponding to menopause.⁴⁸ Serum AMH levels have decreased with age in healthy women and women with PCOS.⁴⁸ This is consistent with our results, and age was significantly increased in the PCO+OA phenotype compared with the classical phenotype and was positively correlated with AMH. Fertility begins to decline in women in their 30s, and Tehrani et al suggest ovarian reserve screening should be considered in women older than 30.⁴⁸ Our study shows that, compared with PCOS women aged 20–29, AMH, LH, LH/FSH, and T levels in women aged 30–39 showed a downward trend, suggesting a decline in ovarian reserve function. In addition, much effort is spent to identify a correct algorithm that considers women's age and ovarian reserve markers as a tool to optimize the recombinant follicle-stimulating hormone (rFSH) starting dose in IVF procedure.^{49,50} Nevertheless, current evidence regarding PCOS women, particularly the ones with high AMH, seems inadequate. Further studies are necessary to prove this clinical utility.

LH is one of the biological features typically found in PCOS women.⁵¹ Researchers believed LH could cause a four-fold elevation in AMH production in ovarian granulosa cells of women with PCOS and elevate AMH expression with or without ovulation.⁵² The correlation between AMH and LH is independent of serum androgen and FSH levels.⁵³ A high level of LH can stimulate the secretion and expression of AMH. AMH can also increase GnRH neurons' activity and up-regulate LH's pulsating secretion.⁵³ AMH is secreted before the FSH-dependent selection of the dominant follicle,²⁹ which is consistent with our current results. In our study, LH and LH/FSH were positively correlated with AMH levels in each phenotype and were independent determinants of AMH, while FSH did not correlate with AMH. Androgens promote the early stages of folliculogenesis, and androgen excess has been recognized as an essential factor in the development of most of the reproductive and metabolic alterations characterizing this syndrome.^{17,52} Excess androgen increases the ratio of estradiol receptor α to estradiol receptor β , resulting in increased AMH expression.⁵³ Bongrani et al found that plasma AMH concentration was independently associated with PCO and intraovarian hyperandrogenism.⁵⁴ In our study, we observed a positive correlation between serum T levels and AMH, especially in the classical PCOS phenotype, which corroborates data in the literature supporting the pathogenic role of androgen excess in the development of PCO.

The relationship between AMH and metabolic abnormalities such as IR has been controversial in the literature. IR is one of the essential mechanisms of PCOS pathogenesis,⁵⁵ and insulin sensitizers, such as inositol, have shown significant advantages in improving ovulation and fertilization in PCOS women in the past two decades.^{55,56} IR and compensatory hyperinsulinemia can lead to androgen-dependent anovulation through different mechanisms, and a direct correlation has been found between sinus follicle count, ovarian volume, and hyperinsulinemia.⁵⁷ Furthermore, LH and androgens appear to be related to the correlation between IR and AMH levels in PCOS.⁵⁸ Although the internal mechanism of the relationship between AMH levels and IR in PCOS is unclear, some authors have reported a positive correlation between AMH and IR. IR-induced hyperinsulinemia appears to increase the premature differentiation of granulosa cells, suggesting that IR plays a role in AMH secretion in these cells. Excessive insulin levels have also been shown to alter granulosa cell receptivity and AMH production.^{59–62} Furthermore, relevant analysis of AMH genotypes in PCOS found significant differences in the distribution of AMH (rs10407022) gene polymorphisms between women with PCOS with IR and healthy women. However, there were no differences in the distribution of AMH genotypes between women with PCOS without IR and healthy women.⁶³ When metformin, an insulin sensitizer, was used to treat PCOS for two months, the serum AMH level decreased, and ovulation increased, suggesting an etiological relationship between AMH levels and IR-PCOS.⁶⁴ In this study, when IR was defined by $\text{HOMA-IR} \geq 2.69$, AMH levels in women with IR-PCOS were significantly higher than in women with NIR-PCOS.

In previous studies on the correlation between AMH and IR, the results are contradictory due to the different classifications of PCOS and the difference in the HOMA-IR boundary point. Wiweko et al's study also revealed that serum AMH was significantly correlated with the HOMA-IR level, and there were differences between different PCOS phenotypes.⁶⁵ Forenseca et al defined IR as $\text{HOMA-IR} > 3$ and found higher serum AMH concentrations in IR-PCOS compared to NIR-PCOS.⁶⁶ Sezai et al used the HOMA-IR cut-off as 2.5 in women with PCOS, and no significant difference was found in serum AMH levels between the IR and non-IR groups.³⁵ The cut-off point of 2.69 was obtained according to the IR survey data of the China Diabetes Association, which was more consistent with the value of the Chinese IR population.⁴⁰ In addition, all patients that met our inclusion criteria also met Rotterdam standards, providing comparability. Previous studies have shown that AMH is associated with the PCOS phenotype, as defined by the Rotterdam criteria (phenotype A: OA + HA + PCO; Phenotype B: OA + HA; Phenotype C: HA + PCO; Phenotype D: OA + PCO). Among them, the highest serum AMH levels were found in phenotype A, whereas phenotype C was found to have the lowest mean serum level of AMH.^{61,67,68} The inclusion criteria of this study covered the population with phenotypes A, B, and D, which were more in line with AMH levels. Besides, our study with a large sample size was more suitable for studying the influencing factors of AMH in the Chinese context. We also divided the PCOS population into three phenotypes, A, B, and D, mentioned above. We found that the levels of AMH, LH, LH/FSH, and T were significantly higher in phenotypes A and B, and there was no significant difference between A and B. Although HOMA-IR showed no significant difference among different phenotypes, FINS and HOMA-IR were significantly positively correlated with AMH levels in classical phenotypes (phenotypes A and B) with high expression of AMH.

Li et al demonstrated that high levels of AMH may increase the risk of IR in obese PCOS patients,⁶⁹ suggesting AMH's effect on IR. A possible mechanism is that the release of AMH by the granulosa cells of PCOS patients through the uptake of androgens leads to hyperinsulinemia.²³ In vitro studies have shown that elevated levels of AMH in beta cells of the pancreas may trigger insulin secretion. High peripheral AMH may affect islet function and increase the risk of IR and diabetes later in life.⁶⁹ In our study, AMH was slightly positively associated with fasting glucose levels under the classical phenotype. A recent epidemiological survey of 3293 female participants found that lower age-specific AMH levels were associated with a higher risk of type 2 diabetes in women, suggesting a negative effect of AMH on islet function.

In China, 34.1–43.3% of women with PCOS are obese.⁷⁰ The adverse effects of obesity on reproductive health and fertility, such as ovulation dysfunction, infertility, abortion, and related pregnancy complications, are well documented.⁷¹ Studies have also found that obese women with PCOS have higher infertility rates, poor response to ovulation induction drugs, poor embryo quality, a low success rate of in vitro fertilization, and significantly increased adverse pregnancy outcomes.⁷² In obese women, changes in the ovarian follicular microenvironment, including steroidogenesis, metabolism, and inflammation, indirectly affect AMH levels.⁷³ A decrease in AMH levels has been suggested to be the result of metabolism, storage, and clearance in obese individuals.⁷³ Increased leptin production associated with obesity directly inhibits AMH production.⁷⁴ It has also been suggested that reduced AMH levels in obese women may be due to the blood-thinning effect of increased body size.⁶² Piouka et al demonstrated that the serum AMH levels of overweight and obese women with PCOS were significantly lower than those of lean women with PCOS.⁷⁵ A meta-analysis based on 26 studies demonstrated that BMI was negatively correlated with AMH.⁶⁷ Moreover, Buyukkaba et al found that the significantly increased AMH levels by losing weight with bariatric surgery in patients with morbid obesity with and without PCOS may indicate the improvement of fertilization potential, which could be considered when evaluating fertility in patients with morbid obesity.⁷³ In this study, although differences were not significant with adjustment for potential confounding factors, AMH, LH/FSH, and LH levels were lower in obese individuals than in non-obese individuals. Furthermore, correlation and regression analysis of AMH showed that BMI was independently and negatively associated with AMH levels, supporting the concept that follicular development may be impaired in women with PCOS with increased BMI.

However, the relationship between obesity biomarkers and AMH levels in women with PCOS has also revealed conflicting reports, which can vary depending on the definition of obesity and grouping based on BMI. Zeng et al found that AMH was independently associated with central obesity but not general obesity in women with PCOS.³⁶ Although obese women with PCOS primarily show abdominal obesity, large waist and hip circumferences, and a high waist-to-hip ratio, these were not included in our present study. Therefore, there may be some bias in the committed relationship between obesity and AMH levels, as one of the limitations of our study.

Other limitations of our retrospective cross-sectional study population consisted of only subfertile PCOS women; hence, it is impossible to generalize the findings to adolescent PCOS. Moreover, the antral follicle count was not included because of the lack of specific values once their number exceeded 12 on ultrasound and the large number of reports on the correlation between AMH and AFC. The exact mechanism of the relationship between AMH levels and IR and obesity in PCOS needs to be further elucidated. There is no consistent serum AMH diagnostic threshold for PCOS.^{71,76–78} Moreover, because of the lack of a control group, we did not further elaborate on the diagnostic significance of AMH levels in PCOS. Finally, due to the selection of Chinese PCOS diagnosis and treatment standards, patients with HA+PCO phenotype were not included, which may be biased in the correlation analysis of AMH. However, the sample size of this study is large, and the diagnosis of PCOS follows Chinese diagnosis and treatment standards, which is more consistent with the characteristics of PCOS in the Chinese population and provides a new perspective for AMH-related research in Chinese PCOS women. Therefore, we hope that more preclinical and clinical studies are conducted to verify the role of AMH levels in the prediction, prevention, and treatment of PCOS and to provide more of a theoretical basis for exploring the etiology of PCOS.

Conclusion

We found that serum AMH levels were associated with metabolic abnormalities in Chinese women with PCOS. Chinese women with PCOS-IR showed an association with greater AMH levels. AMH was significantly correlated with BMI

under PCOS classical phenotype, while AMH seems to be affected only by LH/FSH in the non-hyperandrogenic PCOS. Future studies are needed to explore the potential mechanism linking BMI, IR, and AMH that might lead to important insights into ovarian physiology in patients with PCOS.

Abbreviations

PCOS, Polycystic ovary syndrome; AMH, Anti-Mullerian Hormone; T, Testosterone; BMI, Body mass index; FPG, Fasting plasma glucose; FINS, Fasting insulin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; IR, Insulin resistant; NIR, Non-insulin resistant; HA, Hyperandrogenism; PCO, Polycystic ovary; OA, Oligomenorrhea.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

Study complies with the Declaration of Helsinki. The Institutional Review Board approved our study at China Medical University (approval number: 2022PS674K), and informed consent was obtained from each patient before the study.

Author Contributions

H.Z. conceived the study. C.L. and L.Z. designed the study. H.Z. and Z.D. wrote the study design and registered the study protocol. H.Z. and Z.D. developed the statistical methods and analyzed the data. H.Z. wrote the first draft of the manuscript. Z.D., C.L., and L.Z. critically checked its content and approved its final version. All authors agreed with the results and conclusions of this article and agreed on the journal to which the article will be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version was accepted for publication, and any significant changes were introduced at the proofing stage. All authors agreed to take responsibility and be accountable for the article's contents.

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Disclosure

The authors declare that they have no competing interests.

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