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Original Article

Retrospective analysis of the association between anti-Müllerian hormone levels and metabolism and reproductive outcome across different PCOS phenotypes

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Abstract: Objective: The aim of this study is to explore the relationship between the levels of anti-Müllerian hormone (AMH) and metabolic and reproductive outcomes across different polycystic ovary syndrome (PCOS) phenotypes. Methods: In this retrospective study, 286 PCOS patients undergoing intrauterine insemination (IUI) were defined into a high AMH group (>7.0 ng/mL, n = 159) and a low AMH group (≤7.0 ng/mL, n = 127) based on the upper normal limit. Serum AMH, basal hormones (testosterone [TESTO], basal follicle-stimulating hormone [bFSH], basal luteinizing hormone [bLH]), and metabolic indicators (triglycerides [TG], total cholesterol, fasting blood glucose, fasting insulin [FINS], homeostasis model assessment of insulin resistance [HOMA-IR]) were measured on menstrual cycle days 2-4. Reproductive outcomes were recorded. Results: The high AMH group had higher prevalence of polycystic ovarian morphology (81.13% vs. 70.08%, P = 0.029) and classic phenotype (35.22% vs. 19.69%, P = 0.004). TESTO (50.82 vs. 45.28 ng/dL, P = 0.002), bLH (8.17 vs. 7.46 IU/L, P = 0.013), TG (0.96 vs. 0.87 mmol/L, P = 0.008), FINS (9.79 vs. 8.86 mIU/L, P = 0.006), and HOMA-IR (2.28 vs. 2.09, P = 0.009) were notably elevated in the high AMH group, as was the rate of early miscarriage (10.06% vs. 2.36%, P = 0.009). A multivariate analysis revealed that high AMH independently increases the risk of early miscarriage (OR = 2.844, P = 0.023). Conclusions: Elevated AMH is associated with more severe PCOS phenotypes, adverse metabolic profiles, and increased early miscarriage risk, suggesting its utility as a biomarker for stratification and prognosis in PCOS patients.

Keywords: Anti-Müllerian hormone, metabolism, reproductive outcome, polycystic ovary syndrome, phenotypes

Introduction

Polycystic ovary syndrome (PCOS), a prevalent endocrine disorder among women in their reproductive years, is distinguished by symptoms such as hyperandrogenemia, chronic anovulation, and the presence of polycystic ovaries. The heterogeneity of PCOS presents significant challenges in diagnosis and treatment, making it imperative to identify reliable biomarkers that can aid in patient stratification and personalized management [1, 2]. The underlying pathophysiology of PCOS encompasses intricate interplays among genetic, hormonal, and environmental elements. Hyperandrogenism and insulin resistance are central features that contribute to the clinical manifestations of the syndrome. Elevated androgen levels interfere with the regular development of follicles and ovulation, resulting in menstrual irregularities and infertility. Insulin resistance exacerbates this disruption by enhancing androgen synthesis in the ovaries and adrenal glands, further complicating the condition. Although there has been considerable research, the precise mechanisms responsible for these disruptions are still poorly understood, highlighting the need for more comprehensive biomarkers to guide clinical decision-making [3-5].

Produced by the granulosa cells within the ovaries, anti-Müllerian hormone (AMH) is essential for the regulation of follicular development. Its levels are typically elevated in women with PCOS, reflecting increased ovarian activity and higher numbers of small antral follicles. This characteristic elevation makes AMH a potential marker not only for ovarian reserve but also for

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assessing the severity of PCOS. Studies have shown that AMH levels correlate with various clinical features of PCOS, such as hyperandrogenism and polycystic ovaries. Additionally, AMH has been linked to metabolic parameters, including insulin resistance and lipid profiles, suggesting its broader utility in evaluating systemic health. These findings indicate that AMH may offer a more holistic view of PCOS, encompassing both reproductive and metabolic aspects [6-8].

The diverse clinical presentation of PCOS has led to the classification of different phenotypes based on the presence or absence of specific criteria. Classic PCOS, characterized by menstrual abnormalities and hyperandrogenism, with or without polycystic ovaries, is often considered the most severe form of the syndrome. In contrast, non-hyperandrogenemia PCOS includes menstrual abnormalities and polycystic ovarian changes without hyperandrogenism, potentially representing a milder condition. Differences in these phenotypes suggest varying underlying pathophysiological mechanisms, which may influence response to treatment. Identifying how AMH levels differ across these phenotypes could help in tailoring therapies to individual patient needs, thereby improving clinical outcomes [9-11].

Reproductive outcomes in women with PCOS undergoing assisted reproductive technologies (ART) are influenced by multiple factors, including ovarian response, endocrine dysfunction, and metabolic disturbances [12]. Notably, even after successful conception, women with PCOS remain at a significantly higher risk of early pregnancy loss compared to those without the syndrome [13]. The underlying mechanisms are multifactorial and may involve hyperandrogenemia, insulin resistance, abnormal folliculogenesis, and endometrial dysfunction. Given that AMH reflects not only ovarian follicle density but also correlates with hyperandrogenism and insulin resistance, it may serve as an integrative biomarker for predicting early miscarriage risk in PCOS patients undergoing fertility treatment [14, 15]. Identifying the relationship between AMH levels and early pregnancy loss across different PCOS phenotypes could enhance risk stratification and support personalized treatment strategies to improve pregnancy sustainability [16].

In summary, the multifaceted nature of PCOS necessitates a comprehensive approach to diagnosis and management. By elucidating the relationships between AMH levels and various PCOS phenotypes, this study aims to contribute to a deeper understanding of the syndrome's pathophysiology and improve clinical outcomes for affected women. Future research ought to concentrate on confirming these results and delving into the underlying mechanisms to develop more effective therapeutic approaches.

Materials and methods

Study subjects

A total of 286 PCOS female patients who underwent intrauterine insemination (IUI) for assisted reproduction at Shijiazhuang People's Hospital from September 2020 to August 2024 were selected as the subjects of this study. This research is a retrospective clinical case analysis that obtained ethical approval from the Ethics Committee of Shijiazhuang People's Hospital and was executed in compliance with the Declaration of Helsinki. Given the retrospective design, which utilized only pre-existing clinical information from patients' digital medical records, and after receiving approval from the ethics committee, formal informed consent was not required. All collected data were subject to strict de-identification procedures to ensure patient confidentiality.

Inclusion criteria: (1) Age <40 years; (2) Meeting the diagnostic criteria for PCOS; (3) Undergoing IUI for the first time and fully accepting the treatment plan; (4) At least one patent fallopian tube in the female partner; (5) Complete medical records without any missing data. Exclusion criteria: (1) Use of oral hypoglycemic or lipid-lowering drugs within the past three months; (2) Presence of moderate to severe endometriosis; (3) Bilateral fallopian tube obstruction; (4) Presence of other diseases, including diabetes, hypertension, thyroid disorders, etc.; (5) IUI attempts for fertility assistance exceeding 3 times; (6) Uncorrected clinically significant uterine cavity lesions; (7) Male semen parameters not meeting IUI standards.

Based on the 2003 Rotterdam criteria [17], a diagnosis of PCOS can be made if at least two

out of the following three conditions are met: ① Oligo- or anovulation (OA); ② Hyperandrogenemia or clinical signs of hyperandrogenism (HA); ③ Polycystic ovarian morphology (PCOM) observed via ultrasound. In line with the Chinese diagnostic guidelines for PCOS [18], which emphasize menstrual irregularities (oligoamenorrhea/amenorrhea, i.e., OA) as a fundamental component of phenotypic classification, we categorized PCOS patients into the following three phenotypes: ① Classic phenotype: characterized by hyperandrogenemia (or clinical manifestations), oligomenorrhea/amenorrhea, and polycystic ovarian morphology changes (HA+OA+PCOM); ② Non-PCOM phenotype: marked by hyperandrogenemia (or clinical manifestations) and oligomenorrhea/amenorrhea, but without typical polycystic ovarian morphology changes (HA+OA); ③ Non-HA phenotype: characterized by oligomenorrhea/amenorrhea and polycystic ovarian morphology, but without clear evidence of hyperandrogenemia or clinical manifestations (OA+PCOM).

HA was defined as either biochemical hyperandrogenemia (elevated total testosterone [TESTO] above the laboratory's reference range [>50 ng/dL]) or the presence of clinical manifestations of hyperandrogenism (moderate to severe hirsutism [Ferriman-Gallwey score ≥4], persistent acne unresponsive to conventional treatment, or androgenic alopecia) [19].

Assisted reproductive technology

Ovulation induction plan: Ovulation induction was performed using one of three standard protocols, selected at the physician's discretion based on individual patient characteristics (age, body mass index [BMI], and previous response). The primary oral protocols were: 1) Clomiphene citrate (Approval No. HJ2014-0688, Medochemie Ltd., Cyprus) (50-100 mg/day) or 2) Letrozole (Approval No. H20-133109, Zhejiang Hisun Pharmaceutical Co., Ltd., China) (2.5-5 mg/day), both administered from day 3-5 of the menstrual cycle for five days. If no follicular response was observed by cycle day 10, or in women with a previous poor response to oral agents, 3) Menotropins (Approval No. H10940097, Livzon Group Livzon Pharmaceutical Factory, China) (37.5-75 IU/day) were initiated. The gonadotropin dose was adjusted based on follicular development as monitored by transvaginal ultrasound.

When the leading follicle reached a diameter of 14 mm, daily monitoring of urinary luteinizing hormone (LH) levels was initiated. When an LH surge was detected or at least one leading follicle reached a diameter of 18 mm, 5,000-10,000 IU of human chorionic gonadotropin (hCG) (Approval No. H31020865, Shanghai Shangyao First Biochemical Pharmaceuticals Co., Ltd., China) was administered. Intrauterine insemination (IUI) was then performed 24-36 hours later.

IUI method: Males were required to abstain from ejaculation for 3-7 days before providing a semen sample via masturbation into a collection cup. The semen was processed using the density gradient centrifugation method prior to intrauterine insemination (IUI), ensuring that the post-processing concentration of progressively motile sperm was $\geq 10\times10^6$/mL. After cleaning the external genitalia and vagina with normal saline, an artificial insemination catheter (Approval No. 20152180128, Pacific Kangtai Scientific Instruments (Jinan) Co., Ltd, China) connected to a 1 mL sterile syringe was used to aspirate the sperm suspension (0.3-0.5 mL). Air was expelled from the insemination catheter, which was then gently inserted along the cervical canal into the uterine cavity, and the suspension was slowly injected. Patients remained supine for 30 minutes before being discharged.

Luteal support: After IUI, patients were administered 10 mg of dydrogesterone tablets orally twice daily (Approval No. HJ20170221, Abbott Biologicals B.V., Netherlands). Urine and blood pregnancy tests were conducted 14 days post-IUI to confirm biochemical pregnancy, and a vaginal ultrasound at 35 days was used to identify intrauterine gestational sac and embryo, confirming clinical pregnancy. Live birth was confirmed by complete expulsion or extraction from the female body after 22 weeks of gestation, showing signs of respiratory effort or any other vital signs. If the spontaneous loss of a pregnancy occurred between the confirmation of biochemical pregnancy and the end of the 12th week of gestation without any human intervention, it was defined as early miscarriage [20].

Laboratory testing

Peripheral venous blood samples were collected from all patients in the early morning after

an overnight fast, specifically on days 3 to 5 of their menstrual cycle. Serum levels of AMH and basal hormone, including total testosterone (TESTO), basal follicle-stimulating hormone (bFSH), and basal luteinizing hormone (bLH), were measured using a fully automated chemiluminescent immunoassay system (DxI 800, Beckman Coulter, USA). Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TCHO), and fasting insulin (FINS) levels were measured using a fully automated biochemical analyzer (Cobas 8000, Roche, Switzerland). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: HOMA-IR = FINS × FBG/22.5.

Serum AMH concentration was measured using an automated chemiluminescent immunoassay system (Access AMH assay, Beckman Coulter, Inc., USA) on a DxI 800 analyzer. The assay's lower limit of detection is 0.01 ng/mL, and the intra- and inter-assay coefficients of variation were <5% and <10%, respectively. The standard reference interval for AMH in our laboratory is 2.0-7.0 ng/mL, which is consistent with the manufacturer's guidelines and ranges widely used in clinical practice for assessing ovarian reserve.

Study grouping

Based on the upper limit of the normal reference value for AMH being 7.0 $ng{\cdot}mL^{-1}$, the 286 patients were categorized into a low AMH group (n = 127) and a high AMH group (n = 159). Patients in the low AMH group were defined as having an AMH ≤7.0 $ng{\cdot}mL^{-1}$, while those in the high AMH group were defined as having an AMH >7.0 $ng{\cdot}mL^{-1}$. General information, PCOS phenotypes, basal hormone levels, metabolic indicators, and reproductive outcomes were collected from the electronic medical records of the patients.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 29.0; developed by SPSS Inc., Chicago, IL, USA), with a two-tailed *P* value <0.05 deemed statistically significant. Continuous variables in this study were evaluated for normal distribution using the Shapiro-Wilk test and are reported as means ± standard deviations (M ± SD). Group comparisons for continuous variables were performed using independent samples t-tests. Categorical variables are presented as frequencies and percentages [n (%)] and were compared using the χ^2 test. Spearman correlation analyses were performed to determine the direction of associations between parameters and high AMH level. Subsequently, univariate and multivariate logistic regression analyses were carried out, with early miscarriage as the dependent variable (occurrence = 1, non-occurrence = 0), to identify independent risk factors for the occurrence of early miscarriage.

Results

General information

In the comparison of general information between the low and high AMH groups (**Table 1**), PCOM prevalence were higher in the high AMH group (81.13% vs. 70.08%, $\chi^2 = 4.760$, P = 0.029). Other factors such as age, BMI, smoking history, drinking history, HA, and infertility duration did not differ significantly between the two groups (P>0.05 for all). These results suggest that PCOM are closely associated with AMH levels, potentially indicating their roles in reproductive health.

PCOS phenotypes

In the comparison of PCOS phenotypes between the low and high AMH groups (**Table 2**), significant differences were noted for the classical phenotype and hyperandrogenic phenotype. The classical phenotype was more frequently observed in the high AMH group (35.22% vs. 19.69%, $\chi^2 = 8.394$, P = 0.004), whereas the non-PCOM phenotype was more prevalent in the low AMH group (18.87% vs. 29.92%, $\chi^2 = 4.760$, P = 0.029). There was no significant difference in the distribution of the non-HA phenotype between the two groups (45.91% vs. 50.39%, $\chi^2 = 0.568$, P = 0.451). These results indicate that AMH levels are linked to specific PCOS phenotypes, potentially reflecting underlying pathophysiological differences.

Basal hormone levels

In the comparison of basal hormone levels between the low and high AMH groups (**Figure 1**), significant differences were noted for TESTO and bLH. TESTO levels were notably higher in the high AMH group (50.82 vs. 45.28, t = 3.148, P = 0.002), and bLH levels were also

Table 1. Comparison of general information between the two groups

Parameter	Low AMH group (n = 127)	High AMH group (n = 159)	t/χ^2	P
Age (years)	30.52 ± 3.21	30.47 ± 3.89	0.119	0.905
BMI (kg/m^2)	23.85 ± 2.76	24.24 ± 3.35	1.088	0.278
Smoking history [n (%)]			0.646	0.421
Yes	15 (11.81%)	24 (15.09%)		
No	112 (88.19%)	135 (84.91%)		
Drinking history [n (%)]			0.618	0.432
Yes	18 (14.17%)	28 (17.61%)		
No	109 (85.83%)	131 (82.39%)		
HA [n (%)]			0.568	0.451
Yes	63 (49.61%)	86 (54.09%)		
No	64 (50.39%)	73 (45.91%)		
PCOM [n (%)]			4.760	0.029
Yes	89 (70.08%)	129 (81.13%)		
No	38 (29.92%)	30 (18.87%)		
Infertility duration (years)	4.32 ± 1.21	4.18 ± 0.96	1.091	0.277

AMH, anti-müllerian hormone; BMI, body mass index; HA, hyperandrogenemia; PCOM, polycystic ovarian morphology.

Table 2. Comparison of PCOS phenotypes between the two groups [n (%)]

Parameter	Low AMH group (n = 127)	High AMH group (n = 159)	χ^2	P
Classic phenotype	25 (19.69%)	56 (35.22%)	8.394	0.004
Non-PCOM phenotype	38 (29.92%)	30 (18.87%)	4.760	0.029
Non-HA phenotype	64 (50.39%)	73 (45.91%)	0.568	0.451

AMH, anti-müllerian hormone; PCOS, polycystic ovary syndrome; PCOM, polycystic ovarian morphology; HA, hyperandrogenemia.

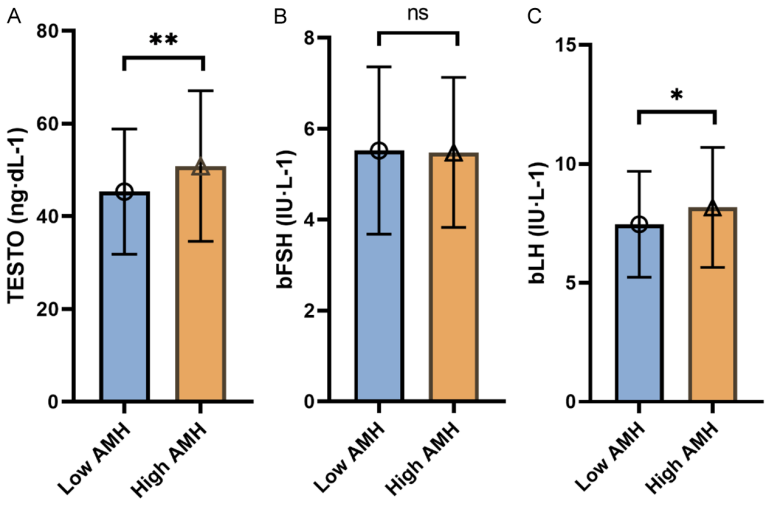

Figure 1. Comparison of basal hormone levels between the two groups. A. TESTO; B. bFSH; C. bLH. ns: no significant difference; *: P<0.05; **: P<0.01. AMH, anti-müllerian hormone; TESTO, testosterone; bFSH, basal follicle stimulating hormone; bLH, basal luteinizing hormone.

elevated in the high AMH group (8.17 vs. 7 .46, t = 2.487, P = 0.013). No significant difference was found in bFSH levels between the two groups (P>0.05). These results indicate that increased AMH levels are linked to higher TESTO and bLH, which may reflect underlying hormonal imbalances in these patients.

Metabolic indicators

In the comparison of metabolic indicators between the low and high AMH groups (**Table 3**), significant differences were observed for TG, FINS, and HOMA-IR. TG levels were higher in the high AMH group (0.96 vs. 0.87, t = 2.655, P = 0.008), and both FINS (9.79 vs. 8.86, t = 2.742, P = 0.006) and HOMA-IR (2.28 vs. 2.09, t = 2.645, P = 0.009) were also elevated in the high AMH group. No significant

Table 3. Comparison of metabolic indicators between the two groups

Parameter	Low AMH group (n = 127)	High AMH group (n = 159)	T	P
TG (mmol·L^{-1})	0.87 ± 0.26	0.96 ± 0.29	2.655	0.008
TCHO (mmol·L^{-1})	4.65 ± 0.79	4.73 ± 0.85	0.796	0.427
FBG (mmol·L^{-1})	5.32 ± 0.48	5.24 ± 0.46	1.485	0.139
FINS (mIU·L^{-1})	8.86 ± 2.65	9.79 ± 3.02	2.742	0.006
HOMA-IR	2.09 ± 0.57	2.28 ± 0.66	2.645	0.009

AMH, anti-müllerian hormone; TG, triglyceride; TCHO, total cholesterol; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model insulin resistance index.

Table 4. Comparison of reproductive outcome between the two groups [n (%)]

Parameter	Low AMH group (n = 127)	High AMH group (n = 159)	χ^2	P
OHSS rate	2 (1.57%)	7 (4.40%)	1.041	0.308
Biochemical pregnancy rate	21 (16.54%)	29 (18.24%)	0.142	0.706
Clinical pregnancy rate	16 (12.6%)	22 (13.84%)	0.094	0.759
Live birth rate	15 (11.81%)	18 (11.32%)	0.017	0.897
Early miscarriage rate	3 (2.36%)	16 (10.06%)	6.751	0.009

AMH, anti-müllerian hormone; OHSS, ovarian hyperstimulation syndrome.

Table 5. Correlation analysis between high AMH level and various parameters

Parameters	r	P
PCOM	0.129	0.029
Classic phenotype	0.171	0.004
Non-PCOM phenotype	-0.129	0.029
TESTO	0.181	0.002
bLH	0.137	0.021
TG	0.165	0.005
FINS	0.151	0.010
HOMA-IR	0.151	0.010
Early miscarriage	0.154	0.009

AMH, anti-müllerian hormone; PCOM, polycystic ovarian morphology; TESTO, testosterone; bLH, basal luteinizing hormone; TG, triglyceride; FINS, fasting insulin; HOMA-IR, homeostasis model insulin resistance index.

differences were observed in TCHO and FBG levels between the two groups (P>0.05 for both). These results imply that elevated AMH levels are linked to increased TG, FINS, and insulin resistance as indicated by HOMA-IR, potentially indicating a greater risk of metabolic disturbances.

Reproductive outcome

In the comparison of reproductive outcomes between the low and high AMH groups (**Table 4**), the early miscarriage rate was significantly higher in the high AMH group (10.06% vs. 2.36%, χ^2 = 6.751, P = 0.009). There were no significant differences in OHSS rate, biochemical pregnancy rate, clinical pregnancy rate, or live birth rate between the two groups (P>0.05 for all). These findings suggest that while higher AMH levels are linked to a higher risk of early miscarriage, they do not significantly affect OHSS, pregnancy or live birth rates.

Correlation analysis

In the correlation analysis between high AMH levels and various parameters (**Table 5**), significant positive correlations were found with PCOM (r = 0.129, P = 0.029), classic PCOS (r = 0.171, P = 0.004), TESTO (r = 0.181, P = 0.002), bLH (r = 0.137, P = 0.021), TG (r = 0.165, P = 0.005), FINS (r = 0.151, P = 0.010), HOMA-IR (r = 0.151, P = 0.010), and early miscarriage (r = 0.154, P = 0.009). A significant negative correlation was noted with non-PCOM phenotype (r = -0.129, P = 0.029). These results indicate that high AMH levels are associated with multiple clinical and metabolic factors, including PCOM, certain PCOS phenotypes, hormonal levels, and metabolic indicators.

Univariate and multivariate logistic regression analysis

In the univariate logistic regression analysis of risk factors for the occurrence of early miscarriage (**Table 6**), PCOM (odds ratio [OR] = 1.160, 95% odds ratio [CI] = 1.017-1.322, P = 0.027), classic phenotype (OR = 1.023, 95% CI =

Table 6. Univariate logistic regression analysis of risk factors for the occurrence of early miscarriage

Parameter	Coefficient	Std Error	Wald	P	OR	95% CI
PCOM	0.148	0.067	4.891	0.027	1.160	1.017-1.322
Classic phenotype	0.023	0.011	4.372	0.037	1.023	1.001-1.046
bLH	0.115	0.049	5.505	0.019	1.122	1.019-1.235
HOMA-IR	0.284	0.132	4.635	0.031	1.328	1.026-1.720
High AMH (>7.0 ng·mL^{-1})	1.202	0.432	7.742	0.005	3.327	1.427-7.756

PCOM, polycystic ovarian morphology; bLH, basal luteinizing hormone; HOMA-IR, homeostasis model insulin resistance index; AMH, anti-müllerian hormone; OR, odds ratio; CI, confidence interval.

Table 7. Multivariate logistic regression analysis of risk factors for the occurrence of early miscarriage

Parameter	Coefficient	Std Error	Wald	P	OR	95% CI
PCOM	0.131	0.071	3.416	0.065	1.140	0.992-1.310
Classic phenotype	0.018	0.012	2.250	0.134	1.018	0.995-1.042
bLH	0.097	0.053	3.345	0.067	1.102	0.993-1.223
HOMA-IR	0.227	0.140	2.629	0.105	1.225	0.953-1.652
High AMH (>7.0 ng·mL^{-1})	1.045	0.460	5.162	0.023	2.844	1.154-7.012

PCOM, polycystic ovarian morphology; bLH, basal luteinizing hormone; HOMA-IR, homeostasis model insulin resistance index; AMH, anti-müllerian hormone; OR, odds ratio; CI, confidence interval.

1.001-1.046, P = 0.037), bLH (OR = 1.122, 95% CI = 1.019-1.235, P = 0.019), HOMA-IR (OR = 1.328, 95% CI = 1.026-1.720, P = 0.031), and high AMH levels (OR = 3.327, 95% CI = 1.427-7.756, P = 0.005) were all significantly associated with the risk of early miscarriage.

In the multivariate logistic regression analysis of risk factors for the occurrence of early miscarriage (**Table 7**), after adjusting for PCOM, classic phenotype, bLH, and HOMA-IR, high AMH levels remained an independent risk factor for early miscarriage (OR = 2.844, 95% CI = 1.154-7.012, P = 0.023). Although PCOM (P = 0.065), bLH (P = 0.067), and HOMA-IR (P = 0.105) showed trends toward significance, they did not reach the conventional threshold for statistical independence in the multivariate model, suggesting that their association with early miscarriage may be partially explained by AMH or collinearity with other factors.

Discussion

PCOS represents a multifaceted endocrine disorder characterized by substantial inter-individual heterogeneity, which complicates both its clinical management and prognostic stratification. While elevated anti-Müllerian hormone is a well-recognized feature of PCOS, its role extends beyond a mere reflection of follicular excess. Our results demonstrate that increased AMH levels are strongly linked to a more severe clinical presentation (the classic phenotype), adverse metabolic profiles, and a higher risk of early miscarriage in PCOS patients undergoing IUI. This supports the potential of AMH as an integrated biomarker. Below, we explore these associations in the context of existing literature to hypothesize underlying mechanisms and clarify the position of our findings.

The association between elevated AMH and the classic PCOS phenotype observed in our study aligns with and extends current understanding of its role in disrupting ovarian physiology. Mechanistically, AMH is known to inhibit follicular sensitivity to FSH, impairing the selection of the dominant follicle and resulting in an accumulation of small antral follicles [21], a hallmark of PCOM. Our data corroborates this, showing a significantly greater prevalence of PCOM in the high AMH group (81.13% vs. 70.08%). Furthermore, emerging evidence suggests AMH can actively contribute to hyperandrogenism. Studies indicate that AMH may upregulate ovarian CYP17A1 expression and enhance theca cell responsiveness to LH, thereby amplifying androgen synthesis [22, 23]. This offers a plausible explanation for our observation of significantly higher serum TESTO in the high AMH group. It is crucial to acknowledge that our study did not measure direct fol-

liculogenesis indicators like antral follicular count; thus, the above mechanistic links are discussed as a supported framework from prior research rather than direct evidence from our dataset.

Our observation of a link between high AMH and worsened metabolic indicators (elevated TG, FINS, and HOMA-IR) introduces AMH into the complex pathophysiology of PCOS-related metabolic dysfunction. Traditionally, insulin resistance in PCOS is attributed to obesity and adipose tissue dysfunction. However, a bidirectional relationship between AMH and insulin signaling is gaining recognition [24]. Experimental studies propose that AMH can interfere with insulin-mediated glucose uptake in peripheral tissues by disrupting the IRS-1/PI3K/Akt pathway [25]. Our finding of significantly higher HOMA-IR in the high AMH group, despite comparable BMI between groups, supports the notion of an AMH-related insulin resistance component independent of obesity. Conversely, hyperinsulinemia can stimulate AMH production from granulosa cells, potentially creating a vicious cycle [26].

A pivotal discovery of this study is the identification of high AMH (>7.0 ng/mL) as an independent risk factor for early miscarriage in IUI cycles. While AMH is widely used to predict ovarian response, its association with early pregnancy loss points to broader disruptions in reproductive competence. The mechanisms are likely multifactorial. First, a high-AMH follicular microenvironment, often indicative of arrested follicle development and altered steroidogenesis, may compromise oocyte quality and subsequent embryo viability [27, 28]. This is consistent with our correlation data showing AMH linked to both hyperandrogenemia and insulin resistance, two factors known to impair oocyte quality. Second, AMH may adversely affect endometrial receptivity. Although not measured in our study, evidence suggests AMH can influence gene expression critically for endometrial decidualization [29]. The independent predictive value of AMH after adjusting for HOMA-IR in our multivariate analysis suggests its effect on miscarriage risk may not be entirely mediated by insulin resistance, implicating potential direct effects on the oocyte-endometrium axis, a hypothesis supported by emerging research [29]. Compared to studies focusing on IVF populations [30], our data in an IUI cohort underscore that this risk exists even in less aggressive ovarian stimulation settings.

From a clinical perspective, phenotypic and AMH-based stratification could refine risk assessment. Patients with high AMH, especially those exhibiting the classic phenotype, constitute a high-risk subgroup for early miscarriage. However, an important question is the optimal clinical threshold. While we used the upper limit of the standard laboratory reference range (7.0 ng/mL) as our cut-off, this may not represent the optimal clinical threshold for risk stratification. Future studies with larger cohorts should utilize receiver operating characteristic (ROC) curve analysis to determine the AMH level with the highest sensitivity and specificity for predicting early miscarriage in PCOS patients undergoing IUI. Another important question is whether AMH offers a clinical advantage over existing biomarkers. In our univariate analysis, AMH, HOMA-IR, and bLH were all significant predictors of early miscarriage. However, in the multivariate model, only high AMH remained independently significant. This suggests that while metabolic and hormonal disturbances contribute to risk, AMH may serve as a more integrated marker, capturing the cumulative ovarian impact of these disturbances. Future research should directly compare the area under the curve (AUC) of predictive models with and without AMH to formally quantify its added value over traditional markers like testosterone and HOMA-IR.

A crucial translational question arising from our work is whether AMH is merely a biomarker or a viable therapeutic target. Our observational data cannot answer this. While medications like metformin have been shown to modestly reduce AMH levels in some PCOS patients [31, 32], it is unclear if this reduction is a direct effect or secondary to improved metabolic parameters. Whether specifically lowering AMH, independent of improving the metabolic milieu, can lead to better reproductive outcomes is unknown and represents a critical area for future investigation. Therefore, until interventional studies prove that targeting AMH itself improves outcomes, our findings currently support the use of AMH primarily as a powerful tool for risk stratification. This stratification can identify patients who may benefit from en-

hanced pre-pregnancy counseling, intensive metabolic optimization (e.g., with insulin sensitizers), and closer monitoring during early pregnancy, rather than advocating for AMH reduction as a direct therapeutic goal.

Our study has inherent limitations due to its retrospective nature. The cross-sectional assessment of metabolic parameters precludes causal inferences. Furthermore, we did not assess markers of endometrial receptivity (e.g., integrin β3) or detailed follicular dynamics, which limits our ability to provide direct mechanistic evidence for the observed association with miscarriage. Generalizability may be limited to an IUI population. Future prospective studies are needed to validate these predictive factors and explore longitudinal changes.

In conclusion, our study reinforces that AMH in PCOS is more than an ovarian reserve marker; it is intertwined with phenotypic severity, metabolic dysfunction, and reproductive adversity. By elucidating these associations and framing them within the context of established and emerging mechanistic literature, we highlight AMH's potential as an integrative biomarker to stratify risk and inform personalized management strategies in a heterogeneous PCOS population.

Conclusion

This retrospective analysis suggests that AMH levels might be linked to several key aspects of PCOS. Higher AMH levels are potentially indicative of increased prevalence of hyperandrogenism and polycystic ovaries, as well as more frequent menstrual irregularities. AMH levels also appear to correlate with specific PCOS phenotypes, particularly classic phenotypes, suggesting its role in patient stratification. Elevated AMH is linked to increased testosterone and luteinizing hormone levels, indicating potential hormonal imbalances. Higher AMH levels are linked to elevated TG, FINS, and insulin resistance, pointing to a possible risk for metabolic disturbances. AMH levels may help predict the risk of early miscarriage during assisted reproductive treatments. These findings indicate that AMH could be a useful biomarker for evaluating PCOS severity and guiding personalized treatment strategies, though further validation is needed.

Disclosure of conflict of interest

None.

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