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RESEARCH ARTICLE

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Performance characteristics of the Mindray chemiluminescence anti-Müllerian hormone assay

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Abstract

Background: The aim of this study was to define the performance characteristics of the Mindray chemiluminescence assay for anti-Müllerian hormone (AMH) detection.

Designs and methods: Intra-assay and total imprecision, analytical sensitivity, linearity, and interference were compared between the Mindray and Roche assays using pools of human serum according to Clinical and Laboratory Standards Institute protocols. Additionally, male and female reference intervals were established using serum specimens collected from otherwise healthy groups and patients with polycystic ovary syndrome (PCOS).

Results: The intra-assay and total imprecision percent coefficients of variation for low and high AMH serum levels were 2.74%/ 3.01% and 5.41%/5.35% respectively. The limits of blank, detection, and quantitation were 0.007, 0.01, and 0.03 ng/ml, respectively. The assay displayed good linearity over the range of 0.01–23 ng/ml. The coefficient of determination (R^2) of the Mindray versus Roche assays was 0.9713 with 411 samples with AMH concentrations ranging from 0.014 to 22.1 ng/ml. The slope and intercept of the regression equation were 0.9687 and 0.3419, respectively. There was no significant interference from triglycerides (up to 3000 mg/dl), bilirubin (up to 50 mg/dl), hemoglobin (up to 500 mg/dl), or total protein (up to 10 g/dl). Reference intervals showed the expected decrease in serum AMH levels with age in healthy women and increased levels in women with PCOS.

Conclusion: The Mindray AMH assay demonstrated acceptable analytical performance under routine conditions and is suitable for determining AMH levels in serum samples.

KEYWORDS
analytical performance, anti-Müllerian hormone, Mindray chemiluminescence assay, Roche assay

Jing-Jing Zhao and Chun-Min Kang contributed equally to this work.

1 | INTRODUCTION

Anti-Mullerian hormone (AMH), a 140-kDa dimeric glycoprotein hormone, is a member of the transforming growth factor-β superfamily that plays a predominant role in male and female sexual differentiation.[1] In males, AMH, which is expressed by sustentacular cells in the testis, promotes regression of the Mullerian ducts and maintains normal development of the reproductive system.[2-4] In females, AMH is specifically expressed by granulosa cells of the developing pre-antral and antral follicles and can be measured in the serum. Once these follicles become sensitive to follicle-stimulating hormone (FSH), AMH concentrations decrease to undetectable amounts in antral follicles greater than 8 mm.[5] Therefore, AMH reflects the number of remaining primordial follicles.[6] From the fetal stage to early adolescence, AMH levels are relatively high and then slowly decrease from the age 25 of years, demonstrating a longitudinal decline until concentrations are undetectable at about 5 years before menopaus.[7-9]

Current indices to evaluate functional ovarian reserve include age, FSH, estradiol, inhibin B, and antral follicle count. Among the established endocrine markers of ovarian reserve, serum AMH concentration is superior in reflecting age-related ovarian follicle depletion as compared with other early follicular endocrine markers, such as serum concentrations of FSH, inhibin B, and estradiol.[10]

Current methods for the determination of AMH concentrations include enzyme-linked immunosorbent assay (ELISA) and chemiluminescence methods, with reagents produced by various manufacturers, including Roche Diagnostics (Basel, Switzerland), Beckman Coulter, Inc. (Brea, CA, USA), and Mindray Bio-Medical Electronics Co., Ltd. (Shenzhen, Guangdong Province, China). As compared with the traditional ELISA method, the chemiluminescence method has high sensitivity, good repeatability, a wide linear range, and high degrees of automation and standardization, and thus has been adopted in many hospitals.[11,12] About 30 hospitals in Guangdong province, China, employ the Roche AMH kit. However, the reference interval is derived from a European population. Recently, Mindray developed a chemiluminescence kit to measure serum AMH concentrations.

The aim of the present study was to assess the performance (i.e., precision, sensitivity, linearity, and specificity) of the Mindray chemiluminescence kit to measure serum AMH concentrations as compared to a similar kit manufactured by Roche. Moreover, reference intervals for AMH were established in healthy Chinese adults and female patients with polycystic ovary syndrome (PCOS).

2 | MATERIALS AND METHODS

2.1 | Subjects

Residual serum samples after routine analysis were collected to assess the performance of the Mindray chemiluminescence kit. Samples for the reference value study were collected from 1055 blood donors (150 healthy males, 779 healthy females, and 126 women with PCOS) presenting to Nanfang Hospital (Guangzhou, Guangdong Province, China) from August 2015 to October 2016. The samples were centrifuged at 3500 *g* for 10 min and stored at −70°C until analysis.

2.2 | AMH assay

Serum levels of AMH were detected with the Mindray AMH chemiluminescence immunoassay (CLIA) kit and the Roche AMH electrochemiluminescence immunoassay (ECLIA) kit. For the CLIA, the samples were added to a reaction tube with superparamagnetic particles (magnetic beads) and an alkaline phosphatase marker both coated with anti-AMH antibodies (Abs). After incubation, the AMH in the sample binds to the anti-AMH Abs coated on the beads, while the anti-AMH Abs-alkaline phosphatase label binds to another site of AMH in the sample. After the reaction is completed, a magnetic field is applied to separate the beads from the unbound material. Next, the chemiluminescent substrate (3-(2′-spiroadamantane)-4-methoxy-4-(3″-phosphoryloxy)phenyl-1,2-dioxetane) is added to the reaction tube and decomposed by alkaline phosphatase, which generates an unstable intermediate product (methyl metaoxybenzoate anions) through intramolecular electron transfer. The methyl isovalerate anions in an excited state return to the ground state, resulting in chemiluminescence. Then, the number of photons generated in the reaction, which is proportional to the concentration of AMH in the sample, is measured with a photomultiplier tube. The amount of analyte in the sample is determined in reference to a calibration curve.

For the ECLIA, 50 μl of the sample were incubated with biotin-labeled AMH-specific monoclonal Abs and ruthenium complex-labeled AMH-specific monoclonal Abs, forming an antigen-Ab sandwich complex. Upon the addition of magnetic beads coated with *Streptomyces*, the complex binds to solids through biotin and *Streptomyces* interactions. Then, the reaction fluid is drawn into the measuring tank and the magnetic beads are adsorbed on the electrode surface by electromagnetic action. Materials that are not bound to the magnetic beads are removed by application of a voltage to the electrode with a ProCell/ProCell M, which induces chemiluminescent emission that is measured with a photomultiplier. The final test results are obtained in reference to a calibration curve, which is generated by a two-point calibration and a first-order calibration curve obtained from the reagent bar code.

Precision, linearity, detection capability estimates, interference, and reference intervals were determined with a Mindray CL-2000i analyzer. The CLIA and ECLIA methods were performed with the Mindray CL-2000i analyzer and AMH CLIA kit and the Roche Cobas E602 analyzer and AMH ECLIA kit, respectively.

2.3 | Precision

Serum samples were used in this study. The assay precision was evaluated using two different serum samples with high and low

TABLE 1 Precision of the AMH assay with the Mindray analyzer

	Within-run precision				Total precision			
	N	Mean	SD	%CV	*N*	Mean	SD	%CV
Low	20	1.093	0.03	2.74	80	1.019	0.055	5.41
High	20	4.314	0.13	3.01	80	5.115	0.273	5.35

levels of AMH according to the "Clinical and Laboratory Standards Institute (CLSI) EP5-A3("Evaluation of Precision of Quantitative Measurement Procedures"[13]). Within-run precision was evaluated in a single assay run of 20 replicates of each sample. Total precision was evaluated by running four replicates of each sample on 20 different days with a new calibration each day.

2.4 | Detection capability estimates

Determinations of the limits of blank (LOB), detection (LOD), and quantitation (LOQ) were conducted in accordance with CLSI guideline EP17-A2 ("Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline"[14]). Accordingly, LOB was determined using 12 samples of a zero-concentration calibrator run on five separate days (n = 60). LOD was determined using six patient samples with low AMH concentrations. Samples were analyzed in two batches on five separate days (n = 60). The LOB and LOD were estimated with the use of a nonparametric procedure. The LOQ was determined using five serum samples with low AMH concentrations (i.e., 0.01, 0.02, 0.03, 0.04, and 0.05 ng/ml). Samples were run in three replicates and two batches over a total of 5 days. The acceptable inter-assay precision, expressed as the percent coefficient of variation (%CV), was determined by analysis of variance.

2.5 | Linearity

The proportional linearity of quantitative measurements of AMH was evaluated across the assay range according to the recommendations of CLSI guideline EP06-A2 ("Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach").[15] Assay linearity was determined with the use of two different serum samples with high or low AMH levels. Samples were mixed at ratios of 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, and 10:0 for a total of 11 serum levels, which were measured in two replicates.

2.6 | Method comparison

Because there is no gold standard for AMH to assess accuracy, the Mindray and Roche assays were compared to evaluate the agreement between the results in accordance with CLSI guideline EP09-A3 ("Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition (2013)").[16] For the method comparison, 411 specimens were used with AMH concentrations ranging from 0.014 to 22.1 ng/ml. Single samples were analyzed using the Roche assay as the target system and in duplicate with the Mindray analyzer. All samples were evaluated within five day. The results were analyzed using Deming regression analysis. The statistical parameters of the two methods, including the slope, y-intercept, and coefficient of determination (R^2), were compared.

2.7 | Analytical interference (interference study)

Serum endogenous substances with the potential to interfere with AMH measurements were evaluated following the CLSI guideline EP07-A3 ("Interference Testing in Clinical Chemistry; Approved Guideline—Third Edition").[17] Potential interference was evaluated in two serum samples at high and low AMH concentrations. The following endogenous interfering substances were selected: triglycerides (3000 mg/dl), bilirubin (50 mg/dl), hemoglobin (500 mg/dl), and total protein (10 g/dl). Samples with or without specific concentrations of interferents were prepared and analyzed in three replicates.

2.8 | Reference intervals

Adult male and female reference intervals were established according to CLSI guideline C28-A3[18] ("Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition"). The samples were generally considered to be collected from otherwise healthy patients and patients with PCOS and are, therefore, suitable for determination of reference intervals. For males, subpopulations for ages 20–50 years (n = 150) were evaluated. For females, subpopulation of ages 20–24 (n = 136), 25–29 (n = 126), 30–34 (n = 130), 35–39 (n = 132), 40–44 (n = 124), and 45–50 (n = 128) years were evaluated. For patients with PCOS, subpopulations for ages 20–55 years (n = 126) were evaluated. Nonparametric analyses were used to determine the reference intervals.

3 | RESULTS

3.1 | Precision

The within-run imprecision and total imprecision results are summarized in Table 1. At low and high AMH concentrations, the within-run %CVs of the Mindray assay were 2.74% and 3.01%, respectively,

while the total imprecision %CVs were 5.41% and 5.35%, which indicated that the imprecision of the assay was acceptable.

3.2 | Detection capability estimates

With the use of the Mindray analyzer, LOB, defined as the upper limit in a series of results in samples without analyte, was 0.007 ng/ml. The LOD, according to CLSI guideline EP17-A2, was calculated as 0.01 ng/ml. The LOQ was estimated using five samples (n = 30 each). All %CV and mean values are shown in Table 2. These data support the manufacturer's claimed LOQ of a %CV <30% at 0.03 ng/ml.

3.3 | Linearity

The linear, quadratic, and cubic regression model was performed according to the recommendations of CLSI guideline EP06-A2. The results demonstrated that the linear model is the best fitted model. As a result, linear regression analysis of the successive dilutions of the samples with high (23.25 ng/ml) and low (diluent) values of AMH yielded the regression equation $Y = 0.124 + 1.005X$, where Y is the theoretical concentration and X is the mean concentration for each dilution, which provided a Spearman's correlation (R^2) = 0.9998. The results of this method were linear in the range of 0.01–23 ng/ml, of which the lowest value was based on the LOD. Linearity data for the Mindray system are depicted in Figure 1.

3.4 | Method comparison

With the Roche Elecsys AMH assay and the Roche Cobas analyzer as the reference system, the methods for testing of AMH were compared using a total of 411 plasma specimens in the range of 0.014–22.1 ng/ml. The nonparametric Passing and Bablok regression yielded the following equation: Dimension $Y = 0.9687X + 0.3419$, where X is the Mindray system result and Y is the Roche system result. The result of the Mindray analyzer correlated well with that of the Roche analyzer (R^2 = 0.9713). A Passing-Bablok regression graph and Bland-Altman plot are shown in Figure 2.

3.5 | Analytical interferences

As shown in Table 3, the relative biases of four clinically important potential interferences were all less than 10%, indicating that there was no significant analytical interference with the Mindray analyzer at the tested concentrations of the endogenous interfering substances, which included triglycerides (3000 mg/dl), bilirubin (50 mg/dl), hemoglobin (500 mg/dl), and total protein (10 g/dl).

3.6 | Reference intervals

The calculated medians and 95% percentile reference intervals of the AMH values in healthy men, women, and women with PCOS are summarized in Table 4. The median AMH values in descending order were women with PCOS, healthy men, and healthy women. Moreover, in healthy women, the median AMH values decreased with increasing age.

4 | DISCUSSION

Ovarian reserve is a complex clinical phenomenon influenced by age, genetics, and environmental factors that represents reproductive potential and the ability to produce steroid hormones. A decrease in ovarian reserve is associated with a decrease in the number and quality of oocytes. The number and quality of oocytes are key limiting factors in female fertility.[19] Menopausal transition occurs when the number of oocytes falls below the threshold level.[20] Testing of ovarian reserve first emerged with the rise of assisted reproductive technology in the late 1980s to predict both the responsiveness to superovulation drugs and the odds of pregnancy with treatment.[21] The first test to be introduced was the day-3 FSH (1988), followed by the clomiphene citrate challenge test (1989), gonadotropin-releasing hormone (GnRH) agonist (1989), inhibin B (1997), antral follicular count (1997), and AMH (2002).[21] Among current biomarkers of ovarian reserve, AMH is considered the earliest and most sensitive for several reasons. First, there is no correlation between AMH concentration and female menstruation, age at first delivery, body mass index, waist circumference, alcohol intake, daily exercise, or social status.[22] Second, AMH concentrations decrease with age before other biomarkers, such as serum FSH and inhibin B, and the number

TABLE 2 Limits of quantitation of the AMH assay with the Mindray analyzer

Target values (TV) (ng/ml)	0.01	0.02	0.03	0.04	0.05
Mean (ng/ml)	0.0114	0.0215	0.0305	0.0412	0.0505
SD (ng/ml)	0.0014	0.0018	0.0019	0.0020	0.0025
%CV (%)	12%	8%	6%	5%	5%
Bias (%)	13%	78%	2%	3%	1%
Total error (TE; %)	37%	24%	14%	13%	11%

TE = Bias + 2*%CV; Bias = Mean/TV-1.

of follicles changes.[23] Third, there are no obvious changes in serum AMH concentrations during the follicular phase, pregnancy, or postpartum (or postnatal) period.[24] Moreover, blood samples can be collected at any time during the menstrual cycle and are not influenced by subjective factors. Hence, AMH has been widely recognized as a predictor of the quantity and quality of the ovarian follicle pool and the best marker to reflect early fertility.

Measurement of serum AMH was first described by Hudson et al. with the development of an AMH enzyme-linked immunosorbent assay.[25] The first-generation assays for AMH detection were then introduced by Diagnostic Systems Laboratories, Inc. (Webster, TX, USA) (sensitivity, 0.1 ng/ml) and Immunotech Ltd. (Prague, Czech Republic; sensitivity, 0.1 ng/ml), with different standards and Abs.[25-28] In November 2010, the ELISA Gen II Assay (sensitivity of 0.08 ng/ml) was introduced by Beckman Coulter as a replacement of the first-generation methods.[29] However, because these assays use different Abs pairs and AMH calibrators, the main limitations are related to assay variability and the lack of comparability. More recently, Roche Diagnostics introduced an automatic method, the Elecsys® AMH assay, with low inter-laboratory variability and better reproducibility than manual assays.[30] In this study, the LOB and LOD of the chemiluminescent immunoassay, calculated according to the EP17-A2 guideline, were 0.007 and 0.01 ng/ml, respectively, which were identical to those of the Roche assay. The LOQ for low AMH serum concentrations (0.03 ng/ml) was equivalent to that of the Roche assay with good linearity over the range of 0.01–23 ng/ml. In the method comparison study, the results the Mindray and Roche assays were consistent.

Notably, with the Mindray assay, there was no significant interference from triglycerides (up to 3000 mg/dl), bilirubin (up to 50 mg/dl), hemoglobin (up to 500 mg/dl), or total protein (up to 10 g/dl). However, there are some limitations to the Mindray assay, as the heterophilic Abs in human serum or plasma can react with the immunoglobulins in the kit components.[31] Patients who are often in close contact with animals or are treated with immunoglobulins may produce such Abs that can influence the test results. For example, serum samples collected from patients treated with mouse monoclonal Ab preparations may contain human anti-mouse Abs, which can lead to falsely increased or decreased analytical results.[32,33] The Mindray Chemiluminescence Kit contains anti-interference components that can effectively reduce the impact of human anti-mouse Abs in the sample, but may still interfere with a few samples. Hence, the clinical examination results, history, and other relevant information should be combined for more accurate patient assessments.

The results of the present study provided age-specific reference values in a population of healthy Chinese women in Guangdong Province. The median AMH decreased from 4.90 ng/ml in healthy women aged 20–24 years to 0.30 ng/ml in women aged 45–50 years. EP5, the obtained reference intervals differed from those of European women.[34,35] The results of the current study suggested racial/ethnic differences in AMH levels in healthy premenopausal women. Bleil et al. reported lower AMH levels

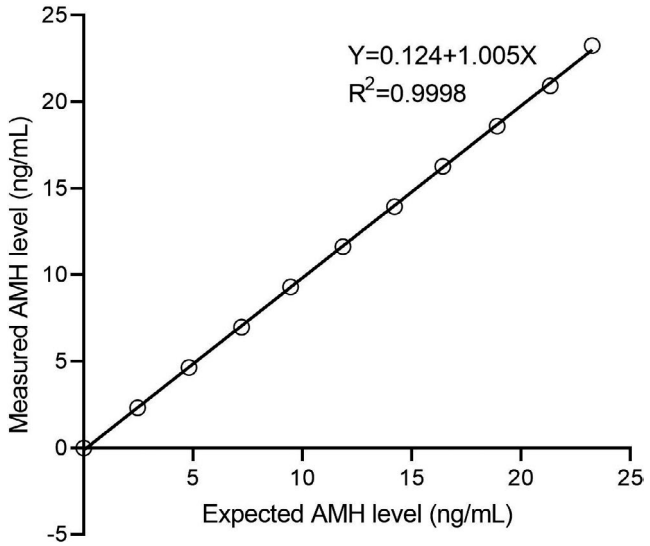

FIGURE 1 The linearity of serum AMH was evaluated by diluting a high AMH concentration with a diluent

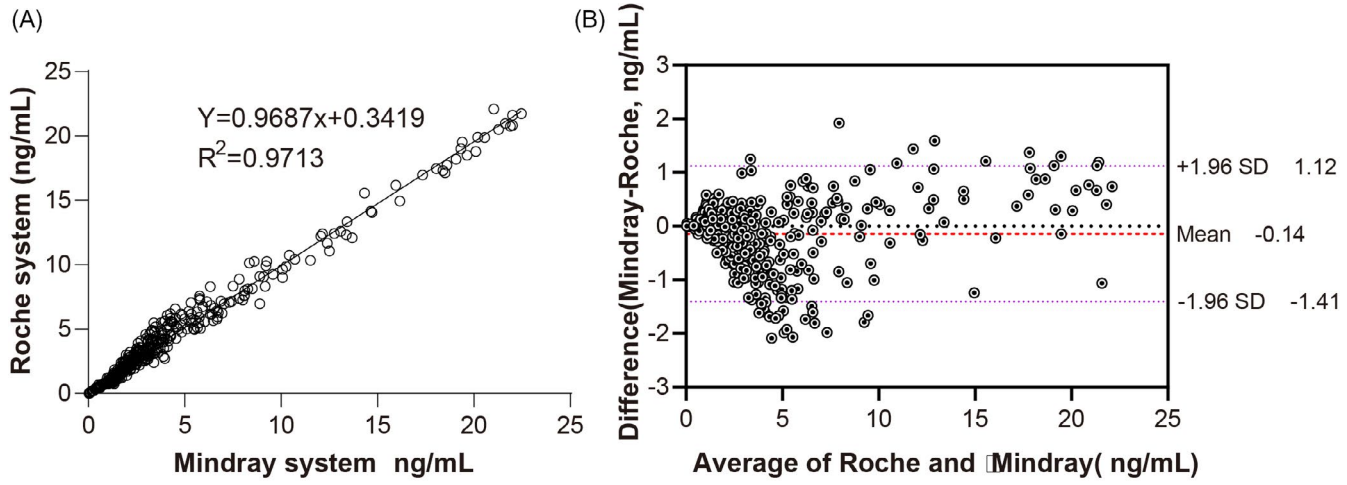

FIGURE 2 Passing-Bablok regression (A) and Bland-Altman plot (B) for the comparison between the Roche and Mindray systems

TABLE 3 Characterization of triglycerides, bilirubin, hemoglobin, and total protein interference

Interferent	Serum sample	Concentration of interferent	Test result (ng/ml)	
			Mean value of AMH	Bias
Triglycerides	Low AMH sample	0	1.113	4.94%
		3000 mg/dl	1.168	
	High AMH sample	0	4.415	5.75%
		3000 mg/dl	4.669	
Bilirubin	Low AMH sample	0	1.109	6.58%
		50 mg/dl	1.182	
	High AMH sample	0	4.54	3.13%
		50 mg/dl	4.682	
Hemoglobin	Low AMH sample	0	1.104	7.16%
		500 mg/dl	1.183	
	High AMH sample	0	4.442	3.13%
		500 mg/dl	4.581	
Total protein	Low AMH sample	0	1.117	6.18%
		10 g/dl	1.186	
	High AMH sample	0	4.489	5.03%
		10 g/dl	4.715	

in African American women at younger ages, but less reduction with advancing age, while Latina and Chinese women had lower AMH levels than Caucasian women.[34] Nelson et al.[35] found age- and ethnicity-related effects on serum AMH concentrations, with Chinese women having substantially lower AMH levels during adulthood than their European counterparts from the age of 25 years onwards. Smoking habits and obesity rates among different ethnic groups may explain the differences in AMH levels.[36,37] Besides, PCOS, characterized by an increased number of follicles at all growing stages, has been widely reported to be associated with elevated serum AMH levels.[38-41] Excessive pre-antral and small antral follicles primarily produce AMH, which reflects an intrinsic dysregulation of granulosa cells.[39] In this study, serum AMH levels increased from 0.3 to 6.9 ng/ml in women with PCOS aged 40–45 years, which further confirmed that AMH is an important feature of PCOS and has a potential role in the diagnosis of PCOS. Although the clinical applications of AMH are extensive, there have been relatively few reports of reference ranges of serum AMH concentrations for women of childbearing age. For example, Bonifacio et al.[42] measured the serum AMH levels of 492 women at childbearing age and established a reference range of AMH for normal women in Australia with the Beckman AMH second-generation detection reagent. However, studies conducted in China tend to focus on the capability of AMH to predict ovarian function and the diagnosis and treatment of PCOS. Notably, there has been no multicenter study of a reference range of AMH among Chinese women of childbearing age with normal fertility.[41,43] AMH, as an accurate and effective indicator of female ovarian function, has been widely used in clinical and epidemiological studies. However, the AMH values determined by different reagents have different degrees of deviation in clinical application. Moreover, the methodologies are also diverse, involving chemiluminescence, ELISA, and so on. The differences in AMH detection values among different regions make it difficult to arrive at a clinical diagnosis or to conduct epidemiological comparative studies. In the present study, reference values of AMH for women of childbearing age in Guangdong were established with the Mindray assay and the results were comparable with those of

TABLE 4 AMH values measured by Mindray assay in healthy men, healthy women, and women with PCOS

Group	*N*	AMH (ng/ml)		
		5th percentile (95% CI)	Median (95% CI)	95th percentile (95% CI)
Men	150	1.32	5.47	12.00
Women (20–24 years)	136	1.58	4.90	10.34
Women (25–29 years)	126	1.25	3.67	9.54
Women (30–34 years)	130	0.65	3.20	8.05
Women (35–39 years)	132	0.53	2.25	6.93
Women (40–44 years)	124	0.09	1.06	5.80
Women (45–50 years)	128	0.01	0.30	3.52
Women with PCOS (45–50 years)	126	2.3	6.9	18

the Roche assay. AMH is negatively correlated with age. An AMH concentration of 2 to 3-fold greater than the normal reference value may indicate PCOS. Therefore, it is of great significance to establish corresponding AMH reference intervals for women of different age groups, which can provide important and reasonable reference data for clinical diagnosis and treatment of ovarian dysfunction and epidemiological research.

In summary, several publications have reported promising results for AMH as a biomarker of ovarian reserve as well as PCOS diagnosis. The Mindray chemiluminescence assay for AMH demonstrated good performance for all evaluated parameters, including precision, detection capability, and linearity. Besides, the AMH reference values determined in this study provide clinicians with age-dependent reference intervals in a population of Chinese women from Guangdong province. This assay can applied in the laboratory for rapid assessment of ovarian reserve assessment and PCOS diagnosis.

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Jing-Jing Zhao and Chun-Min Kang make the same contribution to this article. Peng Zhang and Lei Zheng conceived and designed the study. Jing-Jing Zhao and Chun-Min Kang analyzed the data and generated the tables and figures.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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