The evaluative effectiveness of a combined index exceeded that of a single variable for the ovarian reserve and response of infertile women

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Abstract

Aim of the present study was to explore the evaluative effectiveness of age, ovarian volume, antral follicle count (AFC), serum follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), FSH/LH ratio and ovarian response prediction index (ORPI) to determine which could most advantageously assess ovarian reserve and response.Methods This research enrolled 319 consecutive infertile women who had undergone IVF-ET/ICSI treatments. Abovementioned variables were measured and calculated. Receiver Operating Characteristic Curve analysis was used to analyze the predictive accuracy of variables and to calculate cut-off values and corresponding sensitivity and specificity.Results Our study revealed that the significant variables for evaluating a decline in ovarian reserve include age, total volume of bilateral ovary, FSH, and ORPI. Moreover, the area under the curve (AUC) of ORPI was higher than other three variables (AUC = 0.903), and the cut-off value of ORPI was 0.245 (sensitivity 90.1%, specificity 73.9%). The significant variables forecasting excessive ovarian response were age, AFC, AMH, ORPI, FSH and FSH/LH ratio, and the significant variables forecasting low ovarian response were AMH and FSH/LH ratio. ORPI and FSH/LH ratio presented better effectiveness in evaluating ovarian response. When they were used to predict excessive response, the cut-off values of ORPI and FSH/LH ratio was 0.886 (sensitivity 84.7%, specificity 67.3%) and 1.753 (sensitivity 56.2%, specificity 67.6%), respectively. When used to predict low response, the cut-off value of FSH/LH ratio was 2.983 (sensitivity 75.0%, specificity 83.8%).Conclusions ORPI performed better than did the other variables in evaluating ovarian reserve and predicting excessive ovarian response, and the FSH/LH ratio performed better than did the other variables in predicting low ovarian response. Consequently, we agreed that the evaluative effectiveness of a combined index exceeded that of a single variable for evaluating the ovarian reserve and response of infertile women.

Introduction

Several studies [1-4] have revealed that age, antral follicle count (AFC) and serum anti-Müllerian hormone (AMH) levels reflect the ovarian reserve exactly, so these factors are considered valuable predictors of the ovarian response to exogenous gonadotrophins. Tobler et al. [1] surveyed 796 infertility clinics worldwide; sixty percent of the respondents reported using AMH as a first-line test in in vitro fertilization (IVF) cycles, and 54% reported AMH as the best test for evaluating ovarian reserve; eighty-nine percent reported that AMH results were relevant to clinical practice. Two studies reported that AMH was an effective measure of quantitative ovarian reserve and was strongly associated with the ovarian response and oocyte yield after ovarian stimulation [2,3]. Another study noted that using AMH, AFC and age together constituted the best model for predicting poor or excessive ovarian response [4].

However, several scholars have considered the evaluative effectiveness of the above parameters to be unsatisfactory and inaccurate for clinical practice. For example, Hvidman et al. [5] stated that serum AMH and AFC were not lower in infertile patients aged 20-39 years than in a control group of the same age with no history of infertility. Furthermore, debate exists regarding whether a single parameter or a combined index (follicle-stimulating hormone/luteinizing hormone ratio, FSH/LH ratio; ovarian response prediction index, ORPI) is a superior tool for evaluating the ovarian reserve or response. The FSH/LH ratio can be used to differentiate between decreased and normal response cycles, and the elevated day-3 FSH/LH ratio is associated with an inferior outcome in IVF treatment cycles [68]. Oliveira et al. [9] innovatively used ORPI to assess ovarian response and found that ORPI exhibited an excellent ability to predict low or excessive ovarian response, a collection of greater than or equal to four MII oocytes and the occurrence of pregnancy in infertile women.

We retrospectively enrolled 319 consecutive infertile women who had undergone IVF/intracytoplasmic sperm injection (ICSI) treatments from September 2016 to August 2017 and explored the effectiveness of the parameters to determine which could be used to most advantageously assess ovarian reserve and response.

Materials And Methods

Subjects and study groups

The study population consisted of 319 consecutive infertile women between the ages of 21 and 45 who had experienced infertility lasting 1-18 years, all subjects were the first time to have IVF treatment, and administrated gonadotropin-releasing hormone (GnRH) antagonist protocol to perform ovulation induction. The rates of primary infertility type and secondary type were 37.04% and 62.96%, respectively. The rates of male factor, female factor and double factor infertility were 7.41%, 25.93% and 66.66%, respectively. Patient history and clinical information were obtained from their medical records. All of the women were determined to have both ovaries present, no history of ovarian surgery, no severe endometriosis and no evidence of endocrine disorders. Conventional IVF and/or ICSI were performed according to the cause of infertility. Infertile women were excluded if they were using fertility drugs (for example, clomiphene, letrozole, and gonadotropin) or had any autoimmune, genetic, or iatrogenic conditions, autoimmune endocrinopathies, radiation therapy or pelvic surgery, as these factors have been shown to alter the serum reproductive hormone and AMH levels. Patients were stratified into the following age groups: 21-29 years (Group 1), 30-34 years (Group 2), 35-39 years (Group 3) and 40-45 years (Group 4).

This study was approved by the Biomedical Ethics Committee of Peking University International Hospital, and informed written consent was obtained from all patients.

Ovarian stimulation protocols

The ovarian stimulation protocols performed the GnRH antagonist protocols. The gonadotropin (Gn) used was recombinant FSH (Gonal-f, Laboratoires Serono SA, Aubonne, Switzerland) and human menopausal gonadotrophin for injection (Livzon Pharmaceutical Group Inc. Zhuhai, Guangdong Province, China). The antagonist was Ganirelix Injection (ORGALUTRAN, Ravensburg, Germany). After the third day of treatment, the Gn dose was adjusted to the patient response. The total Gn dose was 2076.72±963.33 IU, and the Gn treatment duration was 9.65±2.74 days in each IVF/ICSI cycle. The trigger drug was recombinant human chorionic gonadotropin alpha for injection (OVIDREL 250 μg, Laboratoires Serono S.A. (LSA), Aubonne, Switzerland).

Measurement of reproductive hormones and AMH

Blood samples were obtained by venipuncture at 7:30 A.M.-10:00 A.M., and the basal serum FSH, LH, estradiol (E2), total testosterone (TT) levels, and serum AMH levels were tested on spontaneous cycle days 2-4, within 2 months of the IVF/ICSI cycle. The FSH, LH, E2, TT (kit from Abbott Ireland Diagnostics Division Lisnamuck, Longford Co. Longford Ireland) and AMH (kit from Roche Diagnostics GmbH, Mannheim, Germany) levels were determined with commercial kits and an electrochemiluminescence immunoassay.

Ovarian volume (OV) and antral follicle count

The experienced and qualified sonographers performed ultrasonographic evaluations for all subjects during spontaneous cycle days 2-4 using a two-dimensional transvaginal probe of 9 MHz frequency (HD11 XE, Philips Ultrasound, Inc., Bothell WA. USA). The total number of 2-9 mm antral follicles in both ovaries was measured and recorded. OV was calculated as the volume of an ellipsoid, that is, 0.52×Length×Width×Depth. The total basal volume of both ovaries was evaluated in each patient.

Calculation of body mass index (BMI), FSH/LH ratio and ovarian response prediction index (ORPI)

Height and weight were used to calculate BMI, that is, weight (kg)/height (m^2). Serum FSH and LH concentration were used to calculate FSH/LH ratio. The ORPI was defined by the following equation: ORPI = (AMH × AFC)/Patient age [9].

Statistical analysis

Microsoft Excel 2013 software (Microsoft Corporation, Redmond, State of Washington, USA) and SPSS 21.0 (IBM Corporation, New York, USA) were used for all statistical analysis. The data were presented as the mean ± standard deviation (SD), as calculated for all subjects and each group. The one-way ANOVA test was used to assess the differences between the mean values of parameters in the different groups. Pearson's correlation analysis was used to assess the correlations between different parameters. Receiver Operating Characteristic Curve (ROC Curve) analysis was used to analyze the predictive accuracy of variables and to calculate the cut-off values and corresponding sensitivity and specificity. Tests were considered statistically significant if $P < 0.05$.

Ethics and informed consent statement

This study, and the accompanying consent forms, were approved by the Ethics Committee and Institutional Review Board of Peking University International Hospital and Tangshan Maternity and Child Healthcare Hospital. Participants were recruited for the study after written informed consent was obtained.

Results

One-way ANOVA analysis between different subgroups

Clinical data and variable data of subjects presented in Table 1, and the boxplots of variables' frequency distribution presented in Figure 1.

BMI, total volume of bilateral ovaries, serum FSH, LH, E2, TT, and FSH/LH ratio were not significantly different among the four subgroups; however, the duration of infertility, AFC, serum AMH levels, ORPI and retrieved oocyte numbers were significantly different among the four subgroups.

Multiple comparisons showed that the durations of infertility were significantly different between Group 1 and Groups 3 and 4 (P = 0.034, P = 0.003). The AFC were significantly different between Group 1 and Groups 3 and 4 (P = 0.000, P = 0.000), between Group 2 and Groups 3 and 4 (P = 0.001, P = 0.000), and between Group 3 and Group 4 (P = 0.004). AFC decreased gradually as age increased, as presented in Figure 1 (a). The AMH levels were significantly different between Group 1 and Group 4 (P = 0.004) and between Group 3 and Group 4 (P = 0.009). The AMH boxplot is presented in Figure 1 (b). ORPI was significantly different between Group 1 and Groups 2, 3, and 4 (P = 0.005, P = 0.000, P = 0.000), between Group 2 and Group 4 (P = 0.001), and between Group 3 and Group 4 (P = 0.002). ORPI decreased gradually as age increased, as presented in Figure 1 (d). The retrieved oocyte numbers were significantly different between Group 1 and Groups 2 and 4 (P = 0.046, P = 0.006), between Group 2 and Group 3 (P = 0.046), and between Group 3 and Group 4 (P = 0.001). The boxplot of retrieved oocyte numbers is presented in Figure 1(f).

Pearson correlation analysis

AFC demonstrated positive correlation with the total volume of bilateral ovaries (P = 0.009), AMH (P = 0.000) and ORPI (P = 0.000); however, AFC was negatively correlated with age (P = 0.000) and serum FSH level (P = 0.000). The above-mentioned parameters could reflect ovarian reserve.

There were positive correlations between the retrieved oocyte numbers and AFC (P = 0.000), total volume of bilateral ovaries (P = 0.020), AMH (P = 0.000), ORPI (P = 0.000), and LH (P = 0.011); however, a negative correlation existed between the retrieved oocyte numbers and age (P = 0.003). The above-mentioned parameters could reflect ovarian response.

There were negative correlations between age and AFC (P = 0.000), AMH (P = 0.018), ORPI (P = 0.000) and retrieved oocyte numbers (P = 0.003). BMI was inversely correlated with FSH (P = 0.015) and FSH/LH ratio (P = 0.010) but did not correlate with AMH or AFC.

ROC Curve analysis for evaluating ovarian reserve

In general, AFC<5 was one of the standards indicating decline of ovarian reserve [10]. Using the abovementioned standards and the ROC Curve to evaluate the significant variables of ovarian reserve decrease, which included age, total volume of bilateral ovary, FSH, and ORPI, the corresponding area under the curve (AUC) was 0.707, 0.629, 0.652, and 0.903, respectively. Although the AUC of AMH was 0.613, it was less valuable to access ovarian reserve (P = 0.065). AUC, cut-off values, sensitivity and specificity of variables evaluating ovarian reserve are presented in Table 2 and Figure 2 (a)-(b).

According to our results, ovarian reserve would decrease when subjects' age and FSH were more than the cut-off values, moreover, the total volume of bilateral ovary and ORPI were less than the cut-off values.

ROC Curve analysis for forecasting ovarian response

According to the retrieved oocyte numbers, ovarian response categories were divided into low response (oocytes ≤3), normal response (4-14 oocytes) and excessive response (oocytes ≥15) [9, 10].

We used the abovementioned standards and the ROC Curve to forecast the significant variables of excessive ovarian response, which included age, AFC, AMH, ORPI, FSH and FSH/LH ratio, and to forecast the significant parameters of low ovarian response, which included AMH, FSH/LH ratio. The AUC, cut-off values, and corresponding sensitivity and specificity of variables evaluating ovarian response are presented in Table 2, Figure 3 (a)-(b), and Figure 4 (a)-(b).

Discussion

Ovarian reserve can be altered or reduced due to age, disease, pelvic operation, chemotherapy or radiotherapy, among other factors, and it is beneficial to create treatment regimes, survey treatment effects and forecast prognoses for infertile women by evaluating ovarian reserve or response. Our results indicated that the AFC, serum AMH levels, ORPI and retrieved oocyte numbers were significantly different among the four subgroups and that there were negative correlations between age and AFC, AMH, ORPI and retrieved oocyte numbers. Thus, we discovered that AFC and ORPI decreased gradually with age. Lee et al. [11] and Raeissi et al. [12] observed increased FSH levels and decreased AMH levels with increasing age in women. Bozkurt et al. [13] reported that AMH was inversely correlated with age; however, AFC revealed a stronger correlation with age in both the fertile and infertile populations compared with basal FSH and AMH; the decrease in ovarian reserve in infertile patients was directly related to age, not infertility.

AFC on day 2-4 of the menstrual cycle, evaluated by transvaginal ultrasound, is commonly used to determine ovarian reserve, but AFC measurement is prone to error because of different sonographers. To explore the evaluative effectiveness of various variables, we analyzed the correlation of AFC with other variables and found that AFC showed a positive correlation with total volume of bilateral ovary, AMH and ORPI; however, AFC showed a negative correlation with age and serum FSH level. However, Somigliana et al. [14] insisted that low serum AMH is not associated with female subfertility.

The literature has reported that BMI is not associated with the AMH levels in the general population of infertile women or in patients without polycystic ovary syndrome (PCOS); however, BMI is significantly and inversely correlated with AMH in women with PCOS [15]. Another study found that age is negatively correlated with AMH and AFC across all races ($P < 0.05$) and that elevated BMI is negatively correlated with AMH in Caucasian women but not in African-American, Hispanic, or Asian women [16]. The results from our research showed that BMI was inversely correlated with FSH and FSH/LH ratio but did not correlate with AMH or AFC. In brief, debate still exists regarding the influence of BMI on ovarian function and AMH levels.

The ROC analysis results in our study revealed that the significant variables for evaluating ovarian reserve decrease included age, total volume of bilateral ovary, FSH, and ORPI. Moreover, the AUC of ORPI was higher than those of the other three variables, and the diagnostic accuracy reached a “high” grade; the cut-off value of ORPI from ROC analysis was 0.245 (sensitivity 90.1%, specificity 73.9%). Assessments of the AMH and FSH levels in combination with female age could be helpful in predicting ovarian reserve in infertile women [12].

Many studies [17-21] have discussed how AFC and AMH could be used to assess ovarian reserve. However, our research did not find that these two variables acted as a single variable to significantly assess ovarian function. Serum AMH and AFC begin to decline in women between 34 and 35 years old, and AMH predicts biological age earlier than FSH or AFC do, and AFC does so earlier than FSH does [17]. By age 32, over 50% of women with subfertility had AMH levels categorized as "low fertility" (AMH ≤ 19.5 pmol/liter), a figure that increased to 75% by age 39, with a decrease in mean AMH of 1.72 pmol/liter/year [18]. The serum AMH cut-off value for the normal ovarian reserve was calculated as 0.37 ng/ml (sensitivity 71.43%, specificity 66.67%, positive prediction 83.33%, negative prediction 50%) [19]. AMH should be considered a more reliable ovarian reserve assessment test compared to FSH because there was a strong positive correlation between the serum AMH level and AFC; further, the use of AMH combined with AFC may improve ovarian reserve evaluation [20]. The present findings suggest the applicability of AMH determination as a marker for actual fertility in subfertile women with elevated basal FSH levels, as AMH was significantly associated with the timing of reproductive stages (i.e., the occurrence of menopausal transition or menopause during follow-up) [21]. Our results showed that the cut-off value of age was 36.50 for predicting ovarian reserve decline and that the corresponding sensitivity and specificity were 88.0% and 40.8%, respectively.

We found that the significant variables forecasting excessive ovarian response included age, AFC, AMH, ORPI, FSH and FSH/LH ratio, and that the significant variables forecasting low ovarian response included AMH and FSH/LH ratio. Interestingly, ORPI and FSH/LH ratio demonstrated better effectiveness in evaluating ovarian response. When used to predict excessive response, the cut-off value of ORPI from ROC analysis was 0.886 (sensitivity 84.7%, specificity 67.3%), and the cut-off value of FSH/LH ratio was 1.753 (sensitivity 56.2%, specificity 67.6%). When used to predict low response, the cut-off value of FSH/LH ratio was 2.983 (sensitivity 75.0%, specificity 83.8%).

In recent years, many studies have focused on the value of a single parameter. For example, AMH was strongly associated with oocyte yield after ovarian stimulation and may therefore predicted ovarian response and the quality of oocytes and embryos [2, 19,22], and AMH had a higher predictive value for the responders and AFC than for FSH, E2 and chronological age, moreover, could predict the risk of ovarian hyperstimulation syndrome (OHSS) among patients [23,24]. Vembu et al. [25] reported ROC curve was plotted to predict the hyper response (OHSS), which showed a serum AMH cut-off value of 6.85 ng/ml with a sensitivity of 66.7% and a specificity of 68.7% for PCOS group and 4.85 ng/ml with a sensitivity of 85.7% and a specificity of 89.7% in non-PCOS group. AFC is superior to AMH in predicting poor ovarian response. The cut-off point for mean AMH and AFC in discriminating between poor and normal ovarian response cycles was 0.94 ng/ml (with a sensitivity of 70% and a specificity of 86%) and 5.5 (with a sensitivity of

91% and a specificity of 91%), respectively [26]. Iranian women with a basal AMH level > 6.95 ng/ml are at a high risk of developing OHSS, and those with AMH level < 1.65 ng/ml are poor responders [27].Our results showed that the AMH cut-off value for excessive ovarian response and low response was 3.955 ng/ml (sensitivity 59.7%, specificity 79.1%) and 1.405 ng/ml (sensitivity 70.8%, specificity 77.8%), AFC cut-off value for excessive ovarian response was 14.50 (sensitivity 77.8%, specificity 77.1%), respectively.

Currently, two popular combined indexes, ORPI and FSH/LH ratio, are used to assess ovarian function. Regarding the probability of collecting greater than or equal to 4 oocytes, ORPI showed an AUC of 0.91 and an efficacy of 88% at a cut-off of 0.2, but for the probability of collecting greater than or equal to 15 oocytes, ORPI showed an AUC of 0.89 and an efficacy of 82% at a cut-off of 0.9 [9]. The cut-off value reported by that study approximated our results. Oliveira et al. [28] reported the ORPI offered excellent ovarian response prediction (AUC = 0.91), and good predictions for the possibility of collecting > 4 MII oocytes (AUC = 0.84) and excessive ovarian response (AUC = 0.89) in infertile women, and ORPI value (≥1.7) was the benchmark that indicated high risk for OHSS. Selcuk et al.[29] found that the level of association between the ovarian response tests and poor ovarian response data was (in descending order): ovarian sensitivity index (OSI), ORPI, AFC, AMH, and age (AUC = 0.976, 0.905, 0.899, 0.864, 0.617, respectively), and OSI and ORPI could be superior to other ovarian responsiveness markers for poor and high ovarian responses on cycles with agonist or antagonist protocols. However, ORPI was more convenient than OSI, because OSI could be calculated after informed of the number of retrieved oocytes. In addition, opposing views on ORPI effectiveness continue to exist. Another study showed that both AMH and AFC were good predictors of ovarian response with an AUC > 0.75 but that combining these variables was necessary as ORPI would not improve the prediction value [30]. Using the cut-off value derived from ROC analysis, cycles with an FSH/LH ratio > or =3 produced fewer mature oocytes (8.25 vs. 11.74) and a higher percentage of poor ovarian response cycles (32.5% vs. 14.3%). Additionally, the serum FSH level and FSH/LH ratio at the commencement of gonadotropin stimulation were inversely correlated to the number of mature oocytes [6]. According to our results and previous reports in the literature, the abovementioned combined indexes had excellent performances in evaluating ovarian reserve and response.

Some shortcomings still exist in our research. First, there were no comparison data on ovarian function between fertile and infertile women. Second, we did not focus on predicting the influence of stimulation protocols and cycle cancellations. Previous research has shown that an elevated FSH/LH ratio >3 is more likely to result in the cancellation of the individual’s cycle (15% vs 5.24%, $p = 0.0001$) and that the total gonadotropin dosage was greater in the higher-ratio group than in lower-ratio group (2636 vs 2242 IU; significant) [31]. Finally, we did not collect data on embryo quality and pregnancy outcome associated with parameters in this research. Several studies have paid close attention to treatment outcomes. An FSH/LH ratio less than 1.26 is associated with good oocyte parameters, high-quality embryos and implantation after ICSI [32].

Conclusion

Comparing the effectiveness of evaluating ovarian reserve and predicting ovarian response on age, ovarian volume, AFC, serum FSH, AMH, FSH/LH ratio and ORPI, we found that ORPI was superior to the other parameters in evaluating ovarian reserve and predicting excessive ovarian response, whereas FSH/LH ratio was superior to the other parameters in predicting low ovarian response. Consequently, we agreed that the evaluative effectiveness of a combined index exceeded that of a single parameter for evaluating the ovarian reserve and response of infertile women.

Abbreviations

AFC: antral follicle count; AMH: anti-Müllerian hormone; AUC: the area under the curve; BMI: body mass index; E2: estradiol; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; IVF/ICSI: in vitro fertilization/ intracytoplasmic sperm injection; LH: luteinizing hormone; OHSS: ovarian hyperstimulation syndrome; ORPI: ovarian response prediction index; OSI: ovarian sensitivity index; OV: ovary volume; PCOS: polycystic ovary syndrome; ROC Curve: Receiver Operating Characteristic Curve; SD: standard deviation; TT: total testosterone.

Declarations

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Consent to publish

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Author Contribution

Conceptualization: Zhou SJ. Data curation: Zhou SJ, Zhao MJ. Formal analysis: Zhou SJ, Zhao MJ. Investigation & Measurement: Zhou SJ, Zhao MJ, Li C, Su X. Methodology & Supervision: Zhou SJ. Writing-original draft: Zhou SJ, Zhao MJ. Writing-review & editing: Zhou SJ.

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Tables

Table 1 Frequencies of 319 subjects’ clinical data and variable data

Variables	319 subjects		Subgroups				
	Mean±SD	Range	Group 1 (n=36) Mean±SD	Group 2 (n=29) Mean±SD	Group 3 (n=164) Mean±SD	Group 4 (n=90) Mean±SD	*P* value#
Age	36.92±4.91	21.00-45.00	26.64±1.97	32.07±1.53	37.19±1.18	42.06±1.72	0.000
Duration of infertility	4.82±3.77	1.00-18.00	3.34±2.00	4.59±2.58	4.85±3.67	5.63±4.76	0.034
BMI	23.31±3.13	17.31-33.12	22.84±2.37	23.06±4.17	23.14±3.13	23.92±2.97	0.228
AFC	13.37±7.31	1.00-32.00	20.04±7.34	18.23±7.46	12.95±6.95	9.78±4.99	0.000
OV (total) (ml)	6.74±2.57	2.76-22.44	6.51±1.65	6.46±2.54	6.92±2.58	6.57±2.87	0.716
AMH (ng/ml)	3.24±2.42	0.11-11.99	3.97±2.25	3.12±2.30	3.44±2.62	2.59±1.98	0.014
FSH (IU/liter)	7.09±3.99	1.08-32.51	6.29±1.73	7.08±5.47	7.22±4.47	7.22±3.10	0.666
LH (IU/liter)	4.28±3.12	0.15-24.14	4.28±3.08	3.92±2.68	4.64±3.47	3.78±2.58	0.240
E2 (pg/ml)	85.80±113.12	9.00-868.00	83.20±116.91	98.04±105.60	80.43±100.34	92.63±136.06	0.823
TT (nmol/liter)	0.53±0.81	0.01-7.40	0.43±0.20	0.42±0.19	0.65±1.10	0.41±0.18	0.437
ORPI	1.45±1.62	0.01-7.79	3.15±2.18	1.94±1.75	1.39±1.51	0.69±0.67	0.000
FSH/LH ratio	2.19±1.81	0.11-15.15	2.23±1.90	2.88±3.50	1.97±1.49	2.32±1.27	0.099
Retrieved oocytes	12.03±6.66	1.00-36.00	13.64±6.77	10.38±6.62	13.02±7.01	10.10±5.41	0.002

#: The differences between the mean values of parameters in the four groups.

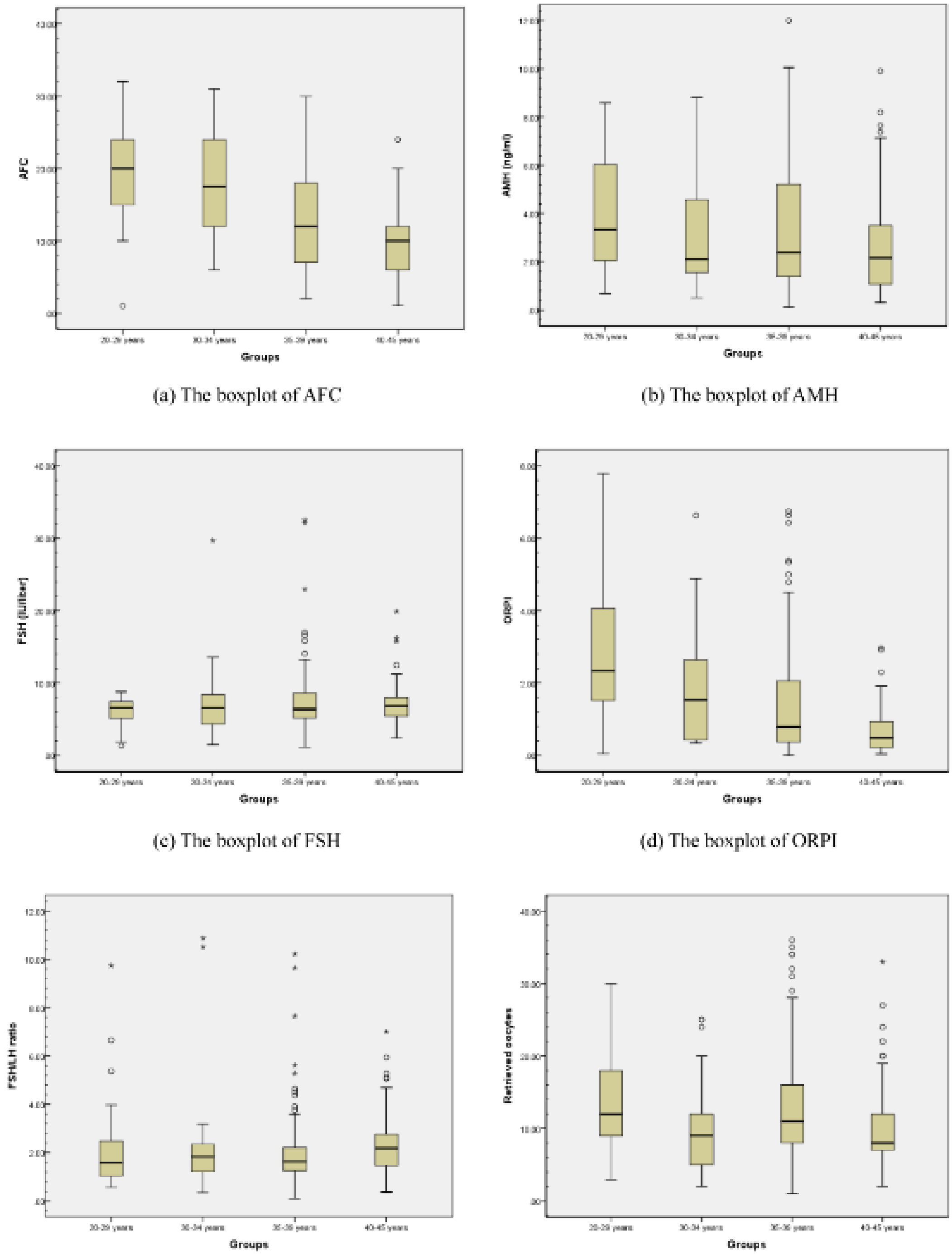
SD: standard deviation; BMI: body mass index; AFC: antral follicle count; OV: total volume of bilateral ovaries; AMH: anti-Müllerian hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; TT: total testosterone; ORPI: ovarian response prediction index.

Table 2 The AUC and cut-off values of variables evaluating ovarian reserve and response

varian nction	Characteristics of state variable	Variables	AUC	*P* value	Cut-off value	Sensitivity (%)	Specificity (%)
varian eserve	Positive reserve	OV	0.629	0.043	5.54	68.3	60.9
		ORPI	0.903	0.000	0.245	90.1	73.9
	Negative reserve	Age	0.707	0.002	36.50	88.0	40.8
		FSH	0.652	0.014	7.05	66.7	61.6
varian esponse	Positive excessive response	AFC	0.798	0.000	14.50	77.8	77.1
		AMH	0.750	0.000	3.955	59.7	79.1
		ORPI	0.833	0.000	0.886	84.7	67.3
	Negative excessive response	Age	0.626	0.002	40.50	27.0	94.6
		FSH	0.615	0.004	5.705	72.4	52.7
		FSH/LH ratio	0.618	0.003	1.753	56.2	67.6
	Positive low response	FSH/LH ratio	0.786	0.047	2.983	75.0	83.8
	Negative low response	AMH	0.751	0.011	1.405	70.8	77.8

AUC: the area under the curve; OV: total volume of bilateral ovaries; ORPI: ovarian response prediction index; AFC: antral follicle count; AMH: anti-Müllerian hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone.

Figures



(a) The boxplot of AFC

(b) The boxplot of AMH

(c) The boxplot of FSH

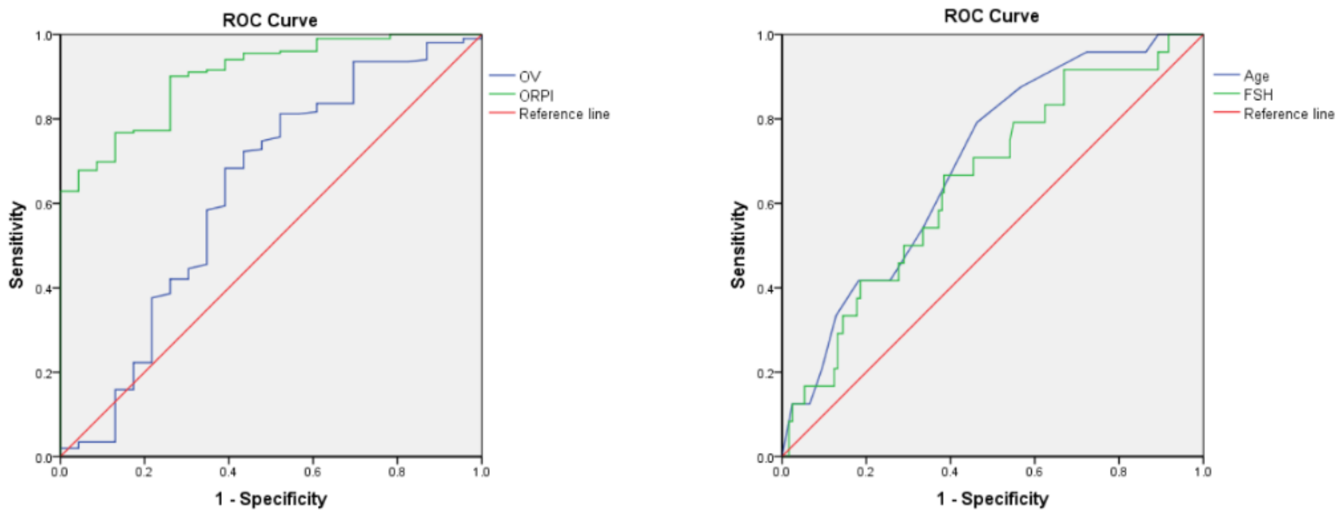
(d) The boxplot of ORPI

(e) The boxplot of FSH/LH ratio

(f) The boxplot of retrieved oocytes

Figure 1

Frequencies of 319 subjects' clinical data and variable data

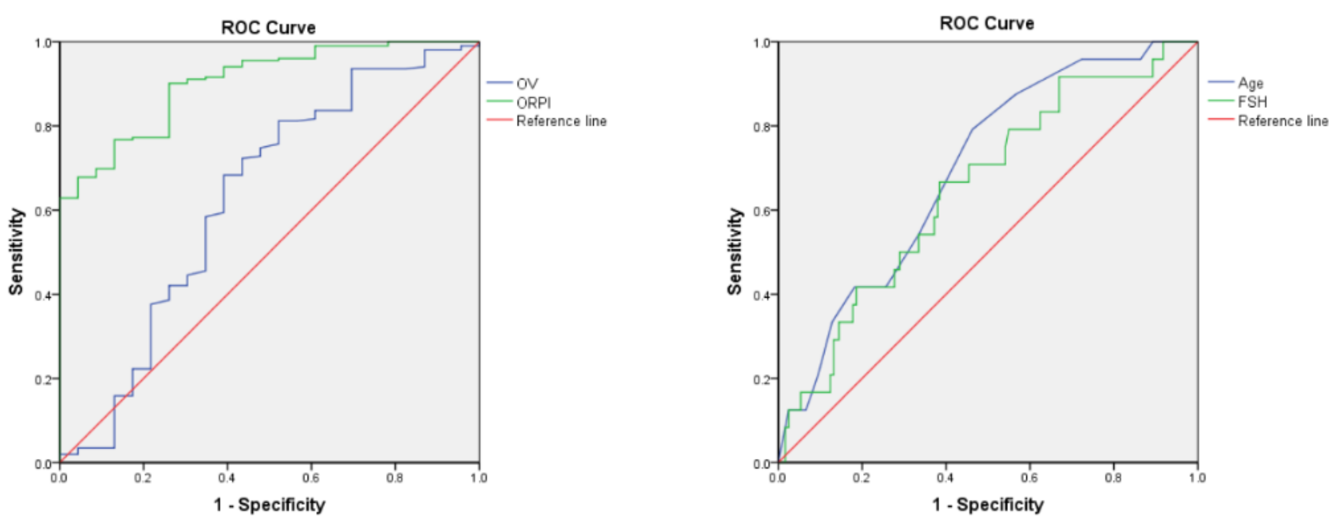


(a) ROC Curve of OV and ORPI evaluating ovarian reserve decrease

(b) ROC Curve of age and FSH evaluating ovarian reserve decrease

Figure 2

ROC Curve of variables evaluating ovarian reserve decrease. ROC Curve: Receiver Operating Characteristic Curve; FSH: follicle-stimulating hormone; OV: total volume of bilateral ovaries; ORPI: ovarian response prediction index.

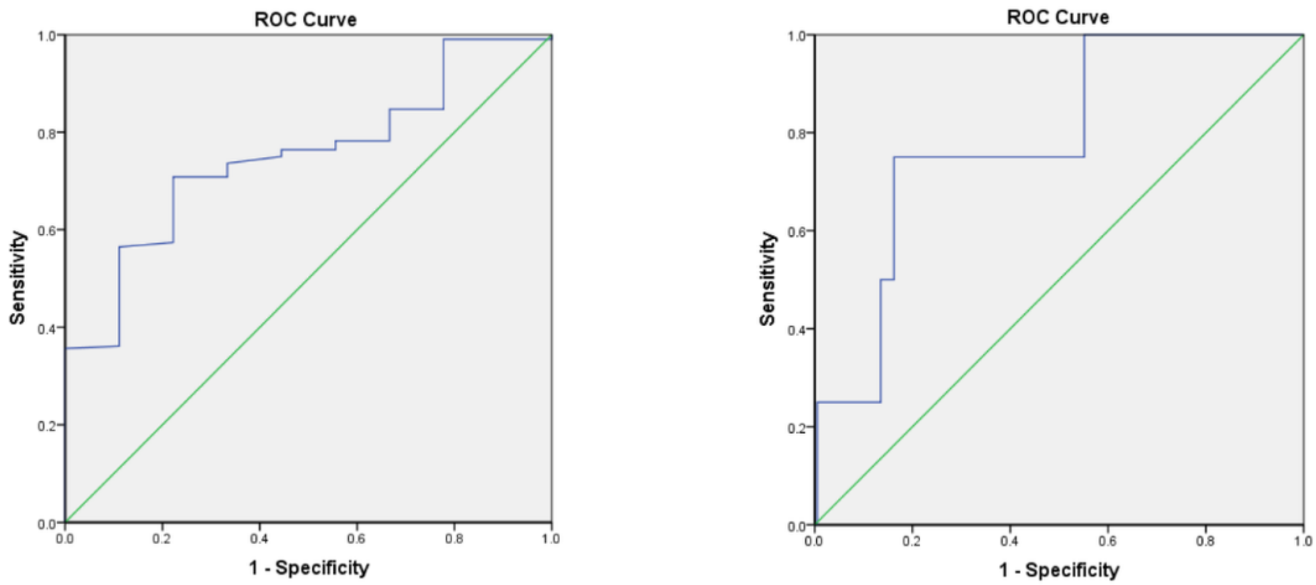


(a) ROC Curve of OV and ORPI evaluating ovarian reserve decrease

(b) ROC Curve of age and FSH evaluating ovarian reserve decrease

Figure 3

ROC Curve of variables forecasting excessive ovarian response. ROC Curve: Receiver Operating Characteristic Curve; AFC: antral follicle count; AMH: anti-Müllerian hormone; ORPI: ovarian response prediction index; FSH: follicle-stimulating hormone; LH: luteinizing hormone.



(a) ROC Curve of AMH forecasting low ovarian response

(b) ROC Curve of FSH/LH ratio forecasting low ovarian response

Figure 4

ROC Curve of variables forecasting low ovarian response. ROC Curve: Receiver Operating Characteristic Curve; AMH: anti-Müllerian hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone.