Comparison of ovarian responsiveness tests with outcome of assisted reproductive technology – a retrospective analysis

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Abstract

Introduction: This study aims to compare the association between the most commonly used ovarian responsiveness markers – age, anti-Müllerian hormone levels (AMH), antral follicle count (AFC), ovarian sensitivity index (OSI), and ovarian response prediction index (ORPI) – and ovarian responsiveness to gonadotropin stimulation in assisted reproductive technology (ART) cycles.
Material and methods: Patients who underwent intracytoplasmic sperm injection treatment using either a gonadotropin releasing hormone (GnRH) antagonist or agonist protocol were enrolled in the study. Data of the patients were abstracted from the hospital's database. Tests were compared for total number of retrieved oocytes, metaphase II (MII) oocytes, embryos, good quality embryos on day 1 and day 3, and ongoing pregnancies per cycle.
Results: The OSI was the ovarian response test that had the strongest relationship with the ART outcomes. The level of association between the ovarian response tests and poor ovarian response data was (in descending order): OSI, ORPI, AFC, AMH, and age ($AUC_{OSI} = 0.976$, $AUC_{ORPI} = 0.905$, $AUC_{AFC} = 0.899$, $AUC_{AMH} = 0.864$, $AUC_{age} = 0.617$). The overall association between OSI and poor ovarian response was significantly higher than the other parameters ($p_1 = 0.0023$, $p_2 = 0.0014$, $p_3 = 0.0001$, $p_4 \leq 0.0001$). In patients with high ovarian response data, OSI had the highest association, followed by AFC and ORPI age ($AUC_{OSI} = 0.984$, $AUC_{AFC} = 0.907$, $AUC_{ORPI} = 0.887$). There was no statistically significant difference among the tests for the data of patients with ongoing pregnancies.
Conclusions: In this study, which is the first study comparing the five most frequently used ovarian responsiveness markers and the second study signifying the role of OSI in an antagonist protocol, OSI was found to be more convenient to calculate, and it could be superior to other ovarian responsiveness markers for poor and high ovarian responses on cycles with agonist or antagonist protocols.

Key words: ovarian sensitivity index, ovarian response prediction index, assisted reproductive technology treatment, antral follicle counts, anti-Müllerian hormone.

Introduction

The ovarian response to controlled ovarian stimulation with gonadotropins is essential for the outcomes of assisted reproductive technology

AMS

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(ART) cycles [1]. Previous studies have demonstrated various clinical, hormonal, and ultrasonographic markers to estimate the ovarian reserve and the ovarian responsiveness to gonadotropin stimulation. Age, ultrasonographic antral follicle count (AFC), basal levels of estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), inhibin B, and anti-Müllerian hormone (AMH) have been defined as ovarian reserve tests, and they have been proposed for the evaluation of ovarian response [2–4].

Moreover, different models with a combination of various markers have been suggested as ways to increase the effectiveness of extrapolating the ovarian response. The ovarian sensitivity index (OSI) and ovarian response prediction index (ORPI) have been shown to be valid and reliable estimation models for ovarian response to gonadotropins in ART cycles [5, 6].

Based on previous studies that have reported strong outcomes for the previously described estimation indices, the issue of which ovarian response model has the best accuracy is still a challenge for managing patients undergoing ART treatment.

Nevertheless, to date, no detailed studies have compared the suggested ovarian response markers and/or a combination of models with ART treatment outcomes in the same patient. Therefore, we conducted a retrospective analysis of five different ovarian response markers (age, AMH, AFC, OSI, and ORPI) to evaluate the ovarian response to gonadotropin stimulation and the chance of ongoing pregnancy after ART treatment.

Material and methods

Study population

In this retrospective study, patients who underwent intracytoplasmic sperm injection (ICSI) treatment at the infertility clinic between 2014 and 2015 were enrolled. The study's protocol was approved by the institution's ethics committee. Informed consent was obtained from all the participants included in this study. Inclusion criteria were: ≤ 42 years of age, body mass index ≤ 35 kg/m^2, regular menstrual cycles, no presence of endocrine disorders, no history of ovarian surgery, and no severe endometriosis. Demographics, clinical data, and ART treatment outcomes of the patients were abstracted from the hospital's database. All patients underwent transvaginal ultrasonographic examination with a 7.5 MHz vaginal probe during the follicular phase of their spontaneous menstrual cycle. Total AFC was calculated with the sum of 2–10 mm antral follicles in both ovaries.

Ovarian stimulation protocol

The controlled ovarian stimulation (COS) protocols consisted of a long gonadotropin-releasing hormone (GnRH) agonist or a multi-dose GnRH antagonist protocol individualized for each patient.

The GnRH agonist protocol was performed using a 1 mg/day dose of long GnRH agonist (leuprolide acetate; Lucrine; Abbott, Turkey) during the 14 days of the luteal phase of the previous menstrual cycle for down-regulation. Then, ovarian stimulation was started by daily injection of recombinant follicle stimulating hormone (r-FSH) (Gonal-F, Merck Serono, Istanbul, Turkey) with a starting dose specific for each individual case, according to the patient's age, body mass index (BMI), ovarian reserve, and AFC.

In the GnRH antagonist protocol, ovarian stimulation was started with subcutaneous injection of gonadotropins, such as r-FSH (Gonal F, Merck Serono, Istanbul, Turkey), and a starting dose was administered based on the patient's age, BMI, ovarian reserve, and AFC from days 2–4 of the menstrual cycle. According to the fixed antagonist protocol, the GnRH antagonist (Cetrotide; 0.25 mg; Merck Serono, Istanbul, Turkey) injection was started beginning on the sixth day of stimulation.

The number and size of the follicles and the serum estradiol levels of all patients were monitored via ultrasound. The gonadotropin dose was chosen based on the patient's response. On cycle days 2–3, each patient underwent a transvaginal ultrasound to determine their AFC and to screen for ovarian cysts. Repeat examination was performed on day 6 of the ovarian stimulation and subsequently every 1–3 days, as clinically indicated until the criterion for subcutaneous administration of recombinant chorionic gonadotropin alpha 250 mg (Ovitrelle; Merck-Serono, Istanbul, Turkey) was ≥ 18 mm in diameter. Ovum retrieval was performed 36 h later.

In all cases, the ICSI procedure was performed on the same day (day 0), and fertilization was confirmed 16–18 h later. Embryo transfer was performed on day 3, day 4, or day 5 based on the quality of the embryos. From the day of ovum retrieval, the luteal phase was supported by vaginal progesterone gel (Crinone 8% gel; Serono, Istanbul, Turkey) twice a day. Clinical pregnancy was described as fetal pole and fetal cardiac activity as determined by ultrasonographic examination. Ongoing pregnancy was defined as a viable pregnancy, as confirmed by ultrasonography at 20 weeks.

Embryo quality

The polarization, presence of a cytoplasmic halo, number of pronuclei, and pronuclear appearance were the morphological features used

in the zygote scoring system. Embryo quality was described based on the size of the blastomeres and the number, degree of fragmentation, and presence of multinucleated blastomeres. An embryo with 7 or 8 equal sized blastomeres and with less than 10% cytoplasmic fragmentation with no multinucleation was accepted as good quality on day 3 [7, 8].

Ovarian sensitivity index calculation

Ovarian sensitivity index was calculated by dividing the total administered r-FSH dose by the number of oocytes retrieved at the oocyte pick-up [5].

Ovarian response prediction index calculation

The ORPI was calculated using the following formula: ORPI = (AMH × AFC)/patient age [6].

Statistical analysis

Statistical analyses of the data were performed using Statistical Package for the Social Sciences (SPSS) version 11.5 software. Data were given as mean ± standard deviation or percentage. Spearman's correlation analysis was used to assess the correlation between the parametric variables (total retrieved oocytes, MII oocytes, embryos, good quality embryos on day 1, and good quality embryos on day 3) and the ovarian response tests. The significance of the difference between two correlation coefficients was analyzed by using the z-test. A comparison of the two paired receiver operating characteristic (ROC) curves of the ovarian response tests is appropriate, and the statistical significance of the difference between the areas under the curve (AUC) of those tests was assessed using the z-test, as defined by Hanley *et al*. The AUC is the combined calculation of sensitivity and specificity, and it is a measure of the overall predictive performance of a predictive test [9]. The overall predictive performances of ovarian response tests can be compared by comparing their AUCs. In the present study, the overall predictive performance of age, AFC, AMH, OSI, and ORPI was calculated for the retrieval of ≥ 4 MII oocytes, ≥ 15 oocytes, and the ongoing pregnancy rate per cycle. Retrieval of < 4 oocytes was accepted as the criterion for poor ovarian response [10, 11], whereas retrieval of ≥ 15 oocytes was accepted as the criterion of excessive response [12, 13]. Data were given as 95% confidential intervals (CI). A *p*-value ≤ 0.05 was considered statistically significant.

Results

Data of 176 patients who underwent the ICSI procedure with either a GnRH agonist (*n* = 37) or a GnRH antagonist (*n* = 139) COS protocol were analyzed. Demographic, clinical, and ART treatment characteristics of the patients are given in Table I. The outcomes of Spearman's correlation coefficients between the ovarian response tests and the total number of retrieved oocytes, MII oocytes, embryos, and good quality embryos on day 1 and day 3 are presented in Table II. The correlation coefficients were compared separately and are given in Tables III and IV. The correlation coefficients for OSI were significantly higher than the other parameters in terms of total number of retrieved oocytes, MII oocytes, embryos, and good quality embryos on day 1 and day 3.

The ROC curve analyses of age, AFC, AMH, OSI, and ORPI were performed for the retrieval of < 4 oocytes, ≥ 4 MII oocytes, ≥ 15 oocytes, and ongoing pregnancy rate per cycle (Figure 1). Pairwise comparison of the AUCs was performed in order to analyze the relationship between the ovarian response tests and the recorded data for the outcomes. Comparison of the two paired ROC curves of the ovarian response tests are shown in Table V. The level of association between the ovarian response tests and poor ovarian response data was (in descending order): OSI, ORPI, AFC, AMH, and

Table I. Demographic, clinic and ART treatment characteristics of patients

Parameter	Median (25th–75th percentiles) or *n* (%)
Age [years]	33.00 (29.25–36.00)
BMI [kg/m²]	24.80 (22.70–26.94)
Duration of infertility [years]	5.00 (3.00–7.00)
Infertility type:	
Primary	156 (88.6)
Secondary	20 (11.4)
Basal FSH [mIU/ml]	6.34 (5.18–8.82)
Basal estradiol [pmol/l]	43.31 (32.00–57.82)
AMH	0.94 (0.39–2.86)
AFC	8.00 (5.00–11.00)
Ovarian stimulation protocol:	
GnRH agonist	37 (21.0)
GnRH antagonist	139 (79.0)
Total dose of gonadotropin [IU]	2400.00 (1575.00–3150.00)
Duration of stimulation [days]	9.00 (7.00–10.00)
Peak serum estradiol level [pmol/l]	1099.00 (667.00–1754.00)
Number of retrieved oocytes	5.00 (2.00–9.00)
Number of MII oocytes	4.00 (2.00–7.00)

Table II. Correlation analysis between ovarian response markers and ART treatment outcomes

Parameter	No. of retrieved oocytes	No. of MII oocytes	No. of embryos	No. of good quality embryos on day 1	No. of good quality embryos on day 3
Age:					
r	−0.233	−0.223	−0.223	−0.216	−0.176
p	0.002	0.002	0.003	0.004	0.019
AFC:					
r	0.729	0.678	0.574	0.474	0.451
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
AMH:					
r	0.608	0.539	0.460	0.412	0.411
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
OSI:					
r	−0.926	−0.850	−0.734	−0.650	−0.611
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
ORPI:					
r	0.695	0.620	0.534	0.468	0.456
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Spearman correlation analysis. Significance level at p < 0.05.

age. The OSI (AUC_{OSI} = 0.976) was found to be the ovarian response test with the highest relationship with poor ovarian response. The overall association of OSI with poor ovarian response was significantly higher than it was for the other parameters. For the retrieval of ≥ 4 MII oocytes, OSI was the parameter with the highest AUC value (0.935), whereas age had the lowest AUC value (0.629) among all the studied parameters. In patients with high ovarian response data, OSI had the highest AUC value (0.984), followed by AFC (0.907) and ORPI (0.887). In addition, the AUC value of OSI had a higher statistical significance than the AUC value of ORPI and AFC (p_1 = 0.023, p_2 = 0.014, respectively). There was no statistically significant difference among the AUC values of the ovarian response tests for the data of patients with ongoing pregnancies.

Discussion

The present retrospective analysis shows that OSI may have a significant role in the selection of patients with a poor or high ovarian response. Which ovarian response marker is more useful in predicting ovarian response and the chance of pregnancy remains to be answered. Unfortunately, there are limited data to determine the most accurate test or model that can be used to estimate ovarian response and the probability of pregnancy or live birth.

Measuring the ovarian response with markers such as AMH, AFC, and ORPI is influenced by the gonadotropin dosage, and the administered dosage of gonadotropin influences the final number of retrieved oocytes. OSI was first defined by Biasoni *et al.* to predict the ovarian response for *in vitro* fertilization (IVF) cycles, and the authors concluded that OSI accurately reflects the AFC and AMH levels of patients who underwent IVF treatment with a long GnRH agonist protocol [5]. In contrast to other markers, OSI is irrespective of gonadotrophin, and it measures the genuine potential of specific ovaries. On the other hand, although the predictive abilities of age, AFC, basal levels of E_2, FSH, inhibin B, and AMH were found to be moderate for large study populations, their predictive performance was reported to be quite low for individual cases [14, 15].

There is a lack of studies in the literature evaluating OSI for ovarian response in women on antagonist protocols. To our knowledge, only one study has demonstrated an excellent correlation between the parameters of ovarian response and OSI [16], and our analysis is the second study to signify the role of OSI in an antagonist protocol. Huber *et al.* demonstrated a positive correlation between pregnancy rate per oocyte pick-up and OSI in patients on a long agonist protocol, and they emphasized the necessity of confirming the OSI for patients on other protocols [15].

The ORPI was first described by Oliveira *et al.* [6]. In their study, ORPI showed excellent predictive ability for poor ovarian response and a good prediction performance for retrieval of MII oocytes ≥ 4, a high ovarian response, and clinical pregnancies in women on both antagonist and agonist protocols [6]. Brodin *et al.* evaluated four different ovarian reserve tests (age, AFC, AMH, and combi-

Table III. Comparison of correlation coefficients of ovarian response markers for: A – total number of retrieved oocytes, B – total number of MII oocytes

Parameter	AFC	AMH	OSI	ORPI
A – Total number of retrieved oocytes				
Age:				
z	−6.41	−4.356	−12.734	−5.768
p	< 0.0001	< 0.0001	< 0.0001	< 0.0001
AFC:				
z		2.054	−6.429	0.642
p		0.04	< 0.0001	0.521
AMH:				
z			−8.449	−1.412
p			< 0.0001	0.158
OSI:				
z				7.061
p				< 0.0001
B – Total number of MII oocytes				
Age:				
z	−9.508	−4.454	−9.415	−4.634
p	< 0.0001	< 0.0001	< 0.0001	< 0.0001
AFC:				
z		2.071	−3.939	0.934
p		0.038	< 0.0001	0.350
AMH:				
z			−5.977	−1.137
p			< 0.0001	0.256
OSI:				
z				4.858
p				< 0.0001

Z-test was used. Significant level at p < 0.05.

nations of basal levels of FSH and LH and menstrual cycle lengths), and they concluded that the combination of AMH, AFC, and age was the best model for predicting ovarian response; moreover, when compared with age, AMH was superior in the estimation of live birth rates after ART treatment [17].

Our data showed that both OSI and ORPI may have important roles for identifying women with a possible poor ovarian response; however, the association between poor ovarian response and OSI was found to be significantly stronger than the association between poor ovarian response and ORPI. Similarly, while ORPI, AFC, and AMH seemed to be capable, to some degree, of identifying women with a possible excessive ovarian response, OSI showed superiority in these cycles. In addition, OSI was found to be more useful than ORPI for the total number of embryos and good quality embryos on day 1 and day 3.

The possible reasons for the lower predictive performances of AFC, AMH, and ORPI in comparison to OSI for estimating ovarian response might be related to the limitations of AFC and AMH. In terms of inter-observer variation, the quality of the ultrasound and difficulties in visualizing the ovaries because of anatomic abnormalities may impair the quality of assessing the AFC and re-

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Table IV. Comparison of correlation coefficients of ovarian response markers for: A – total number of embryos, B – total numbers of good quality embryos on day 1, C – total numbers of good quality embryos on day 3

Parameter	AFC	AMH	OSI	ORPI
A – Total number of embryos				
Age:				
z	−3.968	−2.516	−6.499	−3.431
p	0.0001	0.012	< 0.0001	0.0006
AFC:				
z		1.452	−2.597	0.537
p		0.146	0.0094	0.591
AMH:				
z			−4.025	−0.915
p			0.0001	0.360
OSI:				
z				3.125
p				0.0018
B – Total numbers of good quality embryos on day 1				
Age:				
z	−2.751	−2.033	−5.084	−2.679
p	0.0059	0.042	< 0.0001	0.0074
AFC:				
z		0.718	−2.378	0.072
p		0.473	0.017	0.943
AMH:				
z			−3.085	−0.646
p			0.002	0.518
OSI:				
z				2.449
p				0.014
C – Total numbers of good quality embryos on day 3				
Age:				
z	−2.865	−2.409	−4.872	−2.924
p	0.0042	0.016	< 0.0001	0.0035
AFC:				
z		0.457	−2.054	−0.059
p		0.648	0.04	0.953
AMH:				
z			−2.503	−0.516
p			0.01	0.606
OSI:				
z				1.996
p				0.04

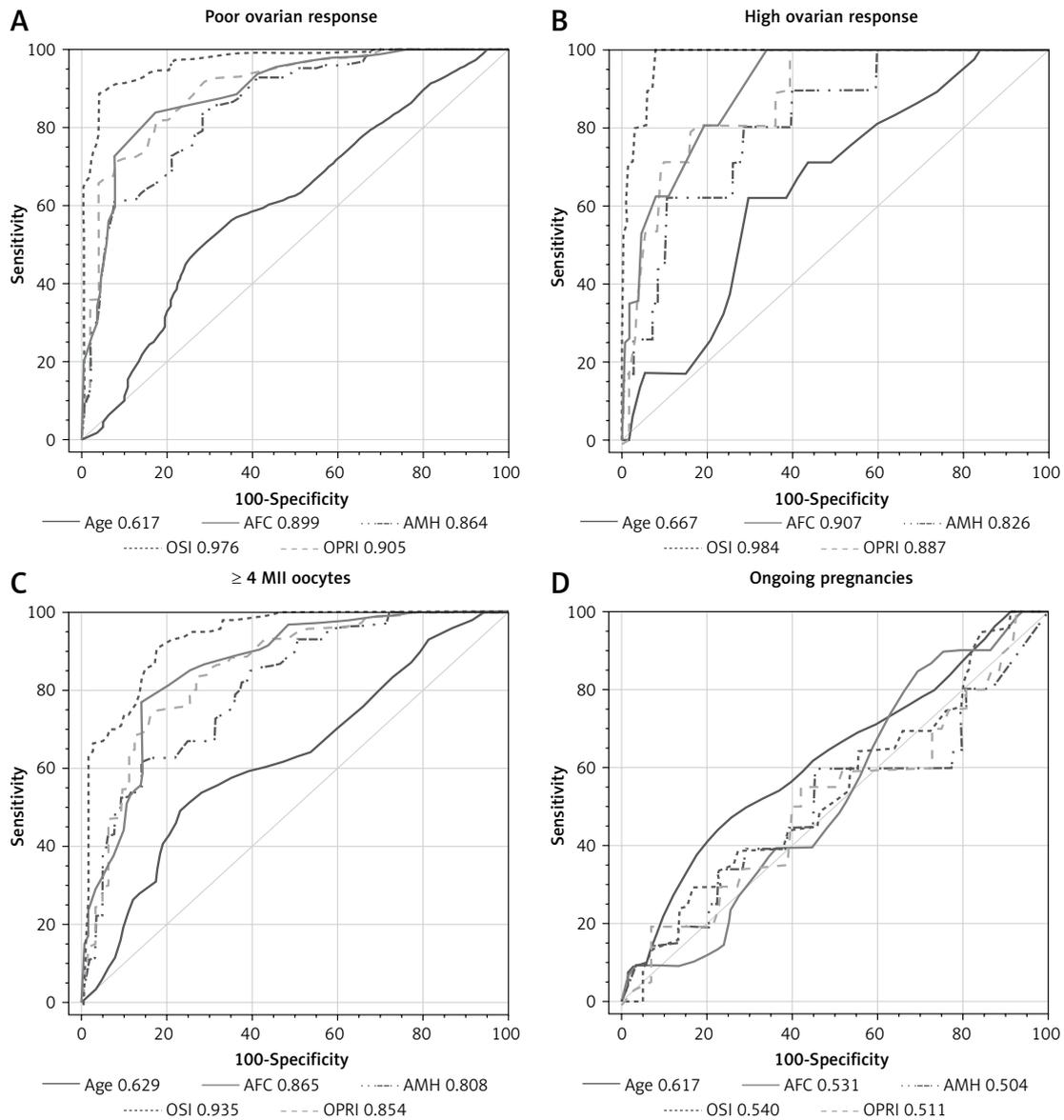*Z-test was used. Significant level at p < 0.05.*

Figure 1. The ROC curve analyses of Age, AFC, AMH, OSI and ORPI regarding the retrieval of < 4 oocytes, ≥ 4 MII oocytes, ≥ 15 oocytes and ongoing pregnancy rate per cycle

duce its predictive ability for ovarian response and pregnancy rates [17]. On the other hand, previous studies have shown that factors such as assay technical issues, sample instability, and inter- and intra-individual variations may affect the AMH measurements and limit AMH's use as a reliable ovarian responsiveness marker [18–21]. The other important limitation of AMH is the influence of ethnicity on serum levels. A recent review suggested the necessity of ethnicity-specific cut-off points in defining expected poor and high responders based on differences in the nomogram of the AMH levels in different ethnic populations [21]. Given the inherent limitations of AFC and AMH measurements, it is not surprising that the ORPI model, which is calculated with these markers, may be inferior to other models, such as OSI.

Recently, studies have reported conflicting results about the associations between ovarian response tests and the estimation of the number of pregnancies [21, 22]. While some studies have reported that AFC and AMH have strong associations with live-birth rates after ART treatment based on their predictive ability for oocyte quantity and oocyte quality [23, 24], other studies found no significant relationship between AMH and oocyte quality/embryo quality [21]. In our study, the correlation coefficients of OSI showed significantly higher correlations with the total number of retrieved oocytes, MII oocytes, embryos, and good quality embryos on day 1 and day 3 than the other ovarian response tests. Although our data showed marked associations between ovarian response markers and the total number of embryos, none of

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Table V. *P*-values of comparison of AUCs of ovarian response markers for: A – poor ovarian response, B – high ovarian response, C – ≥ 4 MII oocytes

Parameter	AFC	AMH	OSI	ORPI
A – Poor ovarian response				
Age	< 0.0001	< 0.0001	< 0.0001	< 0.0001
AFC		0.245	0.0014	0.792
AMH			0.0001	0.0005
OSI				0.0023
B – High ovarian response				
Age	0.0051	0.121	0.0001	0.0142
AFC		0.167	0.0229	0.592
AMH			0.0042	0.0099
OSI				0.0143
C – ≥ 4 MII oocytes				
Age	< 0.0001	0.0005	< 0.0001	< 0.0001
AFC		0.056	0.0046	0.617
AMH			< 0.0001	0.0001
OSI				0.0015

Z-test was used. Significant level at p < 0.05.

the analyzed parameters or models demonstrated similar positive correlations with the number of ongoing pregnancies. It should be taken into account that various factors, such as the abnormality of the sperm parameters and endometrial features, could affect the occurrence of pregnancy [25]. In addition, ongoing or live birth rates may be affected by fetal-maternal risk factors.

One of the limitations of our study is its retrospective nature. It was not possible to report reliable predictive data of the analyzed markers and/or models. A prospective methodology would be much more convincing if it deals with the predictive value of putative ovarian responsiveness and pregnancy markers. It is obvious that prospective verification of the correspondence between prediction and real facts will definitely provide higher quality evidence than a retrospective analysis.

Another limitation is the relatively small sample size of the study, especially in the GnRH agonist cycles. A sample size calculation was considered to be unnecessary because the study aimed to collect as much data of the cycles from the hospital's database as possible to meet our relatively narrow inclusion criteria.

In conclusion, although retrospective, the present study is the first to compare the five most frequently used ovarian responsiveness markers. The retrospective data indicating that OSI might possess superior associations for poor and high ovarian responses to gonadotropin stimulation in ART cycles with GnRH agonist or antagonist protocols than other ovarian responsiveness markers need to be confirmed in larger prospective studies. This may be of particular importance because OSI is calculated without extra effort during an ART cycle, unlike ORPI, in which ultrasonographic assessment and blood sampling are required.

Conflict of interest

The authors declare no conflict of interest.

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