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Prediction of Ovarian Response with Ovarian Response Prediction Index (Orpi) during Controlled Ovarian Stimulation in IVF

Mannem Haritha. M[1], Agarwal Sonal. A[2], Nayak Chaitra[3], Pragnesh Gautham[4], Kamini A Rao.[5]

[1]MBBS, MS (OBG), FMAS, FRM (REP MED) Infertility Specialist, Department of reproductive medicine, Milann Fertility Centre, Bangalore Assisted Conception Centre, Bengaluru, India

[2]MBBS,MS (OBG),FMAS,MNAMS,DNB,FNB(RM) Infertility Specialist, Department of reproductive Medicine, Milann Fertility Centre, Bangalore Assisted Conception Centre, Bengaluru, India

[3]MBBS, MS (OBG), FNB (RM) Infertility Specialist, Department of Reproductive Medicine, Milann Fertility Centre, Bangalore Assisted Conception Centre, Bengaluru, India

[4]MBBS, MD, DNB, Chief Operating Officer, Department of Reproductive Medicine, Milann Fertility Centre, Bangalore Assisted conception Centre, Bengaluru, India

[5]DGO, Dch, FICOG, FRCOG, PGDMLE, FNAMS, Medical Director, Department of Reproductive Medicine, Milann Fertility Centre, Bangalore Assisted Conception Centre, Bengaluru, India

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Abstract

(Background): To evaluate ORPI as an index to predict the response to ovarian stimulation. (Methods): It is an observational prospective study of 734 patients who underwent controlled ovarian stimulation during period of 1.5 years (July 2017 to December 2018) .Inclusion and exclusion criteria were taken into consideration when patients were recruited. ORPI is calculated by multiplying AMH level (ng/ml) and AFC (n) and the result is divided by age (years) of the patient. The primary outcome measured was number of MII oocytes and secondary outcome was total number of oocytes retrieved. (Results): Positive correlation of ORPI with MII oocytes and total number of oocytes is seen. Regarding the probability of collecting ≥4 oocytes under the ROC curve, the AUC for ORPI is 0.68 (95%CI 0.65-0.72) with sensitivity of 78.4 and specificity of 51.4 for a cut off of >0.44. For collecting ≥ 15 oocytes ROC curve had an AUC of 0.72 with sensitivity of 66.7 and specificity of 73.4 for a cut off of >1.28. ROC curve for the probability of collecting ≥4 MII oocytes depicted an AUC of 0.67 with cut off of >0.77. (Conclusion): The results of our study concluded that in a patient undergoing IVF treatment, ORPI has a poor ability to predict retrieval of ≥4 oocytes or ≥ 4 MII and fair ability for hyper response with ≥15 oocytes. ORPI can serve as a counselling tool for predicting ovarian response.

Keywords: Antral follicle count, Anti-Mullerianhormone, Controlled ovarian stimulation

1 Introduction

Different protocols are present for multi follicular development in IVF so as to increase the number of embryos available and decrease time to pregnancy. Hypo response or hyper response cannot be predicted always. Supra physiological oestrogen levels result from large number of follicles which in turn has a negative effect on embryo quality and endometrium (1). Clinicians should individualise the gonadotropin dosage to reduce adverse effects of excessive ovarian response or poor response. Various predictors exist to predict ovarian response such as age, anti-mullerian hormone (AMH), antral follicle count (AFC), ovarian volume, day 2 follicle stimulating hormone, estradiol, inhibin and dynamic tests. Out of these age, AMH and AFC have served in the most effective way (2).

Oocyte number and quality decreases with age with dissimilarities in different races resulting in different responses to ovarian stimulation (3).Chronological age cannot serve as predictor of ovarian response so biological age as predicted by hormonal and functional profiles should be taken into consideration (4). Antral follicle count which is measure of follicles of 2-9 mm in both ovaries on day 2/3 of menstrual cycle seen on trans-vaginal ultrasound is also being used as a predictor of ovarian response (5). Limitation to it is that there is subjective variation with cycle to cycle variability. AMH, a member of the transforming growth factor-beta superfamily, is secreted by granulosa cells of pre antral and small antral follicles (6). Anti-mullerian hormone is a direct indicator of ovarian reserve and is independent of follicle stimulating hormone (FSH). AMH has no cycle variability and decreases throughout reproductive life to become undetectable in post-menopausal period. Thus in a nutshell all markers have errors in their estimation. Systematic reviews of ovarian reserve tests have depicted modest accuracy of all ovarian reserve tests for prediction of both hyper ovarian response and poor ovarian response when calculated individually (7).

Considering advantages like ability to calculate starting dose of gonadotropins, decreasing iatrogenic complications and cancellation rate and improving cost benefit ratio of ovarian stimulation protocols, our study has used a new ovarian response prediction index (ORPI) to assess the response to ovarian stimulation (8).

***Corresponding author:** Haritha Mannem, [1]MBBS, MS (OBG), FMAS, FRM (REP MED) Infertility Specialist, Department of reproductive medicine, Milann Fertility Centre, Bangalore Assisted Conception Centre, Bengaluru, India. E-mail: : harithamannem88@gmail.com

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ORPI ((ovarian response prediction index) is based on three ovarian reserve markers i.e. AMH, AFC and age to serve as a predictor for ovarian response during controlled ovarian stimulation in IVF. ORPI [AMH (ng/ml) x AFC (2-9 mm)/ patient age] is being entitled to predict optimal ovarian response of ≥4 oocytes and hyper response i.e. ≥15 oocytes efficiently (9). ORPI has a cost benefit ratio in favour of benefit as it guides in individualising treatment and serves as a counselling tool for the couple regarding their predicted ovarian response.

2 Materials and Methods

2.1 Population

In the current study inclusion criteria were: age ≤35 years, body mass index (BMI) between 20–30 kg/m2, regular menstrual cycles and both ovaries present. Exclusion criteria were: History of ovarian surgery, severe endometriosis, endocrine disorders, and presence of ovarian cysts assessed by trans-vaginal ultrasound.

Total 734 patients undergoing autologous IVF cycles were recruited for the study in the duration of 18 months. The study was reviewed by local ethical committee and clearance obtained from Institutional Review Board. Written informed consent was taken from all recruited patients. ORPI was calculated by multiplying AMH level (ng/ml) and AFC (n) and dividing it by age (years) of the patient.

2.2 AMH measurement

Venous blood was collected irrespective of day of menstrual cycle and AMH was measured using an enzymatically amplified 2-site immunoassay kit (AMH Gen II ELISA, Beckman Coulter Inc.). The lowest detection limit of this assay is 0.01ng/ml, whereas the maximum intra- and inter-assay coefficients of variation are 3.3% and 6.5%, respectively.

2.3 antral follicle count

Transvaginal ultrasound (5.5-7 MHz) was done on day 2/3 of menstrual cycle by clinician who was blinded to the AMH value and other hormonal parameters. Follicles of 2-9 mm size were measured in both ovaries and total count was labelled as antral follicle count.

2.4. Controlled ovarian stimulation

Prior to starting ovarian stimulation, baseline scan by trans-vaginal ultrasound (Voluson P6) using vaginal probe was performed and follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P4), anti-mullerian hormone (AMH) were done on day 2.Controlled ovarian stimulation (COS) was started on day 2/3 of cycle with either recombinant Follicle stimulating hormone (R-FSH), (Recagon, Organon; Gonal F, Merck) with or without human menopausal gonadotropin (hMG; Menopur; Ferring Pharmaceuticals, Parsippany, NJ). Starting dose was calculated based on age, BMI, AFC, AMH and baseline FSH level. Ovarian response to stimulation was monitored during IVF cycle with trans-vaginal ultrasound and serum E2, LH and P4 measurements. Dose of gonadotropins was adjusted accordingly. Antagonist (Cetrotide, Merck) 0.25 mg subcutaneously by flexible antagonist protocol was added when leading follicle was ≥13-14 mm in diameter or serum E2 > 350-400 pg/mL and was continued until trigger day. Patient was given hCG trigger injection when criteria of atleast 3 follicles ≥17 mm as mean diameter was attained. Transvaginal oocyte retrieval was performed 34-36 hours post trigger under intravenous sedation. Number of oocytes retrieved and number of mature oocytes were noted.

2.5 Endpoints

The primary outcome measured was number of MII oocytes and secondary outcome was total number of oocytes retrieved. ORPI was calculated for retrieval of ≥4 oocytes (adequate response), ≥ 15 oocytes (hyper response) and number of MII oocytes.

2.6 Calculation of Ovarian Response Prediction Index (ORPI)

The ORPI value was calculated by multiplying the AMH (ng/ml) level by the AFC, and the result was divided by the age (years) of the patient: ORPI = (AMH×AFC)/patient age. This definition of ORPI was based on Oliveira et al. (2012) study. The cut-off value was calculated by statistical analysis. This equation is based on previous evaluations that found that ovarian response to stimulation had positive correlations with AMH levels and number of antral follicles and was negatively correlated with patient's age (10). Notably, the calculated value of the ORPI in the study was not influenced by the protocol choice for the induction of ovulation or the doses of gonadotropin (11).

2.7 Statistical analysis

Analysis was done using SPSS software .Mann–Whitney test and chi-square test were used where appropriate. Correlations were performed using Pearson's correlation test. $P < 0.05$ was considered statistically significant. Univariate logistic regression module was used to estimate the value in predicting the likelihood of collecting ≥4 oocytes, ≥ 4 MII oocytes and ≥ 15 oocytes. The odds ratio (OR) and 95% confidence interval (CI) constituted the descriptive analysis. Receiver operating characteristic (ROC) curves were constructed to examine the performance of the ORPI in predicting retrieval of ≥4 oocytes, ≥4 MII oocytes and ≥15 oocytes. The discriminative performance of the model was assessed by the area under the curve (AUC) of the ROC curve.

3 Results

The general characteristics of the study population are summarised in Table 1.Of all 734 women , mean age was 30.9±4.1 years , mean BMI 24.06±2.8, mean AMH level 2.6±2.0 ng/mL and mean AFC was 11.5±5.6 . Mean ORPI calculated was 1.2±1.3. The Pearson correlation analysis demonstrated significant ($P<0.05$) positive correlations between the ORPI and the total number of oocytes collected and total number of MII oocytes collected. Additionally, other variables of ovarian response i.e. age, AMH and AFC showed statistically significant correlation with the variables analysed. However, age and BMI are negatively correlated as depicted in table 2. The performance of the ORPI as a prognostic test was observed using ROC curves. Regarding the probability of collecting ≥4 oocytes, the ROC curve showed an area under the curve of 0.68 (95% CI: 0.65-0.71), indicating that the ORPI had a poor prognostic potency for this point. Setting the threshold of 0.44, it offered a specificity (51.4%) and sensitivity (78.4%) as illustrated in Figure 1.

In regards to the probability of collecting ≥15 oocytes, ROC curve had an area under the curve of 0.72 (95% CI: 0.68-0.75), indicating that the ORPI had a fair prognostic

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potency. Setting the threshold at 1.28 led to specificity (73.3%) and sensitivity (66.6%) as shown in Figure 2. Similarly, figure 3 demonstrates ROC curve for the probability of collecting ≥4 mature oocytes which gave an area under the curve of 0.67 (95% CI: 0.64-0.70), indicating that the ORPI values in this situation had a poor prognostic potency. Setting the threshold at 0.77 depicted specificity of 69% and sensitivity of 59%. When the ROC curves for all other factors (Age, AMH and AFC) are analysed for their predicting ability for retrieval of ≥4oocytes , ≥ 15 oocytes and ≥ 4 mature oocytes the AUC presented by the ORPI was always higher than age and AMH and similar to the AUC presented by AFC as depicted in figure 4.

Table 1: baseline and stimulation characteristics of study population

	Mean	Std. Deviation
No. of Oocytes	6.48	3.504
Matured Oocytes	4.94	2.714
Age	30.94	4.117
BMI	24.060	2.8522
AMH	2.6058	2.01711
AFC	11.551	5.6009
ORPI	1.1633	1.34358

4 Discussion

ORPI serves as a perfect tool for having a precise estimate of patient's ovarian response after controlled ovarian stimulation in autologous IVF cycles and optimising treatment. An estimate based only on age is not always sufficient to accurately predict the ovarian response to gonadotropin stimulation, considering that the ovarian response is highly variable even among women of same age group (12). This inter-individual variation is influenced by genetic and environmental factors that primarily determine the size of the pool of primordial follicles at birth and the rate of the pool's decline throughout the reproductive life (13). An ultrasound evaluation of the antral follicle count has gained acceptance as a good predictor of the ovarian response with low intra- and inter-observer variations (14). Based on these observations, a joint analysis of age and the AFC might combine their advantages and compensate for their disadvantages, thus improving the assessment of ovarian function (15).

The combination of different variables of ORPI have resulted in a more precise index to predict ovarian response. Indeed, the results showed significant correlations (P<0.001) between the ORPI values and number of oocytes and number of MII oocytes. Our study has shown that ORPI and AFC both have similar predictive value for prediction of ovarian response. Oehninger et al in 2015 concluded similar findings. Contrary to these findings, Nelson et al. (2015) found a better predictive value of AMH versus AFC for oocyte yield. It should be noted that in the Nelson study, 19 assisted reproductive technology centres participated. Because AFC has been shown to have important inter-observer variations, this discrepancy could be explained by the fact that our study was performed in a single centre with only a few operators (16). Despite this test not being universally available and recent alterations in the methods, determination of AMH can be performed irrespective of day of menstrual cycle with no consistent fluctuation patterns (17).

Cour Freiesleben et al. found that the best prognostic model to predict a low response included AFC and age. It can be further improved by including serum AMH levels into the calculation of the ORPI (18). In four previous studies, AMH was reported as a stronger predictor than AFC (23, 24, 25, 26, 27, 28). However, our result was in agreement with four studies that found AFC was superior to AMH for discrimination of ovarian response (29, 30, 31, 32)

This prospective study demonstrated that AMH, AFC and ORPI were good predictors for high ovarian response and ORPI and AFC were similar (33,34). The addition of age and AMH did not improve the accuracy of AFC. ROC analysis also revealed that AUC for AMH was lower than AFC and ORPI, but better than basal FSH and age. In contrast to Oliveira et al. study, we found that the new index (ORPI) had no superiority to AFC for prediction of ovarian response (35). On the basis of our knowledge and considering the limited studies in this regard, more well-designed studies are needed for suggesting the potential role of ORPI in the clinical practice for counselling and choosing individual stimulation protocols.

5 Conclusion

As no single ovarian reserve marker has 100% sensitivity and specificity, a combined index of three variables depicted by ovarian reserve prediction index can improve ovarian reserve prediction (36). ORPI serves an excellent counselling tool and key to knowledge enabling proper management of individualized treatment (37).

Table 2: Illustration of correlation between different variables

		Matured Ocytes	Age	BMI	AMH	AFC	ORPI
No. of Oocytes	Pearson Correlation	0.898	-0.141	-0.020	0.284	0.399	0.295
	Sig. (2-tailed)	0.000	0.000	0.596	0.000	0.000	0.000
	N	734	734	734	734	734	734
Matured Oocytes	Pearson Correlation		-0.149	-0.004	0.276	0.379	0.285
	Sig. (2-tailed)		0.000	0.913	0.000	0.000	0.000
	N		734	734	734	734	734

Limitations

We have not taken pregnancy outcome into consideration.

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Conflict of Interest

The authors declare no conflict of interest in the study topic.

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