Performance of ovarian response prediction index (ORPI) in predicting ovarian response and livebirth in the in-vitro fertilisation cycle using a standard stimulation with corifollitropin alpha in a GnRH antagonist protocol

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ABSTRACT

Objective: To evaluate the performance of ovarian response prediction index (ORPI) in predicting ovarian response and livebirth of women undergoing the first in-vitro fertilization (IVF) cycle.

Design: This is a retrospective analysis of 285 women from 2013 to 2016. The outcome measures were area (AUC) under the receiver-operator characteristic (ROC) curves for prediction of excessive and poor response, livebirth in the fresh cycle and cumulative livebirth.

Results: ORPI was significantly correlated with the oocyte number. For prediction of excessive response, AUC for ORPI was comparable to AMH and significantly higher than AFC and age of women. At a cut-off of 0.42, ORPI has a sensitivity and specificity of 84% and 77% respectively for prediction of excessive response. For prediction of poor response, AUC for ORPI was significantly higher than AFC, AMH and age of women. At a cut-off of 0.12, ORPI has a sensitivity of 69% and specificity of 89% respectively for prediction of poor response. For prediction of livebirth, AUCs of ORPI were not significantly different from AFC and age of women.

Conclusion: ORPI is not a good predictor of livebirth. Its prediction of ovarian response is comparable to serum AMH level.

Keywords: Age, ovarian response prediction index, antral follicle count, Anti-Müllerian hormone

Key message:

Neither ORPI and its component parameters are good predictors of livebirth or cumulative livebirth from IVF.

Introduction

Ovarian stimulation is an important component of in-vitro fertilization (IVF) and the response to ovarian stimulation significantly impacts on the treatment success (Li et al., 2013). The ovarian response is also associated with cycle cancellation and ovarian hyperstimulation syndrome (OHSS). A good ovarian response implies a higher chance of having more oocytes and transferrable embryos from the same stimulation cycle, subsequently increasing the chance of achieving cumulative live birth (Li et al., 2013). On the contrary, excessive ovarian response increases the risk of OHSS (Delvigne, 2009) and lowers the pregnancy rate if the transfer is performed in the fresh cycle (Ng, 2009).

Prediction of ovarian response prior to the start of the first IVF cycle is of importance in clinical practice because the women can be counselled regarding the anticipated number of oocytes obtained and the starting dose of gonadotrophin may be determined accordingly. Conventionally, anti-Mullerian hormone (AMH) and antral follicle count (AFC) are the two best parameters to predict a woman's ovarian response (Broer et al., 2013a, 2013b; Broer et al., 2014). Recently, the ovarian response prediction index (ORPI), calculated as the serum AMH level (ng/ml) multiplied by AFC and then divided by age of women (years), has been proposed as a composite score for predicting ovarian response (Ashrafi M., 2017; Oliveira & Franco, 2016; Oliveira et al., 2012).

ORPI was first reported by Oliveira et al. (2012), who showed that ORPI was significantly correlated with and having good prediction on the number of oocytes; it also had fair prediction on the chance of pregnancy. The same group reported again (Oliveira &

Franco, 2016) that after adopting the ORPI for individualizing ovarian stimulation regimen, using ORPI at a cut-off of 1.7 to prompt the usage of FSH <=112.5 IU in the antagonist protocol, OHSS had been eliminated in their centre.

To the best of our knowledge, none of the existing studies evaluated the role of ORPI in predicting live birth and cumulative live birth rates. This retrospective study aimed to evaluate the performance of ORPI in predicting ovarian response, live birth and cumulative live births in women undergoing the first IVF cycle using a standard stimulation regimen with corifollitropin alpha in a GnRH antagonist protocol.

Methods

Subject selection

We retrospectively reviewed all first IVF cycles using a standard stimulation with corifollitropin alpha in the GnRH antagonist protocol from January 2013 and December 2016 at the Centre of Assisted Reproduction and Embryology, The University of Hong Kong–Queen Mary Hospital, Hong Kong. Clinical details of all treatment cycles were prospectively entered into a computerized database, which were retrieved for analysis. All first IVF cycles using the standard stimulation with corifollitropin alpha in an antagonist protocol from January 2013 to December 2016 were included in our study (n=334). Those cases which did not have anti-Mullerian hormone level taken were excluded. A total of 285 women's records were analyzed.

Ethics approval

Ethics approval was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster for this retrospective study (IRB Reference Number : UW 19-752) using existing patient data in an anonymous manner without requiring written consent from individual women. The present study did not involve any additional intervention or modification from the standard treatment.

Ovarian stimulation, AFC and AMH determination

Women attended the clinic for blood tests and pelvic ultrasound examination on day 2-3 of the period before commencing ovarian stimulation for IVF. Two-dimensional transvaginal scanning was performed using a 7-9 MHz vaginal probe (Voluson 730®, GE Healthcare, Wisconsin, USA) to determine AFC (2–9 mm) in both ovaries by an experienced songographer who had at least 3 years of experience in performing transvaginal scanning. Blood was taken for serum oestradiol (E2) and progesterone (P4) levels, and residual serum samples were stored at −20°C. For the current study, these archived serum samples were retrieved and assayed for AMH using the automated Access AMH assay® on the Access 2 analyser (Beckman Coulter, Webster, TX, USA). The assay has a sensitivity of 0.02 ng/ml, and intra- and inter-assay coefficients of variation of less than 1.7% and 2.8% respectively.

If the serum E2 and P4 levels were basal on day 2-3 of the period, corifollitropin alpha (Elonva®, MSD, Ravensburg, Germany) was given to the woman in accordance with the recommendation of the drug company and would not be given to women with AFC >=20. Hundred micrograms was given if the woman was less than 36 years old with body weight <60kg, while 150 micrograms was given if the woman was over 36 years old or weighed 60kg or above. Ganirelix® (MSD, the Netherlands) 250 μg daily was started from the sixth day after Elonva was given. Ultrasound tracking was carried out after 7 days of ovarian stimulation and repeated accordingly depending on ovarian response. The subsequent dose of stimulation ranging from 150-300 IU daily was given according to individual ovarian responses. Human chorionic gonadotrophin (hCG) Pregnyl® (MSD, the Netherlands) 5000 or 10000 units or Ovidrel® (Merck, Italy) 250 μg was given when the mean diameter of the leading follicle reached 18 mm and there were at least two more follicles reaching a mean diameter of 16 mm or above. Decapaptyl® (Ferring, Germany) 0.2mg was given instead of hCG if serum E2 concentration >25,000 pmol/L or >15 follicles >=14mm in diameter on the day of trigger. Transvaginal ultrasound-guided egg collection was then performed about 36 hours later. Fertilisation was carried out either by conventional insemination or intracytoplasmic sperm injection (ICSI) depending on semen parameters.

At most two cleaving embryos or blastocysts were replaced per transfer. Embryo transfer (ET) was performed under transabdominal ultrasound guidance. Fresh embryo transfer would be cancelled if the women had symptoms suggestive of OHSS or received

Decapeptyl for trigger and all the embryos with utilisable quality were cryopreserved on day 2 or 5 after.

Embryo cryopreservation and frozen-thawed embryo transfer (FET)

Embryos were graded based on the number/regularity of blastomeres and the degree of fragmentation (Veeck, 1999). Top quality embryos on Day 2 following egg collection were defined as the presence of at least 4 blastomeres and grade 1 or 2. Surplus embryos of grades 1 to 4 were frozen on the day of ET, whereas embryos with poor quality (Grades 5 and 6) were discarded. Extended culture would be discussed if there were six or more embryos of utilisable quality on Day 2 after egg collection, but this was subject to the couple's informed choice. Cryopreservation of Day 2 embryos was performed by a slow freezing protocol using a programmable freezer (Planer Products Ltd.; Sunbury-On-Thames, UK), and that of blastocysts was performed by vitrification. The frozen embryos were thawed on the morning of FET. Embryos were discarded if more than 50% of the original blastomeres were lysed or degenerated upon thawing. A maximum of two frozen-thawed embryos/blastocyts were transferred in FET.

Frozen-thawed embryos were transferred in natural cycles in women with regular and ovulatory cycles. Women with irregular cycles were given clomiphene 50mg-150mg per day for 5 days from Day 2 of the cycle. They attend the clinic from Day 10 of the cycle and pelvic ultrasound was performed to measure the size of the growing follicles. When the leading follicle was >14mm in diameter, serum E2 and LH levels were then checked

daily until there was LH surge which was defined as an elevation of serum LH levels by 2 times of the average LH levels in the previous 3 days and was >20IU/L. Endometrial thickness was measured on the next day after the LH surge. FET was performed 3 days later for Day 2 embryos and 6 days for blastocysts.

For anovulatory women, FET was performed in hormone replacement cycles. Blood was taken for serum E2 and P4 levels on Day 2-3 of the cycle. Estrofem® is started orally at 2 mg thrice a day for 14 days. Then endometrial thickness was measured by transvaginal scanning and serum E2 and P4 concentrations were repeated. Vaginal Endometrin® (Ferring, Israel), 100mg three times per day was started when the endometrial thickness reached 8mm. For Day 2 embryos, FET was scheduled on the 4th day of starting progesterone while for blastocysts FET was on the 7th day of starting progesterone. A urinary pregnancy test was done 18 days after starting progesterone. The hormone treatment was stopped if the pregnancy test was negative. If the pregnancy test was positive, the woman was asked to continue oral Estrofem® 2mg thrice per day and Endometrin® 100mg three times a day up to 12 weeks of gestation.

Pregnancy outcome

A urine pregnancy test was done 18 days after LH surge in natural or clomiphene cycles or starting progesterone in hormone replacement cycles. Those who were pregnant underwent pelvic scanning 2 weeks later to confirm intrauterine pregnancy and the

number of gestational sacs present. Pregnancy outcomes were traced from all pregnant women by postal questionnaire or by phone.

Calculation of ovarian response prediction index (ORPI)

The ORPI values were calculated by multiplying the AMH level (ng/ml) by AFC and dividing it by the age of the woman (years) (Oliveira et al., 2012).

Statistical analysis

The outcome measures were the number of oocytes obtained, livebirth in the fresh cycle as well as cumulative livebirth (including that from the fresh cycle and/or frozen-thawed transfer cycles derived from the index cycle). Only women who had completely replaced all available embryos derived from the index cycle and women who were pregnant without replacing all the embryos in the index cycle were included in the cumulative livebirth analysis.

Statistical tests were performed by IBM SPSS Statistics version 25 (IBM Corporation, New York, USA). The values for the ORPI, age of the woman, AMH, AFC, total number of oocytes retrieved, number of top quality embryos and the number of utilisable Day 2 embryos were treated as continuous variables for analysis. Correlations were performed using the Spearman's rank correlation test. A P value of <0.05 was considered statistically significant.

Univariate logistic regression was used to estimate the value of an independent variable in predicting the likelihood of collecting <5 oocytes (poor ovarian response) and >15 oocytes (excessive ovarian response), the livebirth rate per fresh transfer and cumulative livebirth rate. 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 prediction of poor ovarian response, excessive ovarian response, livebirth per transfer in the fresh cycle and cumulative livebirth. An optimised threshold was determined. The discriminative performance of the model was assessed by the area under the curve (AUC) of the ROC curve. Sensitivity was defined as the fraction of cycles in which the expected outcome (poor and excessive ovarian response) was predicted correctly, and the specificity was defined as the fraction of cycles not resulting in the expected outcome that was predicted correctly.

Results

This is a retrospective analysis of all first IVF cycles using a standard stimulation with corifollitropin alpha in an antagonist protocol from January 2013 to December 2016. A total of 334 cases fulfilled the inclusion criteria, out of which 285 had archived serum samples available and were included in the present study.

Correlation of ORPI, AMH, AFC and age with other clinical parameters

The Spearman's correlations of ORPI, AMH, AFC and age of women with other clinical parameters are shown in Table 1. ORPI was significantly correlated with the number of oocytes (ρ=0.736, P<0.001), the number of utilizable Day 2 embryos (ρ=0.432, p<.001) and the number of top quality Day 2 embryos (ρ=0.336, P<0.001).

Performance of the ORPI using ROC curves

The performance of ORPI as a prognostic test was evaluated using ROC curves (Figure 1). For the prediction of excessive ovarian response, the ROC curve showed an AUC of 0.850 (95% CI: 0.802–0.890), indicating that ORPI had good prognostic value. ORPI at 0.42 had the best sensitivity and specificity in predicting excessive ovarian response. Setting the threshold at 0.42, ORPI had a sensitivity of 84% and a specificity of 77% in predicting excessive ovarian response. The ROC curve for ORPI was comparable to that of AMH (AUC = 0.857, 95% CI: (0.810–0.896)) and significantly higher than those of AFC (AUC = 0.741, 95% CI: (0.685–0.792)) and age (AUC = 0.618, 95% CI: (0.558–0.675)).

For the prediction of poor ovarian response (Figure 2), the ROC curve had an AUC of 0.884 (95% CI: 0.840–0.919) indicating that the ORPI also had a good prognostic value. ORPI value at 0.12 was shown to have the best sensitivity and specificity in predicting poor ovarian response. Setting the threshold at 0.12, ORPI has a sensitivity of 69% and a specificity of 89% respectively in predicting poor ovarian response. The AUC for ORPI was

significantly higher than those for AFC (AUC=0.838, 95% CI: (0.789–0.879)), AMH (AUC=0.845, 95% CI: (0.797–0.886)) and age (AUC=0.678, 95% CI: (0.619–0.732)).

For the prediction of livebirth per fresh transfer (figure 3) and cumulative livebirth (figure 4), the ROC curve showed an AUC of 0.623 (95% CI: 0.550–0.693) and 0.689 (95% CI: 0.629–0.745) respectively, indicating that ORPI was not a good predictor of livebirth of the fresh transfer or cumulative livebirth. The AUCs of OPRI in predicting both livebirth following fresh embryo transfer and cumulative livebirth were significantly higher than that of AMH ($p<0.05$) but not significantly different from those of AFC and age of women.

Discussion

This retrospective study showed that ORPI was significantly correlated with the number of oocytes. It is a good predictor of both excessive and poor ovarian responses, similar to serum AMH level. For prediction of livebirth of the fresh transfer and cumulative livebirth, ORPI was not a good predictor.

Although both AMH and AFC are good markers in predicting ovarian responses during IVF, discordant results may result in some women, and when this happens, an intermediate ovarian response has been reported (Li et al., 2014). Therefore, prediction of ovarian response based on a single biomarker may not be the best to determine the formulation of a treatment plan. In order to increase the prognostic values and to adjust for the discordance between individual markers, combining the ovarian reserve markers has been proposed.

ORPI is the combination of age of the woman, AMH and AFC and has been proposed to be a more reliable indicator of ovarian response. Previous studies have suggested that ORPI is a more precise index of ovarian response than each of the constituent parameters alone (Ashrafi M., 2017; Oliveira et al., 2016; Oliveira et al., 2012).

ORPI was first reported by Oliveira et al. (2012) in 101 women undergoing the first ICSI cycle in either long GnRH agonist or antagonist protocol stimulated by FSH with LH supplementation. It showed that ORPI was significantly correlated with the number of eggs and associated with the likelihood of pregnancy. Women in that study received either the GnRH agonist or antagonist and individualised gonadotrophin dose was based on age of women, there may have been the possibility of bias. In our study, such bias was eliminated as all women received a standard stimulation with corifollitropin alpha in a GnRH antagonist protocol.

The same group reported that after adopting the ORPI in individualizing ovarian stimulation regimen, using ORPI at a cut-off of 1.7 to prompt the usage of FSH <=112.5 IU in the antagonist protocol, OHSS has been eliminated in their centre (Oliveira & Franco, 2016). Another study (Ashrafi et al., 2017) conducted in 550 women undergoing IVF using the long GnRH agonist protocol stimulated by follitropin alfa showed that AFC, AMH and ORPI were reasonably good in predicting low ovarian response (AUC 0.85, 0.79 and 0.83 respectively) and high ovarian response (AUC 0.79, 0.73 and 0.77 respectively). All were not useful in predicting livebirth (AUC 0.41, 0.47 and 0.44). In these reported studies, the starting dose was determined based on the age of women only, and hence it might have

led to bias again. In our study, the starting dose of corifollitropin alpha was standardized based on age of women and their body weight in accordance with the recommendations of the drug company.

Our study has limitations. Firstly, although the ovarian stimulation was with a standard stimulation with corifollitropin alpha, the subsequent dosage of gonodotrophin depended on the ovarian response of individual women and was not fixed. This is a common clinical practice but may have led to some bias. Secondly, pelvic scanning for AFC was done by different sonographers with different levels of experience. This may have resulted in some inter-observer error. Thirdly, although the embryos were not transferred at the same stage of development, there is no difference in the cumulative livebirth for transfer of early cleavage embryos and blastocysts (Martins et al., 2017).

In our study, ORPI is found to be marginally better than AMH in the prediction of ovarian response. However, it is important to consider cost effectiveness and the additional effort required for the ORPI calculation in contrast to a simple blood test for AMH. At present, there is no test that can reliably predict the livebirth of women undergoing IVF. To the best of our knowledge, there were no reported studies that evaluated the role of ORPI in predicting cumulative livebirth. This was examined in our study and showed that ORPI, similar to that of AMH ad AFC, were not good predictors of livebirth of fresh transfer or cumulative livebirth from IVF.

Randomized controlled trials are needed to prove if ORPI can improve the livebirth rate if it is used to adjust the starting dose of FSH. In women having IVF, AFC-based

individualized FSH dosing does not improve livebirth rates or reduce costs as compared to a standard FSH dose (Tilborg, 2017). A recent meta-analysis (Lensen et al, 2018) also concluded that individualized dosing is not effective for improving livebirth rates, but may decrease OHSS incidences.

Conclusion

ORPI is not a good predictor of livebirth. Its prediction of ovarian response is comparable to serum AMH level alone.

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Table 1: Spearman's correlations of ORPI, AMH, AFC and age with other clinical parameters (n=285 cases).

Parameter	ORPI		AMH		AFC		Age of women	
	ρ	P value	ρ	P value	ρ	P value	ρ	P value
Number of oocytes	0.736	<0.001*	0.684	<0.001*	0.599	<0.001*	-0.303	<0.001*
Number of utilizable Day 2 embryos	0.432	<0.001*	0.399	<0.001*	0.378	<0.001*	-0.218	<0.001*
Number of top quality Day 2 embryos	0.336	<0.001*	0.294	<0.001*	0.307	<0.001*	-0.147	0.013*
Number of utilizable blastocysts^	0.076	0.572	0.087	0.521	0.158	0.241	-0.207	0.123

ρ=correlation coefficient
^those cycles with extended culture +/- blastocyst transfer (n=57)

Table 1. Basic demographic and clinical parameters of the studied cohort (N=285).

Parameter	**Median (25^{th} – 75^{th} percentile) or N(%)**
Women's age	37 (34 – 39)
Body mass index (kg/m^2)	22.1 (20.2 – 24.1)
Smoking	
Never smoker	317 (94.9%)
Current smoker	13 (3.9%)
Ex-smoker	4 (1.2%)
Duration of infertility (years)	3 (2 – 5)
Type of infertility	
Primary	242 (72.5%)
Secondary	92 (27.5%)
Cause of infertility	
Male factor	142 (42.5%)
Tubo-peritoneal factor	36 (10.8%)
Endometriosis	19 (5.7%)
Unexplained	100 (29.9%)
Mixed factors	37 (11.1%)
Antral follicle count	8 (6 – 12)
Serum anti-Mullerian hormone (ng/ml)	1.22 (0.72 – 1.88)
Ovarian response prediction index (ORPI)	0.29 (0.12 – 0.54)
Total dose of subsequent gonadotrophin administered after corifollitropin alpha (IU)	975 (675 – 1500)
Duration of ovarian stimulation (days)	11 (10 – 13)
Peak serum oestradiol level (pmol/L)	6213 (4124 – 9177)
Number of oocytes retrieved	11 (10 – 13)
Number of fertilized oocytes	5 (3 – 8)
Number of top quality embryos on Day 2	1 (0 – 3)