Evaluation of Ovarian Response Indexes as Predictors to the Outcome of Intracytoplasmic Sperm Injection

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Abstract

Background: Knowing predictors of pregnancy in assistant reproductive technology, knowing of predictors of pregnancy is helpful for clinicians to individualize treatment 14 Plans and improve patient counseling, and for patients to decide whether to undergo infertility treatment. Therefore, it is important to evaluate ovarian reserve prediction indexes as an index to predict response to assistant reproductive technology. **Objectives:** To evaluate the ovarian reserve index (AMH*AFC/Age), taking into account the total number of MII oocytes retrieved and the quality of embryo obtained as well as the pregnancy rate. **Materials and Methods:** This study is designed as a cohort prospective study and was conducted in Al-Sadder Teaching Medical City, Al Najaf Province. Sixty couples were enrolled. The gynecological examination was performed on day 2 of the cycle (CD2): vaginal ultrasound (U/S) and blood tests for FSH, LH, AMH, estradiol (E2), serum prolactin, and thyroid function test. The ovarian response prediction index (OPRI) values were measured by multiplying the AMH serum level (ng/mL) by the number of antral follicles with a diameter of 2–9 mm and then dividing the result by the age of the subjects (years). **Results:** The current study showed that the pregnancy rate of the studied group was 33.33%. There was a significant difference between pregnant and nonpregnant women in their AMH level (*P* value was 0.004). ORPI was significantly higher in pregnant women than nonpregnant women. Binary logistic regression analysis shows that there was a significant positive correlation of ORPI and higher AMH, AFC, lower BMI, MII, oocytes, and embryo number. ROC curve shows that ORPI had an AUC of 1.00 at cutoff point 2, giving a sensitivity and specificity of 97% and 100%, respectively, and an AUC of 1.00 at a cutoff point 1, giving a sensitivity and specificity of 100% and 95%, respectively, which indicate that ORPI is an important predicting factor for ICSI success rate. **Conclusion:** ORPI was significantly higher in pregnant women than in the nonpregnant group; AMH was significantly higher in pregnant women than in the nonpregnant group. Women with higher AMH, AFC, and lower BMI are more likely to have higher ORPI.

Keywords: Age, anti-Müllerian hormone (AMH), antral follicle count (AFC), infertility, intracytoplasmic sperm injection (ICSI), ovarian response prediction index (ORPI)

Introduction

The ability of the ovaries to provide viable oocytes was used to describe ovarian reserve (OR), which was mainly determined by the number of primordial follicles in the ovary.[1,2] With aging, there will be a decline in the OR and the biological ovarian age (BOA) in humans has a life span of about 50 years, with a rapid decline after the age of 37.[1,2]

There are several biochemical and biophysical markers for ovarian reserve, commonly termed as ovarian reserve tests (ORTs). Genrerally, ORTs were performed on a woman before assisted reproductive technique (ART) to predict specific ovarian response.There are biochemical testing and ultra-sonography markers to evaluate OR. One of the biochemical markers is the estimation of antiMüllerian hormone (AMH) serum level, which can be done on any day of the cycle. Antral follicle count is one of the ultrasonic markers of ORT.[3]

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AMH is a peptide glycoprotein consisting of two very similar glycoprotein subunits bounded by disulfide bridges.[4] It is secreted by granulosa cells of small, developing follicles in the ovaries. Serum AMH level is tightly related to the number of small and growing developing follicles, therefore AMH is considered an important biomarker of ovarian reserve.[5]

The antral follicular count can be defined as a follicle that appears as a small, fluid-filled sac contains premature oocytes. AFC estimation is done on day 2 or day 3 of the menstrual cycle by transvaginal ultrasound. At that time, the measured follicles in both ovaries vary in size from 2 to 10 mm.

Age can play an important role in determining success rates in treating infertile cases.[6] Many infertile patients are treated with assisted reproductive techniques. These techniques include intra-cytoplasmic sperm injection, a common clinically assisted reproductive technique with the advantage of being independent of sperm count and morphology and having a high fertilization rate.[7]

The aim of this study was to evaluate the OPRI in expectation of ICSI outcome. The primary outcome measured will be the total number of oocytes retrieved, number of MII oocytes, and number and quality of embryos obtained. The secondary outcome is the pregnancy rate.

Materials and Methods

Patients and study design

The current study was designed as a cohort prospective study and was conducted in Al-Sadder Teaching Medical City, Al Najaf Province. A total of 60 couples who underwent intracytoplasmic sperm injection cycles were recruited for this study, through the period from September 2022 to July 2023. Females were interviewed about their gynecological and medical history, underwent a complete medical examination, and had height and weight measurements. On day 2 of the cycle (CD2), a gynecological examination was performed along with vaginal ultrasound (U/S) and blood tests for FSH, LH, AMH, estradiol (E2), serum prolactin, and thyroid function test.

Inclusion criteria

The inclusion criteria of this study included: regular menstrual cycle of 28–35 days, both ovaries are normal and visible on ultrasound, the cause of infertility is either unexplained or tubal factor infertility, females are with normal ovulation, and no endocrine cause for their infertility.

Exclusion criteria

The exclusion criteria included: severe endometriosis, history of ovarian surgery, endocrine disorders, and the presence of ovarian cysts that were assessed by the usage of transvaginal ultrasound.

Controlled ovarian hyper-stimulation

The initial dose used as controlled ovarian stimulation was calculated based on the age of the subjects, BMI, AFC, AMH, and baseline FSH level. The selection of protocol types for ovarian stimulation is based on the direction. According to the instruction of the clinician, controlled ovarian stimulation was either GnRH-agonist protocol or GnRH-antagonist protocol.

GnRH-agonist protocol

In this protocol, there will be downregulation of the pituitary gland that was started during the luteal phase of the previous menstrual cycle (on day 23 of the menstrual cycle) with either recombinant follicle stimulating hormone (R.FSH) 75 IU (INTAS, India), LG Chem KOREA, (GONAL-F) with or without human menopausal gonadotropin vial contains hMG corresponding to 75 INU FSH and 75 IU LH (hMG; menopur) (FERRING Gmbh Wittiand 11, D-24109 Kiel, Germany).

GnRH-antagonist protocol

This regime of treatment is flexible, antagonist protocol was added when the leading follicle was >13–14 mm after day 3 of the stimulation, or when the serum level of E2 was >350–400 pg/mL and it was continued until trigger day.

Following, human chorionic gonadotropin injection (hCG) injection of 5000 IU 2 ampules were used either IM or subcutaneously by (Skypharma Ltd (London, UK) to support the final maturation of the oocyte.

ICSI procedure will be done, which includes:

a. **Oocyte retrieval:** Through the usage of transvaginal ultrasound, the gynecologist will insert a thin needle through the wall of the vagina and then into her ovaries. This step is done with a mild anesthetic. Then a suction device has been joined and linked to the needle to pick up and collect oocyte.
b. **Laboratory techniques:** Oocyte denudation, sperm preparation, injection of the sperm into the cytoplasm of the oocyte.
c. The embryologist will screen the fertilized oocyte in the lab for any signals of a successful fertilization during 2 to 3 days when a good embryo (grade I or grade II embryo) will be transferred to the mother.

Calculation of ovarian response prediction index (OPRI): The ovarian response prediction index values were measured by multiplying the AMH (ng/mL) serum level by the number of the antral follicles with a diameter of 2–9 mm and then divide by the age of the subjects (years).

Ethical approval

This study is approved by the medical ethical committee of College of Medicine, University of Babylon, under reference no. 1-1 on June 30, 2022. All subjects involved in this work will be informed, verbal and written agreements will be obtained from each participant before enrollment.

Statistical analysis

All statistical analyses will be performed using SPSS software, version 23 (SPSS, IBM Company, Chicago, IL 60606, USA). For continuous data, use *t* test and represent as mean ± SD; for categorical data, use Chi-square test and represent as number and percentage. The binary logistic regression analysis for the group of pregnant versus nonpregnant women was done to determine odds ratio. ROC curve will be done to determine the cutoff value based on the sensitivity and specificity of ORPI. *P* value < 0.05 was considered significant.

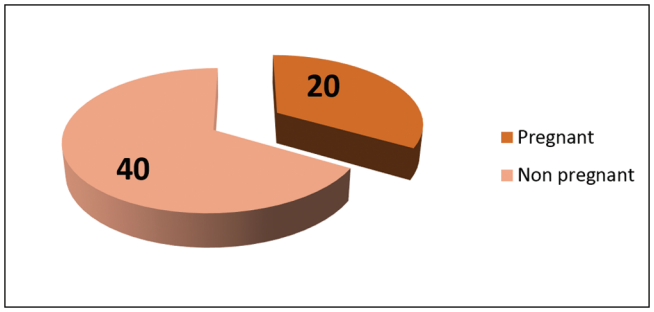

Figure 1: The pregnancy rate of the studied group (*N* = 60)

Results

The pregnancy rate of the studied group was 33.33% as shown in Figure 1.

The demographic characteristics of the pregnant and nonpregnant women are shown in Table 1. There were insignificant differences between pregnant and nonpregnant women in age, BMI, type of infertility, duration of infertility, and residence ($P > 0.05$).

Hormonal level at day 2 or 3 of MC was measured and showed in Table 2, AMH was significantly higher in pregnant women than nonpregnant group, (*P* value < 0.05)

Binary logistic regression analysis was done to assess the prognostic effect of ORPI in pregnant women compared to the nonpregnant group as a reference group, as shown in Table 3, where AMH, AFC, and BMI appeared to be significant influencing factors on the ORPI. However, the higher odds ratio (OR) were reported with AMH (OR = 2.72) and a significant ratio for AFC (OR = 2.34). Women with higher AMH, AFC, and lower BMI were more likely to have higher ORPI.

Receiver operating characteristics (ROC) curve analysis was performed to assess the validity of ORPI in predicting ICSI success rate [Figure 2]. ORPI showed an AUC of 1.00 at a cutoff point giving a sensitivity and specificity of 97% and 100%, respectively, which indicate that ORPI is highly predicting factor for ICSI success rate.

AUC	Cutoff value	Sensitivity	Specificity	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
1.00	2	97%	100	1.000	1.000
	1	100	95		

Table 1: Demographic characteristics of the pregnant and nonpregnant women (studied group *N* = 60)

Variable		Pregnant (20)		Nonpregnant (40)		*P* value
		N	%	*N*	%	
Address	Rural	9	45	9	22.5	0.069
	Urban	11	55	31	77.5	
Type of infertility	Primary	11	55	28	70	0.194
	Secondary	9	45	12	30	
Duration of infertility (years) (mean ± SD)		5.75±2.88		5.91±2.67		0.87
Age (mean ± SD) years		29.78±3.05		29.70±5.33		0.20
BMI (kg/m²) (mean ±SD)		23.85±2.72		24.85±2.99		0.94

BMI = body mass index

Table 2: Hormonal level on day 2 of the menstrual cycle of the pregnant and nonpregnant women

Hormones	Nonpregnant (40)	Pregnant (20)	*P* value
FSH (mIU/mL)	6.94 ± 1.62	7.51 ± 1.36	0.15
LH (IU/L)	5.24 ± 1.48	4.73 ± 1.04	0.13
Prolactin (ng/mL)	18.26 ± 5.25	19.54 ± 5.72	0.41
AMH (ng/mL)	1.41 ± 0.50	3.35 ± 1.10	0.001
E2 (pg/mL)	43.27 ± 11.19	45.31 ± 10.06	0.47
TSH (ng/mL)	2.07 ± 0.75	2.18 ± 0.57	0.53

FSH = follicle stimulating hormone, LH = luteinizing hormone, E2 = estradiol, AMH = anti- Müllerian hormone, TSH = thyroid stimulating hormone

*P value < 0.05 was significant

Table 3: Binary logistic regression analysis was done to assess the prognostic effect of ORPI of Pregnant women compared to nonpregnant group as reference group

Pregnant	*P* value	Odds ratio	95% Confidence interval for odds ratio	
			Lower bound	Upper bound
Age	0.142	0.825307	0.12	0.91
AFC	0.03	2.341	0.85	5.43
AMH	0.004	2.72	0.9996	3.56
BMI	0.047	0.772	0.595	0.99
Oocyte	0.015	1.92	0.404	2.37
MII	0.010	1.85	0.722	4.13
Embryo no.	0.012	1.93	0.8731	2.34
ET	0.117	0.93	0.7067	1.40

FSH = follicle stimulating hormone, LH = luteinizing hormone, E2 = estradiol, AMH = anti- Müllerian hormone, TSH = thyroid stimulating hormone, ORPI = ovarian reserve prediction index, MII = meta phase II, BMI = body mass index, AFC = antra follicle count, ET = embryo transverse

*P value < 0.05 was significant

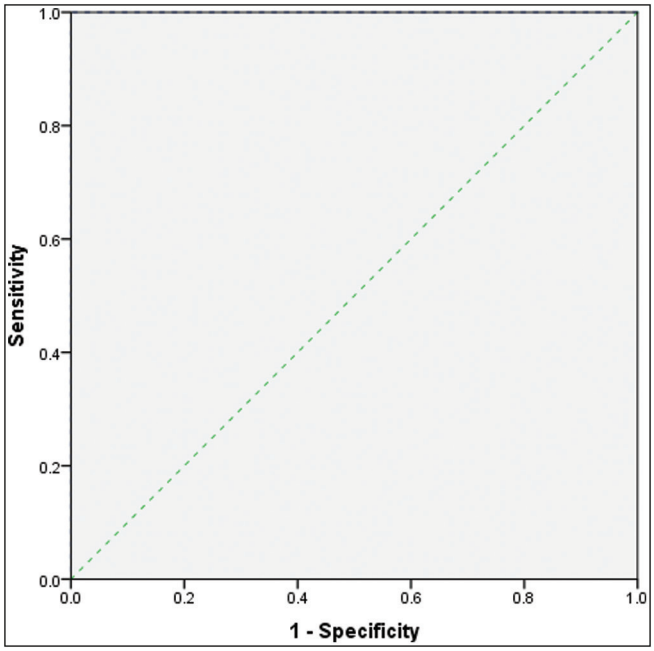

Figure 2: Receiver operating characteristics (ROC) curve giving a sensitivity and specificity

Discussion

Women's age alone as an indicator is not sufficient to give an accurate prognostication of the ovarian response, and even women of same age group might have different ovarian responses.[8] Estimation of antral follicle count using ultrasound had earned approval to be beneficial prognosticator of the ovarian response.[9]

The advantage of combined use of both age and AFC to predict ovarian response more than the usage of any one of them alone, also ORPI have an accurate and ideal prognostication of ovarian response with the usage of different parameters.[10]

In our current study that demonstrate a significant difference in ORPI between pregnant women and nonpregnant group, and ORPI was significantly higher in pregnant women than in nonpregnant group.

The ORPI might be used to improve the cost–benefit ratio of ovarian stimulation regimens by guiding the selection of medications and by modulating the doses and regimens according to the actual needs of patients.[11]

The pregnancy rate demonstrated by the studied group was 33.33%. Ahmeid *et al.*[12] found that the pregnancy rate in Baghdad IVF fertility center following ICSI was 20.4%. Bushraa and her team in Baghdad found that the rate of clinical pregnancy was 46.7% following ICSI.[13] Pregnancy rate of (51%) was recorded by some Iraqi authors in a study carried out at the High Institute for Infertility Diagnosis and Assisted Reproductive

Technologies, AL-Nahrain University and Specialist Fertility Department, Al-Bonook hospital.[14] In nearby countries (e.g., Iran), the successful clinical pregnancy rate following ART has ranged from 21.5% to 33.9%[15] suggesting that the rate of positive clinical pregnancy in the current study is one of the best-achieved rates.

However, in a number of fertility centers in the United States, the rate of positive clinical pregnancy has reached relatively high level between 43.9% and 54.2%.[16] This difference is related to the fact that their studies were done in more than one ART center and they started using ART many years before us, so the number of cases in their centers is higher.

Regarding AMH levels, there was a significant difference between pregnant and nonpregnant women, which was compatible with other studies, indicating that AMH could also independently predict pregnancy outcomes.[17]

Binary logistic regression analysis was done to assess the prognostic effect of ORPI in pregnant women, there was a significant positive correlation of ORPI and higher AMH, AFC, and lower BMI, which compatible with other results that also showed a significant positive correlation between them.[18]

In accordance with the study conducted by Joao Batista et al., they suggested that a combination of different variables of ORPI (AMH, AFC, and age) have resulted in a more precise index to predict ovarian response to controlled ovarian stimulation hormones, also they found a significant correlation with *P* value ($P < 0.001$) between ORPI and number of MII oocytes.[10] Gupta *et al*.[19] have similar findings in their study, where they found a positive relation between ORPI with AFC, AMH, oocytes, MI oocytes, and embryo (MS of MII 9.48 ± 5.55, MS of Embryo No. 5.88 ± 3.87). They concluded that ORPI is a novel ovarian response markers.

In addition, Hussain *et al*.[20] suggested the prognostication of ovarian response to COS hormones during ART cycles can depend on ORPI; they found a strong relation between ORPI and the number of oocytes pickup with maturity of collected oocytes.

Preference to that, Gupta *et al*. found a better prognostic evidence of AMH vs. AFC for oocyte retrieval. In Nelson *et al*.[21] study conducted at 19 ART centers, they concluded that AFC has been shown to have important inter-observer variation. This difference (Nelson *et al*.'s study was conducted in a single center, whereas Gupta *et al.*'s study was done in 19 ART centers, hence there are differences between their results) can be explained by the truth of the present study, which was carried out in a single center.

Zhao *et al*.[22] indicated that AMH could independently predict pregnancy outcomes. 20 AMH is the gold standard biomarker for assessing ovarian reserve and predicting ovarian response.

Also, our study was supported by other studies that indicated the benefit of using serum AMH values in the prediction of the number of oocytes retrieved during IVF cycles and AMH values are the strongest markers and the most beneficial indicators and predictors for the ovarian reserve and response for the ovarian controlled stimulation.[23]

Age has a strongly negative effect on the chances of pregnancy and ART does not compensate for basic physiological preconditions of reproductive senescence because there is a decrease in ovarian reserve and a rise in the development of aneuploidy embryos with very low implantation rates. Advancing female age has been reported to be a negative prognostic factor, and the decline in implantation rates with advancing age is primarily linked to poor oocyte quality rather than uterine function, because the number of good-quality embryos is significantly lower in women aged >40 year, and less embryos are available for replacement.[24] Therefore, the achievement of IVF can be as high as 40% at the age of 20 years in comparison with 5% of those with age > 40 year. Overall, it has been shown that ongoing pregnancy rates in assisted reproductive technology decreased significantly with advancing age.[24]

While other studies[25] illustrated that variable parameters in patients with infertility can predict pregnancy success rates following ICSI. These parameters are patient characteristics, total dose of gonadotropin, endometrial thickness, number of previous cycles, and quality of embryo transferred were evaluated as predictors of success rates following ICSI.

Swadi *et al.*[26] found that Folliculogenesis and oogenesis may be significantly influenced by THs. The FF also contains T3 and T4, which could have an immediate impact on the oocyte. So, through spontaneous conception or through the use of assisted reproductive technologies, thyroid dysfunction is prevalent in women of childbearing age and may negatively impact fertility and pregnancy.

Rhee *et al.*[27] blame BMI effect on oocyte quality and subsequent embryonic development. Some researchers found that obesity is associated with low progesterone levels produced by corpus luteum, obesity impairs decidualization and alters a mid-luteal endometrial protein profile. Also Al-Yasiry *et al*.[28] show that obesity was reported to influence the quality and number of oocytes and embryos, receptivity of endometrium, and implantation process in both natural and assisted conception. The need to lose weight before pregnancy should be highlighted to overweight and obese patients, who should be encouraged to lose weight prior to any therapy intervention to avoid the negative consequences of obesity.

Finally, receiver operating characteristics (ROC) curve analysis was done to assess the validity of ORPI in the prediction of ICSI success rate. ORPI showed an AUC of 1.00 at cutoff point 2, giving a sensitivity and specificity of 97% and 100%, respectively, and AUC of 1.00 at cutoff point 1, giving a sensitivity and specificity of 100% and 95%, respectively, which indicate that ORPI is highly predicting factor in of ICSI success rate.

The performance of ORPI as a prognostic test was observed using ROC curves. The ROC curves also revealed good prognostic potency.[19]

Conclusion

Ovarian reserve prediction index was significantly higher in pregnant women than nonpregnant group, AMH was significantly higher in pregnant women than in nonpregnant group. Women with higher AMH, AFC, and lower BMI are more likely to have higher ORPI.

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Conflicts of interest

There are no conflicts of interest.

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