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A Novel Method for Prediction of the Optimal Ovarian Stimulation Protocol during ICSI Cycles Using AMH Levels Estimate

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Abstract

Individualization of ovarian stimulation protocol in the intracytoplasmic sperm injection allows gynecologists to treat and manage infertile females according to their unique physiognomies. Ideally this would increase the clinical pregnancy rate, lessen the iatrogenic hazards such as ovarian hyperstimulation syndrome, and decline the risk of cancellation of cycles. Anti-Müllerian hormone (AMH) emitted via the granulosa cells from small growing follicles in ovary, is a key player in preserving the "follicle pool". The aim of this work is to explore whether AMH could be a predictive marker for the selection of the optimal ovarian stimulation protocol for cases that undergo intracytoplasmic sperm injection. This study was a retrospective study, that analyzed data from 1005 patients whose underwent intracytoplasmic sperm injection at a university ART unit from January 2017 to December 2020 where 3 groups were validated according to the level of AMH. group1, includes patients with serum AMH<1 ng/ml, group2, includes patients with AMH 1-3 ng/ml and group3 with AMH>3 ng/ml. Our results had shown that the long agonist protocol had the superlative outcome in all groups of the study. Serum AMH levels concentration correlated strongly with oocyte yield. AMH level should be determined before embarking on COS protocol. Surprisingly, our results revealed that long agonist protocol had the best outcome in all groups.

Keywords: AMH; ICSI; Controlled Ovarian Stimulation

Abbreviations: ICSI: Intracytoplasmic Sperm Injection; OHSS: Ovarian Hyperstimulation Syndrome; AMH: Anti-Müllerian Hormone; COS: Controlled Ovarian Stimulation; ART: Assisted Reproductive Technology; PCO: Polycystic Ovary; AMH: Anti-Müllerian Hormone; AFC: Antral Follicle Count; BMI: Body Mass Index.

Introduction

Up till now, extremes of ovarian response after controlled ovarian stimulation (COS) are still a substantial drawback in numerous programs regardless many innovations in the field of human assisted reproductive technology (ART). For utmost fertility doctors, the choice of the protocol largely relies besides experience from their clinical practice, on the lady's age, the existence or lack of polycystic ovary (PCO), and the basal FSH concentrations to settle on the gonadotrophins starting dose for stimulation [1]. Optimum ovarian response is a crucial portion of COS formulas. The ability to predict ovarian reserve is crucial to obtain an adequate response and an optimal outcome from assisted reproductive technologies (ART) and offers the possibility of tailoring COS protocols for each individual patient [2]. Individualization of the stimulation therapy permits fertility clinicians to handle

each of the infertile cases in consistent with their unique physiognomies; this would supremely maximize the clinical profits as regards increasing the pregnancy rate, reducing the iatrogenic hazards for instance OHSS, and diminishing the risk of cycle cancelation. Above all, the competence to forecast a distinct patient's ovarian response to stimulation is very convenient for electing a gonadotropin dosage that is credible to be efficient and safe together [3].

Anti-Müllerian hormone (AMH) is emitted via small growing follicles in the ovary and it is a key player in preserving the "follicle pool" [4]. As antral follicle count (AFC) is more dependent on the clinical experience of individual doctors, which varies from center to center and may have higher inter-observed variability. Nelson, et al. showed AMH was a stronger predictor of ovarian response to gonadotropin dosing than AFC [4]. Nowadays, AMH, tagged as an ovarian reserve maker, since its relationship to ovarian response was first noted has well acknowledged to be a mainstay of the fertility workup in a multitude of countries[5] for the above reasons AMH alone may be more subjective method in prediction of the best protocol for ovulation induction. The objectivity and potential standardization of AMH levels, as well as their readily detectable convenience throughout the menstrual cycle, make AMH levels the gold standard biomarker for assessing ovarian reserve and predicting ovarian response to stimulation [5]. In this study we tried to investigate the role of AMH only in prediction of the optimal ovarian protocol during ICSI cycles at three different levels for serum AMH. According to our knowledge, this is the first study to be designed to explore this relation.

Patients and Methods

This study was a retrospective cohort study in which we used data file from 1005 patients who underwent ICSI trial at the International Islamic Center for Population Studies and Research, Assisted Reproduction Unit Al-Azhar University from the period January 2017 - December 2020. The patients were divided into 3 groups were which categorized according to the level of AMH. Group1, includes patients with serum AMH<1 ng/ml, group 2, includes patients with AMH 1-3 ng/ml and group3 with AMH>3 ng/ml. The entire included cases underwent ICSI cycles.

Inclusion Criteria

Patients who were free from chronic diseases& malignancy and did not receive chemotherapy or radiotherapy.

Exclusion Criteria

Patients with history of canceled stimulation cycle's cycle during ICSI, for any reason and patients with male factor infertility were excluded from the study.

Depending on presentation of the collected data from patients' files; the following variables were retrieved for analysis: - patient age, body mass index (BMI), serum AMH level (ng/ml), data about the used Protocol (Type, Duration of stimulation, Dose of stimulation), retrieved oocytes data and quality, fertilized oocytes, embryos quality, transferred embryos, cryopreserved embryos, and pregnancy outcome. The primary outcome was the pregnancy rate among groups. The secondary outcomes included, were the number of oocytes retrieved, oocyte quality, fertilization rate, the number of embryos transferred and the quality of embryos.

Statistical Analysis

Statistical analyses of data were carried out via SPSS version 23. Shapiro –Wilks test was used to test normal distribution of variables. Numerical data were expressed as mean ± standard deviation or median and range. The probability (P) values of ≤0.05 were considered statistically significant indicated.

Results (Tables 1-4)

		AMH < 1 (No. = 225)			P-value
		Short agonist	Antagonist	Long agonist	
		No. = 56	No. = 161	No. = 8	
Retrieved Oocytes	Median (IQR)	3 (2 – 4)	3 (3 – 6)	6 (3 – 10.5)	0.014
	Range	1 – 10	1 – 14	2 – 15	
Oocytes quality MII	Median (IQR)	2 (1 – 3)	2 (1 – 3)	2.5 (1 – 4.5)	0.292
	Range	1 – 7	1 – 8	1 – 6	
Fertilized Oocytes	Median (IQR)	2 (1 – 3)	3 (2 – 3)	4.5 (2.5 – 6)	0.013
	Range	1 – 7	1 – 9	2 – 8	

Transferred Embryos	Median (IQR)	2 (1 – 3)	2 (2 – 3)	3 (2 – 3)	0.047
	Range	1 – 4	1 – 4	2 – 3	
Embryos quality	Median (IQR)	2 (1 – 3)	2 (1 – 3)	3 (2 – 3)	0.08
	Range	1 – 5	1 – 4	2 – 3	
Pregnancy outcome	Negative	39 (69.6%)	116 (72.0%)	4 (50.0%)	0.401
	Positive	17 (30.4%)	45 (28.0%)	4 (50.0%)	
Post hoc analysis					
		Short agonist Vs Antagonist		**Short agonist Vs Long agonist**	**Antagonist Vs Long agonist**
Retrieved Oocytes		0.018		0.031	0.121
Fertilized Oocytes		0.114		0.006	0.019
Transferred embryos		0.037		0.053	0.296

Table 1: Comparison between the studied protocols types regarding reproductive outcome variables in group 1 (AMH < 1ng/ml).

In group1(AMH<1 ng/ml), the pregnancy rate was higher in patients received antagonist protocol group(45% versus 17% and 4%) in antagonist, short and long protocols respectively. However, this difference is not statistically significant.

		AMH (1 - 3) (No. = 404)			**P-value**
		Short agonist	**Antagonist**	**Long agonist**	
		No. = 33	**No. = 237**	**No. = 134**	
Retrieved Oocytes	Median (IQR)	5 (3 – 7)	6 (5 – 10)	8 (6 – 10)	0.000
	Range	1 – 16	1 – 23	2 – 20	
Oocytes quality MII	Median (IQR)	3 (2 – 6)	3 (2 – 5)	5 (3 – 6)	0.002
	Range	1 – 9	1 – 9	1 – 9	
Fertilized Oocytes	Median (IQR)	4 (2 – 5)	3 (2 – 5)	5 (3 – 7)	0.000
	Range	1 – 8	1 – 9	1 – 9	
Transferred Embryos	Median (IQR)	3 (2 – 3)	2 (2 – 3)	3 (2 – 3)	0.022
	Range	1 – 4	1 – 4	1 – 9	
Embryos quality	Median (IQR)	3 (2 – 3)	2 (2 – 3)	3 (2 – 3)	0.029
	Range	1 – 4	1 – 4	1 – 3	
Pregnancy outcome	Negative	20 (60.6%)	171 (72.2%)	69 (51.5%)	0.000
	Positive	13 (39.4%)	66 (27.8%)	65 (48.5%)	
Post hoc analysis					
		Short agonist Vs Antagonist	**Short agonist Vs Long agonist**		**Antagonist Vs Long agonist**
Retrieved Oocytes		0.012	0.000		0.003
Oocytes quality MII		0.700	0.164		0.000
Fertilized Oocytes		0.488	0.067		0.000
Transferred Embryos		0.411	0.605		0.005
Embryos quality		0.439	0.630		0.007
Pregnancy outcome		0.172	0.347		0.000

Table 2: Comparison between the studied protocols types regarding reproductive outcome variables in group 2 (AMH 1-3ng/ml).

In group2 (AMH 1-3 ng/m) the pregnancy rate was significantly higher in patients received long agonist protocol (48.5 versus 39.4 and 27.8) in long, antagonist and short protocol, respectively.
HS: highly significant
S: significant

		AMH > 3 (No. = 376)			P-value
		Short agonist	Antagonist	Long agonist	
		No. = 2	No. = 300	No. = 74	
Retrieved Oocytes	Median (IQR)	8.5 (8 – 9)	10 (7 – 14)	10 (7 – 12)	0.114
	Range	8 – 9	2 – 25	3 – 20	
Oocytes quality MII	Median (IQR)	4 (2 – 6)	4 (2 – 6)	4 (3 – 6)	1
	Range	2 – 6	1 – 9	1 – 9	
Fertilized Oocytes	Median (IQR)	4.5 (3 – 6)	3 (1 – 6)	5 (3 – 7)	0.001
	Range	3 – 6	1 – 9	1 – 9	
Transferred Embryos	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.798
	Range	2 – 3	1 – 11	1 – 3	
Embryos quality	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.907
	Range	2 – 3	1 – 10	1 – 3	
Pregnancy outcome	Negative	1 (50.0%)	128 (42.7%)	35 (47.3%)	0.759
	Positive	1 (50.0%)	172 (57.3%)	39 (52.7%)	
Post hoc analysis					
		Short agonist Vs Antagonist	Short agonist Vs Long agonist	Antagonist Vs Long agonist	
Fertilized Oocytes		0.618	0.682	0.000	

Table 3: Comparison between the studied protocol types regarding reproductive outcome variables in group 3 (AMH > 3 ng/ml).

In group 3 (AMH) >3 ng/ml, the pregnancy rate was higher in patients received antagonist protocol (57.3%versus 52.7% and 50%) in antagonist, long agonist, and short protocol, respectively. However, this difference is not statistically significant.

Variable	Group 1(AMH <1)	Group2 (AMH 1-3) *	Group3 (AMH>3)
Pregnancy rate	Antagonist Protocol	Long Protocol	Antagonist Protocol
Number of retrieved Oocytes	Long	Long	Non superiority
Oocytes quality	Non superiority	Antagonist	Non superiority
Fertilized oocytes	Long	Long	Long
Number of transferred embryos	Long	Long =short	Non superiority
Embryo quality	Non superiority	Long =short	Non superiority

Table 4: the prediction of the optimal protocol among groups and superiority of protocols regarding reproductive outcome.
*The difference in pregnancy rate among groups is statistically significant.

Discussion

There is a consensus that the optimization and individualization of controlled ovarian stimulation (COS) is very crucial. On a trial to find out retrospectively what is the best controlled ovarian stimulation protocol based on AMH levels (AMH tailored protocol), 698 cases had taken antagonist protocol, 91 cases had taken short agonist protocol and 216 had taken long agonist protocol. According to AMH level cases were divided into 3 groups: cases with AMH <1 ng/ml (225 cases) with AMH 1-3 ng/ml (404 cases), and cases with AMH >3 ng/ml (376 cases). Our results

retrieved that the long agonist protocol had the superlative outcome for all strata of cases alienated according to AMH levels (cases at AMH <1 ng/ml, AMH 1-3 ng/ml, and >3 ng/ml).

The Reproductive Outcomes

The pregnancy rate was higher in group 2 with the long protocol. However, it is higher in group1 and 3 if the antagonist protocol was used. Regarding the number of oocytes retrieved was higher in group 1and 2 if long protocol was used while none of the protocols was superior in group 3. Regarding the oocyte's quality, the number of MII oocytes was higher in group 2 when the antagonist protocol was prescribed but no superiority among protocols in group1 and 3. When considering the number of fertilized oocytes, surprisingly the long protocol was the gold standard in all groups. Also, regarding the number of transferred embryos, the long protocol is the one with higher number of embryos transferred in group1, while long is equal to short in group 2 but there is no superiority among the three protocols in group 3. In addition to the previous results, the embryo quality among groups was not affected by the protocol prescribed except in group 2 where the short protocol was equal to long protocol regarding the embryo quality with the least quality registered with the antagonist protocol.

In agreement with our findings, Behery MA [6] registered that the long protocol resulted in better outcome than short agonist and antagonist protocol in a specific age (from 30 to 40 years) respecting the number and quality of retrieved oocytes and the fertilization rate. Although, short and GnRH antagonist protocols may propose noteworthy cost-saving over the long GnRH agonist. the GnRH antagonist protocol appeared to be the least efficient compared with both GnRH agonist regimens and resulted in outcome less but approximately equivalent to those attained by standard long GnRH agonist protocol. It has also been found to offer significant cost-saving over long protocol owing to the diminution the treatment duration along with the total gonadotropin stimulation dose, permitting more flexibility of treatment and more comfortability for patient. So, it can be considered the ideal protocol for patients not responding to a long GnRH agonist protocol. Cota AMM, et al. and Xiao JS, et al. [7,8] found that there was noteworthy increase in long over the antagonist protocols concerning the entire number of oocytes, number of MII oocytes, thickness of the endometrium, E2 concentrations at the day of HCG, and total quantity of embryos. The retrieved oocytes increased number may be predisposed by greater recruitment with better quality of oocytes that yielded more E2 in long protocol group as an echo of the preliminary flare up effect after down-regulation with GnRH agonist, and this elucidates the momentous dissimilarity in endometrial thickness, elevated E2 level at day of hCG and the more embryos obtained.

In a trial of AMH tailored protocols, Thomas S, et al. [9] found similar effectiveness in terms of clinical pregnancy rate, number of mature oocytes, number of cancelled cycles, and incidence of OHSS episodes when personalized treatment regimens of AMH-tailored protocol were compared to the conventional protocol for ART and they suggested that before merging the AMH-tailored regimens in scheduled IVF practice, further prospective and randomized-controlled trials were still indispensable. In their AMH-tailored protocol, Cases whose AMH levels were less than 0.5 ng/ml, received antagonist or short agonist protocol while those with AMH 0.5-1.1 ng/ml received antagonist protocol, and those with AMH 1.1-4.8 ng/ml received antagonist or long agonist protocols, while those with AMH >4.8 ng/ml received antagonist protocol.

It was also found that antagonist protocols had superior outcomes at both low and high ovarian reserve extremes Vela G, et al. [10] and they acknowledged that the favorable outcomes in ART cycles, especially the reductions in poor- and over-response, could be to some extent allied to the institution of these protocols. These results agreed with earlier studies, which found AMH to be superior to FSH in predicting not only the response to ovarian stimulation but also, the likelihood of clinical pregnancy Barad DH, et al. & Lee TH, et al. [11,12].

Further interrogation of facts that had been stated via Yates AP, et al. and his co-workers in 2011 [13] exhibited a general upsurge in the rate of ongoing pregnancy and live births in the AMH-tailored treatment cluster of cases irrespective to the type of protocol or ART technique utilized, or the number of embryos transferred. These facts may supplement further weight to the hypothesis that AMH-tailored protocols optimize stimulation. They stated that categorizing patients based on AMH levels had assisted the proper integration of the antagonist protocol into routine COH and had also lessened the cost of fertility drugs consumed and the costs of hospital admissions related to OHSS. Another prospective study designated that AMH and basal FSH were significantly favorable predictors of both the retrieved oocytes number and the occurrence of an extreme ovarian response, whereas AMH was independently the foremost predictor for low ovarian response in IVF/ICSI Andersen AN, et al. [14].

The study has some points of weakness and strength. The weak points are being a retrospective cohort and not a clinical trial. Also, the study was not estimating the incidence of ovarian hyper stimulation syndrome among groups. The power of the study comes from being the first study designed to select the protocol for ovulation induction depending on

one factor (that is AMH marker) liberating the patients from the person-to-person variability when selecting the protocol depending on the basal ultrasound assessment of the ovaries that is considered a non-subjective method in situations like untrained sonographer, obese patients, or the low-quality ultrasound tool.

Conclusion

The study revealed that the serum AMH level may be used solely as a predictor for the best ovarian stimulation protocol correlated with the reproductive outcome. It is plausible that AMH might also be associated with qualitative and quantitative outcomes of ovarian stimulation and pregnancy rate after ICSI cycles. So, AMH level should be determined before embarking on COS protocol. Surprisingly, our results revealed that long agonist protocol had the best reproductive outcomes among all groups.

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