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ORIGINAL ARTICLE

Serum anti-Müllerian hormone and basal serum FSH as predictors of poor ovarian response in assisted conception cycles

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KEYWORDS

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Abstract *Objective:* The aim of the study was to correlate serum AMH and serum FSH levels with ovarian response to stimulation in IVF–ICSI cycles.

Design and settings: This was a prospective observational study conducted in a private assisted conception unit.

Subjects and methods: One hundred and two patients were selected on their first IVF cycle. Basal serum FSH and serum AMH were measured one month before the stimulation cycle. A fixed dose GnRH antagonist protocol was used in all cycles transferring a maximum of three day-3 cleavage stage embryos. We defined poor ovarian response as retrieval of fewer than four mature oocytes in cycles requiring $\geqslant$ 3000 IU of gonadotropins for stimulation or cycle cancellation due to poor response. The correlation between different parameters was expressed as a Spearman's correlation coefficient. The clinical value of AMH and FSH as predictors of poor ovarian response as well as predictors of pregnancy was evaluated by constructing relevant receiver operator characteristics curves (ROC curves).

Results: Of these 102 cycles, 28 fitted our definition of poor response while the remaining 74 cycles all produced an adequate response to stimulation. There was a statistically significant difference between the adequate responders group and poor responders group regarding their mean age (31.5 versus 39.6, $p < 0.001$), the mean value of AMH (2.84 ng/ml versus 0.9 ng/ml, $p < 0.0001$) as well as the mean value of basal FSH (7.6 IU/ml versus 9.7 IU/ml, $p < 0.0001$).

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Serum AMH level had a positive correlation while serum FSH had a negative correlation with the number of oocytes collected while only serum AMH had a significant positive correlation with the occurrence of pregnancy. ROC curve analysis of our results showed that serum AMH with an optimal cut-off value of 1.2 ng/ml is a reliable predictor of poor ovarian response with an area under the ROC curve of 90.4%. Serum basal FSH with an optimal cut-off value of 8.9 IU/ml was of lower value than AMH as a predictor of poor ovarian response with an area under the ROC curve of 81.9%. However, neither serum AMH nor basal serum FSH was found to able to reliably predict the occurrence of pregnancy with an area under the ROC curve of 59.4% and 58.6% respectively.

Conclusion: Our results show that serum AMH level is more reliable than basal serum FSH as a predictor of poor ovarian response to stimulation with a cut-off value of 1.2 ng/ml shown to predict poor ovarian response with a sensitivity of 91.7%.

1. Introduction

Determining a patient's ovarian reserve is important before starting assisted reproductive treatment (ART) because it carries prognostic information about the chances of success as well as helping in deciding the optimal protocol for treatment (1).

Ovarian response to adequate stimulation may be considered the most accurate, though still indirect, representation of the status of the primordial follicle pool, as it is a condition that is continuously present in the individual who undergoes the test. In contrast, the occurrence of pregnancy in such an individual may be influenced by many more factors than oocyte, and hence embryo quality, alone (1). Many investigators have attempted to define poor ovarian response using varying criteria depending on the number of mature follicles developed or the number of mature oocytes retrieved. Kailasam et al. (2), suggested that the definition of poor ovarian reserve should take into account the degree of stimulation used and found in their study that when $\geqslant$ 3000 IU FSH was required for stimulation and less than 4 oocytes were retrieved the pregnancy rate was only 4%.

Anti-Müllerian hormone (AMH) has been evaluated by many investigators and found to be useful as a marker for ovarian response in ART (3–5). AMH is a dimeric glycoprotein belonging to the transforming growth factor-beta (TGF-β) superfamily, which acts on tissue growth and differentiation (6). It is produced by the granulosa cells from pre-antral and small antral follicles. Together with two other factors (growth and differentiation factor-9 and bone morphogenetic protein-15), it inhibits the initiation of premature follicle growth and decreases the sensitivity of follicles to FSH (7).

AMH levels decline with age from adulthood toward menopause reflecting the size of the ovarian follicle pool (8). Several studies have shown that serum AMH measurement is more accurate than serum FSH, inhibin B or estradiol in predicting ovarian response (3,9–12). Furthermore, AMH levels appear to remain constant throughout the menstrual cycle and thus can be reliably measured at any time unlike other hormone markers that must be measured in the early follicular phase (13–16).

Serum and intra-follicular AMH levels are elevated in patients with polycystic ovary syndrome (PCOS) due to increased number of small follicles and an increased secretion within each of these small follicles. This excess of AMH is strongly suspected to play a role in the follicular arrest of PCOS by a negative action on aromatase expression and on action of FSH (17).

1.1. Aim

The aim of the study was to correlate serum AMH and basal serum FSH levels with ovarian response to stimulation in IVF–ICSI cycles. We also used our results to construct a ROC curve to determine the validity of serum AMH and serum FSH measurements as diagnostic tests for the prediction of ovarian response in IVF–ICSI cycles.

2. Patients and methods

This prospective study was conducted in a private assisted conception unit (Hayat Fertility and Women's Health Center) on patients scheduled for IVF–ICSI cycles from February 2010 to July 2011. The internal ethics committee of our unit approved the study protocol and all enrolled patients signed an informed consent before starting treatment. Enrolled patients underwent a basic infertility evaluation on the month before starting treatment including detailed fertility, medical and surgical history as well as a comprehensive gynecological examination. This was followed by a baseline trans-vaginal ultrasound to exclude local pathology as well as a basal hormonal profile on day 2–3 of the menstrual cycle (FSH, LH, and Prolactin) as well as serum AMH. Serum AMH was measured by enzyme-linked immunosorbent assay (ELISA) kit (Immunotech-Beckman Coulter, Webster, TX, USA) and expressed in ng/ml. Serum concentrations of FSH were measured using Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex (ARCHITECT system, Abbott Laboratories, Abbott Park, IL, USA) expressed as mIU/ml.

Criteria for inclusion in the study included:

1. Patient age below 45 years.
2. Body mass index (BMI) $<$40.
3. No evidence of polycystic ovary syndrome (according to the Rotterdam criteria (18)).
4. No evidence of other endocrine disorders.
5. Patients possessing both ovaries with no history of ovarian surgery (cystectomy or oophorectomy).
6. Patients in their first IVF–ICSI cycle.

A fixed dose GnRH antagonist protocol was used in all cycles as it was found by many investigators to reduce the risk of ovarian hyper-stimulation syndrome (19–21) as well as produce favorable results in patients with low ovarian reserve (22–23). The treatment cycle was preceded by low dose monophasic combined oral contraceptive pill for 21 days followed by a trans-vaginal ultrasound to exclude the presence of functional cysts on the first day of withdrawal bleeding. Treatment with purified urinary FSH 150–300 IU/day (Fostimon, IBSA, Switzerland) was started on the second day of the cycle. The starting dose was chosen according to the patient's age and body mass index (BMI). The dose was adjusted according to the patient's response, which was monitored by ultrasound folliculometry. A GnRH antagonist (Cetrotide_ 0.25 mg, Serono, Switzerland) was started on day 6 of stimulation and continued daily until the day of hCG administration for triggering of ovulation. The criteria for human chorionic gonadotropin 5,000–10,000 IU administration (Choriomon_, IBSA, Switzerland or Pregnyl_, Organon, USA) were the presence of two or more follicles $\geqslant$ 18 mm in diameter with $\geqslant$ 4 follicles measuring $\geqslant$ 14 mm. Ovum pick-up was scheduled 34–36 h later followed by IVF or intra-cytoplasmic sperm injection (for severe semen abnormalities). The cycle was canceled when there were <3 follicles with diameter <14 mm after 8–9 days of gonadotropin therapy or after 4–5 additional treatment days without attaining the criteria for HCG administration.

We performed day-three embryo transfer and all patients had a maximum of three embryos transferred per cycle. The maturational status of the oocytes and the embryo grading was recorded according to published criteria (24); embryos of Veeck grades 1 or 2 were considered high quality and thus suitable for transfer. Natural progesterone (Prontogest_200 mg, Marcyrl Pharmaceutical Industries, Egypt) rectal suppository twice daily was used for luteal support starting on the day of oocyte retrieval. A serum quantitative hCG pregnancy test was performed 14 days after oocyte retrieval and repeated after 48 h if positive. Ongoing pregnancy was confirmed by ultrasound examination 14 days later showing an intrauterine gestation with fetal pole having positive cardiac activity.

The main outcome measure was ovarian response to stimulation. We defined poor ovarian response as retrieval of fewer than four mature oocytes in cycles requiring $\geqslant$ 3000 IU of gonadotropins for stimulation based on the criteria suggested by Kailasam et al. (2) or cycle cancellation due to inadequate or absent ovarian response to ovarian stimulation. An adequate ovarian response was defined as collection of 4–16 oocytes while patients with more than 16 oocytes collected were considered high responders with increased risk of OHSS.

The pregnancy rate was also reported but considered as a secondary outcome measure because of the heterogeneous nature of the couples included in the study and because many other factors other than oocyte quality influence the outcome.

3. Statistical analysis

Data were statistically represented in terms of mean and standard deviation (SD). Statistical comparisons between poor responders and adequate responders were made using the Mann–Whitney *U* test for continuous data and the Chi-square (χ^2) test for parametric data. The correlation between different parameters was expressed as a Spearman's correlation coefficient (Rho). The clinical value of both AMH and FSH as predictors of poor ovarian response as well as predictors of pregnancy was evaluated by constructing relevant receiver operator characteristics curves (ROC curves). The ROC curve plots the relationship between sensitivity and false-positive rate at varying values. The suggested cut-off levels for predicting poor ovarian response or pregnancy were derived from the ROC curve. Sensitivity and specificity were calculated for each cut-off level. The area under the ROC curve was also calculated to determine overall accuracy.

A value of $p < 0.05$ was considered to be significant for all the above tests. Statistical analysis was done using Microsoft Excel 2010 & Arcus Quickstat Biomedical version 1.0.

4. Results

During the study period we carried out 102 cycles: 65 cases of male subfertility, 15 cases of tubal pathology, 12 cases of endometriosis and 10 cases of unexplained infertility with at least two previous failed IUI attempts. Of these 102 cycles, 28 fitted our definition of poor response with 24 cycles having 3 or less retrieved oocytes and 4 cycles canceled because of inadequate response to stimulation. The remaining 74 cycles all produced an adequate response to stimulation with 4–16 collected oocytes and no cycles were canceled because of excessive response.

Table 1 presents a comparison between the adequate response group and the poor response group of the main demographic as well as the outcome variables. Our results show that there was a statistically significant difference between the two groups regarding all the variables with the exception of the mean BMI.

The scatter plots in Fig. 1 show the relationship between the level of AMH and FSH in the study population with both patient's age and the number of oocytes collected.

Our results (Table 2) show that the level of serum AMH had a significant negative correlation while serum FSH had a significant positive correlation with maternal age, the number of days required for stimulation as well as the total dose of gonadotropins. Conversely, serum AMH level had a positive correlation while serum FSH had a negative correlation with the number of oocytes collected while only serum AMH had a significant positive correlation with the occurrence of pregnancy. In addition there was a significant negative correlation between serum AMH and serum FSH.

We used receiver operating characteristics (ROC) analysis to predict the ability of both serum AMH and basal serum FSH to predict poor ovarian response to stimulation as well as the occurrence of pregnancy (Table 3 and Fig. 2).

5. Discussion

The aim of this prospective study was to determine the usefulness of routine serum AMH measurement as a predictor of ovarian response for patients undergoing IVF–ICSI cycles. For this reason we selected patients in their first IVF–ICSI cycle in order to avoid being guided in our starting dose of gonadotropins by the results of their previous IVF cycles. We also excluded patients with PCOS criteria, who have been

Table 1 Comparison between the demographic and outcome variables in the two groups.

NUMBER (%)	Adequate response 74 (72.5%)		Poor response 28 (27.5%)		*P*-value
	Mean	S.D.	Mean	S.D.	
Age (years)	31.5	3.9	39.6	2.2	< 0.001*
BMI	25	2.369	26.4	3.3	0.065
AMH (ng/ml)	2.84	1.222	0.9	0.3	< 0.0001*
FSH (mIU/ml)	7.6	1.3	9.7	1.3	< 0.0001*
Gonadotropin units (IU)	2871.5	976.5	4541.7	1205.4	< 0.0001*
Stimulation days	10.6	1.2	12.4	1.4	< 0.0001*
OocyteS	10.8	2.4	2.4	0.8	< 0.0001*
Pregnancy (%)	25 (33.7%)		3 (10.7%)		0.025*

* Statistically Significant.

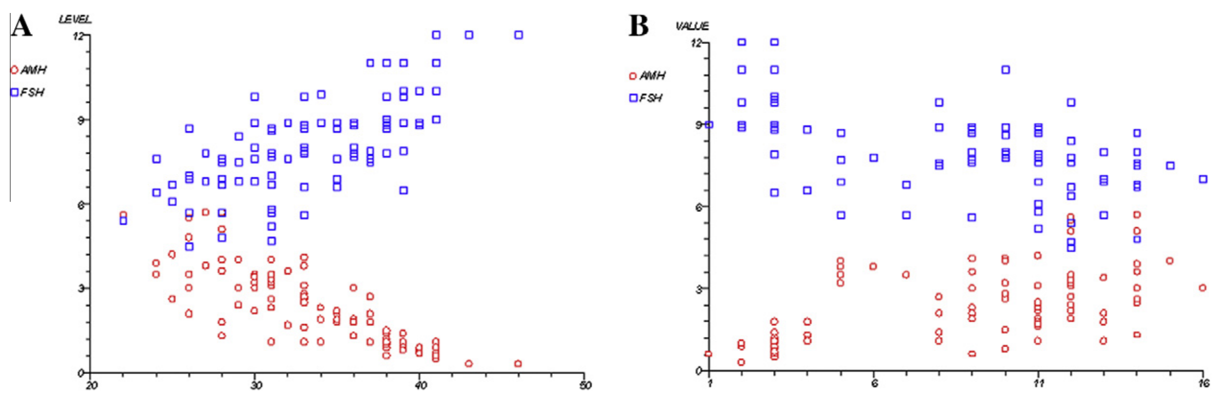

Figure 1 Scatter plots showing the distribution of AMH and FSH levels in relation to patient's age (A) and to the number of collected oocytes (B).

Table 2 Correlation of AMH and FSH with the demographic and outcome variables.

	AMH			FSH		
	Spearman's Rho	95% CI	*P*	Spearman's Rho	95% CI	*P*
Age (years)	−0.83	−0.88–−0.76	< 0.0001*	0.72	0.61–0.80	< 0.0001*
BMI	−0.14	−0.33–−0.55	0.16	0.24	0.04–0.41	0.06
AMH (ng/ml)	–	–		−0.61	−0.72–−0.47	< 0.0001*
FSH (mIU/ml)	−0.61	−0.72–−0.47	< 0.0001*	–	–	
Gonadotropin units (IU)	−0.65	−0.75–−0.52	< 0.0001*	0.66	0.53–0.76	< 0.0001*
Stimulation days	−0.62	−0.73–−0.49	< 0.0001*	0.59	0.44–0.71	< 0.0001*
Oocytes	0.72	0.61–0.80	< 0.0001*	−0.66	−0.76–−0.53	< 0.0001*
Pregnancy	0.33	0.15–0.50	0.0007*	−0.24	−0.17–0.22	0.82

* Statistically significant.

Table 3 The area under the ROC curve, the optimal cut-off level as well as the sensitivity and specificity of both AMH and FSH for the prediction of poor ovarian response and the occurrence of pregnancy.

	Poor response				Pregnancy			
	Cut-off	Sens. (%)	Spec. (%)	A U ROC (%)	Cut-off	Sens. (%)	Specif. (%)	A U ROC (%)
AMH	1.2 ng/ml	91.7	92.5	90.4	1.4 ng/ml	79.2	44.4	59.4
FSH	8.9 mIU/ml	83.5	81.4	81.9	7.8 mIU/ml	67.8	65.2	58.6

Sens.: sensitivity, Spec.: specificity, A U ROC: area under the ROC curve.

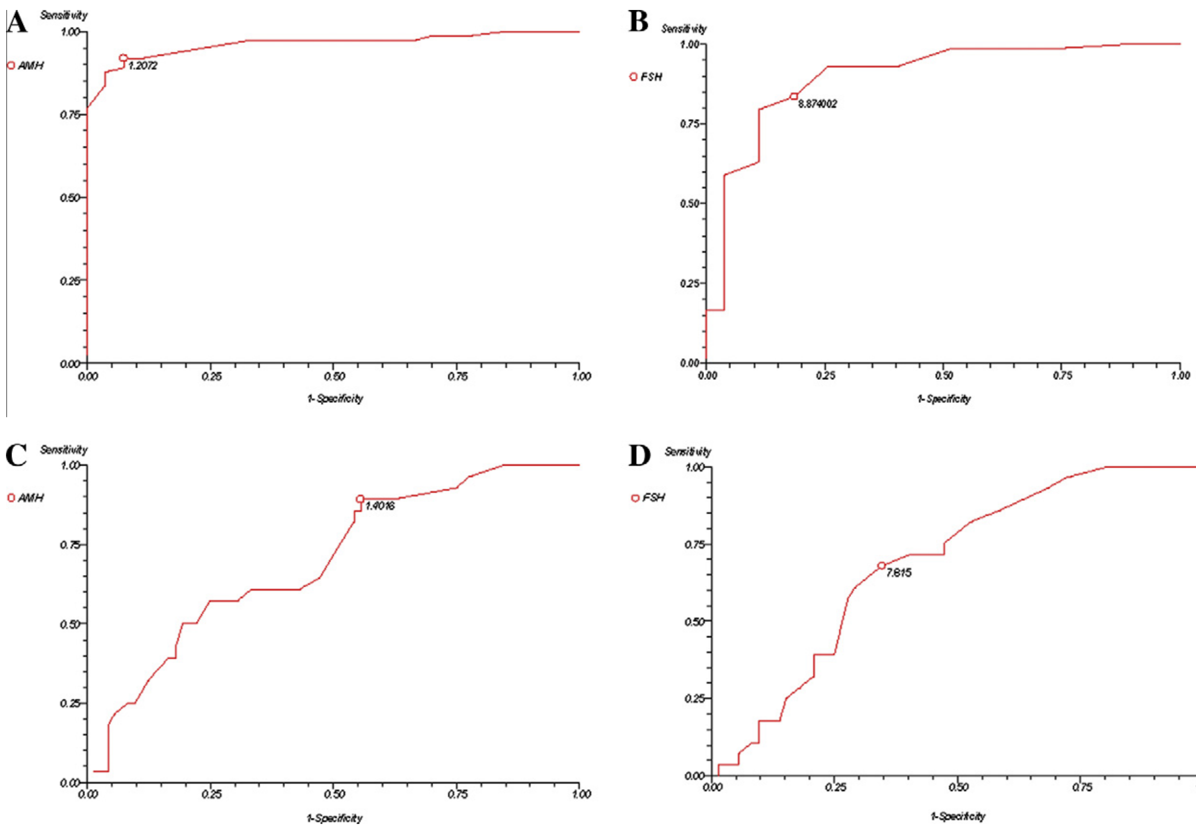

Figure 2 Receiver operating characteristic (ROC) curve showing the sensitivity on the y-axis and the 1-specificity (false-positive rate) on the x-axis as well as the optimal cut-off value of AMH (A) and FSH (B) to predict poor ovarian response as well as AMH (C) and FSH (D) to predict the occurrence of pregnancy.

shown to exhibit elevated serum AMH levels (17), to avoid falsely elevating the mean value of measured serum AMH in the study.

Although the antral follicle count is a reliable marker shown to predict poor ovarian response (1), it is subject to inter-observer variability due to variation in observer experience and the anticipated ovarian reserve based on patient's age. For this reason we excluded the antral follicle count from this study and relied only on objectively measured endocrine markers thus avoiding observer related errors.

Our results (Table 1) show that the 28 patients in the poor ovarian response group were statistically significantly older, required a higher cumulative dose of gonadotropins, more days of stimulation as well as producing fewer oocytes on stimulation than the 74 patients in the adequate response group. There was also a statistically significant difference between the two groups regarding the mean values of both serum AMH and basal serum FSH. The scatter chart in Fig. 1A shows that the patient age had a negative correlation with serum AMH while having a positive correlation with serum FSH. La Marca et al. (25) studied the ability of AMH to predict ovarian response in assisted conception cycles. Their definition of poor ovarian response was similar to ours, the collection of fewer than 4 oocytes or cycle cancellation due to inadequate response to stimulation. Their findings were similar to ours, showing that poor responders were older, required a higher dose of gonadotropins for stimulation, had a significantly lower serum AMH level as well a significantly lower pregnancy rate than normal or high responders.

Our results show a significant correlation between serum AMH (positive correlation) as well as basal serum FSH (negative correlation) with ovarian response expressed as the number of retrieved oocytes. Serum AMH levels but not serum FSH levels showed a significant positive correlation with the occurrence of pregnancy as shown in Table 2. The scatter chart in Fig. 1B shows that the number of oocytes had a positive correlation with serum AMH while having a negative correlation with serum FSH.

Gnoth et al. (26), in a study evaluating the usefulness of serum AMH measurement in a routine IVF program also found a significant positive correlation between serum AMH levels and ovarian response. They also found that poor responders were significantly older and had a significantly lower clinical pregnancy rate. However, they found that serum FSH, although elevated was still within the normal range and was weakly achieving statistical significance ($p = 0.034$) in discriminating between low and normal responders.

Nelson et al. (27) studied the role of both serum AMH and FSH in predicting live-birth and extremes of response in IVF cycles. They concluded that age was positively correlated with FSH, and was negatively related to AMH and oocyte yield. In their study, increasing FSH was associated with a reduction in AMH and oocyte yield while AMH demonstrated a remarkably strong correlation to oocyte yield and appeared to be the best predictor of oocyte yield.

Jayaprakasan et al. (28) compared three-dimensional ultrasound parameters, antral follicle count (AFC), ovarian volume, and ovarian vascularity indices with anti-Müllerian hormone (AMH) for the prediction of poor response to controlled ovarian hyperstimulation (COH) during assisted reproduction treatment (ART). Their results show that AFC and AMH are the most significant predictors of poor response to ovarian stimulation during ART.

In a similar study, Kunt et al. (29) compared anti-Müllerian hormone (AMH) with other ovarian reserve markers such as AFC, basal serum FSH and LH, serum E2 and inhibin B for predicting ovarian response in an in vitro fertilization (IVF) program. They found that AMH is the best marker of those tested in predicting the outcome of in vitro fertilization.

Gnoth et al. (26), in their study, performed a stepwise and linear discriminant analysis and calculated an AMH cut-off value for poor ovarian response (defined as $\leqslant 4$ collected oocytes) of < 1.26 ng/ml. They found that AMH alone showed the best performance by detecting 32 out of the 33 poor responders in their study group while patient age, basal FSH, inhibin B alone or in combination were less precise. Using AMH alone with a cut-off level < 1.26 ng/ml, they were able to identify 97% of all women with a reduced ovarian reserve and correctly predict low response to gonadotrophin stimulation in 88% of cases in groups of comparable age.

From the ROC curve analysis of our results it is apparent that serum AMH with an optimal cut-off value of 1.2 ng/ml having a sensitivity of 91.7% and a specificity of 92.5% is a reliable predictor of poor ovarian response with an area under the ROC curve of 90.4%. Serum basal FSH with an optimal cut-off value of 8.9 mIU/ml was of lower value than AMH as a predictor of poor ovarian response with a sensitivity of 83.5% and a specificity of 81.4% and an area under the ROC curve of 81.9%. However, neither serum AMH nor basal serum FSH was found to able to reliably predict the occurrence of pregnancy with an area under the ROC curve of 59.4% and 58.6% respectively.

In conclusion, our results show a good correlation between patient age and serum AMH level that in turn is a reliable predictor of poor ovarian response to stimulation. An AMH cut-off value of 1.2 ng/ml has been shown to predict poor ovarian response with a sensitivity of 91.7%. Based on the results of the present study and others (12,13,25,26) serum AMH measured on any day of the cycle can be used as a reliable predictor of poor ovarian response thus providing prognostic information to patients about their expected response to stimulation and directing their physicians in choosing stimulation protocols that will maximize oocyte yield in expected poor responders.

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