Anti-mullerian hormone cut-off values for predicting poor ovarian response to exogenous ovarian stimulation in in-vitro fertilization

ABSTRACT

OBJECTIVES: (a) To establish the cut-off levels for anti-Mullerian hormone (AMH) in a population of Indian women that would determine poor response. (b) To determine which among the three i.e., age, follicle stimulating hormone (FSH), or AMH, is the better determinant of ovarian reserve. STUDY DESIGN: Prospective observational study.

SETTING: In vitro fertilization (IVF) unit of a tertiary hospital. MATERIALS AND METHODS: The inclusion criterion was all women who presented to the center for in-vitro fertilization/Intracytoplasmic sperm injection (IVF/ICSI). The exclusion criteria were age >45 years, major medical illnesses precluding IVF or pregnancy, FSH more than 20 IU/L, and failure to obtain consent. The interventions including baseline pelvic scan, day 2/3 FSH, luteinizing hormone (LH), estradiol estimations, and AMH measurement on any random day of cycle were done. Subjects underwent IVF according to long agonist or antagonist protocol regimen. Oocyte recovery was correlated with studied variables. The primary outcome measure was the number of oocytes aspirated (OCR). Three categories of ovarian response were defined: poor response, OCR ≤ 3; average response, OCR between 4 and 15; hyperresponse, OCR > 15. RESULTS: Of the 198 patients enrolled, poor, average, and hyperresponse were observed in 23%, 63%, and 14% respectively. Correlation coefficient for AMH with ovarian response was r = 0.591. Area under the curve (AUCs) for poor response for AMH, subject’s age, and FSH were 0.768, 0.624, and 0.635, respectively. The discriminatory level of AMH for prediction of absolute poor response was 2 pmoL/l, with 98% specificity and 20% sensitivity. CONCLUSIONS: AMH fares better than age and FSH in predicting the overall ovarian response and poor response, though it cannot be the absolute predictor of non-responder status. A level of 2 pmol/l is discriminatory for poor response.

KEY WORDS: Age, anti-Mullerian hormone, follicle stimulating hormone, poor ovarian response

INTRODUCTION

The success of in vitro fertilization (IVF) depends to a large extent on the number and quality of mature oocytes obtained at the time of oocyte retrieval after controlled ovarian stimulation. This ovarian response is determined largely by the ovarian reserve, which is defined as an estimate of oocytes remaining in the ovary that are capable of fertilization resulting in a healthy and successful pregnancy.[1] There are a myriad ways of checking ovarian reserve, none of which are complete in themselves, either in their sensitivity or their accuracy.[2-5] Amongst the ones in current or past use have been the subject's chronological age, basal follicle stimulating hormone (FSH), inhibin B, antral follicle count, and ovarian volume; or dynamic reserve tests like Gonadotropin Agonist Stimulation Test (GAST), Clomiphene Citrate Challenge Test (CCCT), and Exogenous FSH Ovarian Reserve Test (EFORT).[2-5]

As a prognosticator of individual ovarian potential, chronological age is of limited value because women of the same age can be at different stages in the process of follicular depletion. This feature is also related to the wide range of age at the onset of menopause, which marks total follicular depletion.[6] Basal FSH has been shown to be a better marker of individual ovarian reserve than...
Anti-mullerian hormone (AMH) has been a new molecule on the horizon that is now being used as a measure of ovarian reserve testing in some centers of the world. Many report it to be useful marker of ovarian response, but no defined cut-off levels exist that help in deciding whether to enrol the patient for IVF or not. Also, it remains to be seen if the cut-off levels of AMH in Indian population are any different from those of the Caucasians.

This study was undertaken with an objective to determine if AMH could predict ovarian response better than age and FSH, the currently available markers at the center of study, and to establish AMH cut-off levels that could help in segregating the poor responder from the good responder.

**MATERIALS AND METHODS**

This was a prospective observational study conducted at a tertiary referral center, over a period of 13 months extending from October 2008 to October 2009. Women presenting to the infertility clinic were screened for fitness to undergo IVF. All women with an indication for IVF like bilateral tubal block, severe male factor infertility, severe endometriosis, more than 4 cycles of failed intrauterine insemination (IUI) in unexplained infertility, more than 12 failed ovulatory cycles in anovulatory infertility, or age-related infertility were included in the study. Exclusion criteria were age > 45 years, FSH > 20 IU/L, major illnesses (like stage III heart disease, severe hypertension, uncontrolled diabetes mellitus, HIV positivity, severe bleeding dyscrasias, etc.), and known case of POF or bilateral oophorectomy. All women thus selected for IVF or ICSI during the period of study and who agreed to participate in the study were enrolled. Baseline characteristics like age, type and duration of infertility, indication for IVF, history of exposure to chemotheraphy or radiotherapy, history of smoking, presence of pelvic inflammatory disease (PID) or endometriosis, and history of previous pelvic surgeries were noted. The type of surgeries was divided into three groups based on the conjecture that an ovarian surgery would lead to a greater loss of ovarian reserve than a non-ovarian surgery and a surgery that altered the blood supply to the ovary would lead to a greater ovarian reserve reduction than a surgery that did not. Hence, three groups of pelvic surgeries were created: surgeries leading to ovarian tissue loss (oophorectomy, cystectomy); surgeries leading to alteration in blood supply (salpingectomy, tubal ligation, extensive adhesiolysis); and surgeries that did neither (diagnostic laparoscopy, lower segment caesarean section (LSCS), myomectomy, etc.).

All enrolled women had a baseline pelvic ultrasound scan; day 2 or 3 FSH, luteinizing hormone (LH), and estradiol (E2) estimations by the AIA 360 automated ELISA test kit manufactured and supplied by Tosoh Corporation, Japan, and Tosoh Biosciences Inc., USA, respectively. AMH measurement was done on any random day in the cycle by the ACTIVE AMH ELISA two-site immunoassay supplied by Diagnostics systems laboratories (a Beckman Coulter company) that has a sensitivity of 0.043 pmol/l (0.006 ng/ml). FSH and LH were reported in IU/l, E2 in pg/ml, and AMH in pmol/l units (7.18 pmol/l of AMH is equivalent to 1 ng/ml of AMH). Enrolled women then started IVF cycles using either the long agonist or the antagonist protocol. Controlled ovarian stimulation commenced from day 2 or 3 of the subsequent cycle with a urinary or recombinant gonadotropin, the dose of which was individualized based on anticipated response. Ovarian response was monitored with ultrasound and E2 estimation. The human chorionic gonadotropin (hCG) trigger was given on the day when three or more developing follicles were seen on transvaginal sonography of 14 mm size or more. Total gonadotropin dose used to achieve the said response and E2 levels on the day of hCG were noted. Oocytes were aspirated 36 h later transvaginally under ultrasound guidance using propofol anesthesia by suitably experienced doctors in the discipline. Ovarian response was defined as the number of oocytes obtained during the oocyte aspiration procedure. This was divided into three sub-categories as poor, average, and good response.

- Poor response: Cycle cancellation or oocyte recovery (OCR) of three or less
- Average response: OCR of 4–15
- Hyperresponse: OCR of more than 15

The women who had their oocyte aspiration cancelled because of growth of no or less than three dominant follicles were considered to have an oocyte retrieval of zero.

**Statistical analysis**

The distribution of all the studied variables (clinical and hormonal) was compared in the three groups of
ovarian response using the one-way analysis of variance (ANOVA) model. The difference in distribution of studied variables across the three groups of ovarian response was quantified by calculating correlation coefficients (Pearson’s coefficients for normally distributed variables and Spearman’s coefficients for skewed variables). Receiver Operator Characteristic curves (ROC curves) for the three variables in question, namely, subject age, FSH, and AMH, were compared to determine which of the three defined poor ovarian response the best. Finally cut-off levels of AMH for defining poor response were obtained using ROC curves.

All calculations were made using the Statistical Package for Social Sciences software (SPSS), version 17.0.

RESULTS

A total of 676 women were screened for fitness to undergo the IVF procedure. Five hundred sixty-five women were found eligible to participate in the study period, out of which 198 gave consent. There was no loss to follow-up [Figure 1].

The general characteristics of the participants are shown in Table 1. 23% of the enrolled subjects were poor responders, 63% were average responders, and 14% were hyperresponders based on the number of oocytes retrieved during IVF.

The baseline clinical and endocrine parameters in the three groups of responders are shown in Table 2. Amongst the baseline variables studied at the time of patient induction, only mean age, baseline FSH levels, FSH/LH ratio, and AMH levels showed a significant difference between the three groups of responders. Poor responders had a significantly higher age at enrollment, a higher mean basal FSH level, and a significantly low AMH level; also, their FSH/LH ratios were significantly higher. It is also seen that poor responders required significantly more gonadotropin dose to reach the endpoint of three or more follicles of size 14 mm or more. The terminal E2 levels were also found to be significantly lower in this group.

The correlation coefficients for AMH, age, FSH/LH ratio, and FSH with overall ovarian response were 0.591, -0.224, -0.225, and -0.308, respectively. To determine if AMH could determine poor response better than the other three variables and not just the overall ovarian response, ROCs were obtained for all four variables, namely, AMH, age, FSH, and FSH/LH ratio, with the outcome variable being poor response. Area under the curve (AUCs) were found to be significant for AMH (AUC = 0.768, P = 0.000), age (AUC = 0.624, P = 0.012), and FSH (AUC = 0.635,
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\[P = 0.006\], but not for FSH/LH ratio (AUC = 0.553, \(P = 0.281\)) [Figures 2 and 3].

**DISCUSSION**

AMH is a glycoprotein dimeric hormone that belongs to the transforming growth factor beta (TGF-β) superfamily. It is expressed by the granulosa cells of primary, preantral, and small antral follicles. It controls folliculogenesis by inhibiting the process of recruitment of primordial follicles\(^{[16,17]}\) and modifying the growth of preantral and antral follicles by diminishing the sensitivity of follicles to FSH.\(^{[18]}\) The level of this hormone decreases with age, reaching undetectable levels in postmenopausal period since the pool of recruitable follicles goes on diminishing with age.\(^{[19,20]}\) AMH exhibits a fairly stable expression during the menstrual cycle,\(^{[21-23]}\) making it an attractive determinant of ovarian activity. Because of this low variability, AMH in this study was measured on any day in the cycle and correlated with ovarian response.

At the time of conducting this study, no consensus existed in literature to define poor response\(^{[24]}\) (poor response being defined as OCR of anywhere from three to six).\(^{[25]}\) Poor response (OCR), ideally, should be so defined such that no desirable events (pregnancy) should have been recorded at this level. Therefore, poor response in this study was defined as an OCR of three or less since only 8% (3/36) pregnancies have been recorded at this level in historical controls at the center of study over the past 2 years and none have continued beyond 8 weeks of gestation as opposed to a pregnancy rate of 20% (10/48) at oocyte retrieval of 4 with continuation rate of 15% (7/48).

| Table 2: Comparison of baseline clinical and hormonal profile between poor, average, and hyperresponders |
|-------------------------------------------------------------|
| Poor response \((n = 45)\) | Average response \((n = 125)\) | Hyperresponse \((n = 28)\) | Significance |
| Mean age (years) ±SD | 34.8 ± 4.7 | 32.9 ± 4.4 | 31.6 ± 4.7 | \(0.008^*\) |
| Primary infertility vs. secondary | 26 (57.8%) | 81 (64.8%) | 20 (71.42%) | 0.481 |
| Duration of infertility (years) | 9.2 ± 5.4 | 7.2 ± 4.3 | 6.7 ± 4.7 | \(0.035^{**}\) |
| Tubal factor | 17 (37.8%) | 46 (36.8%) | 8 (28.6%) | 0.94 |
| Male infertility | 15 (33.3%) | 33 (26.4%) | 10 (35.7%) | 0.6 |
| Endometriosis | 4 (8.9%) | 10 (8.8%) | 2 (7.14%) | 0.94 |
| Unexplained | 8 (17.8%) | 25 (20%) | 5 (17.9%) | 0.94 |
| Type I surgery | 7 (15.5%) | 17 (13.6%) | 2 (7.14%) | 0.877 |
| PID | 14 (31.1%) | 42 (33.6%) | 7 (25%) | 0.673 |
| Mean FSH levels (IU/l) | 10.2 ± 4.0 | 9.0 ± 3.8 | 7.0 ± 1.9 | \(0.002^*\) |
| Mean LH levels (IU/l) | 5.1 ± 2.5 | 4.75 ± 2.5 | 5.85 ± 3.5 | 0.145 |
| Mean baseline E2 levels (pg/ml) | 62 ± 5.7 | 51 ± 2.7 | 47.5 ± 4.9 | 0.083 |
| Mean FSH/LH ratio | 2.3 ± 1.1 | 2.3 ± 1.3 | 1.6 ± 1.0 | \(0.011^*\) |
| Mean AMH levels (pmol/l) | 9.1 ± 8.2 | 20 ± 18.1 | 44 ± 35.6 | 0.00 |
| Mean total gonadotropin dose required (IU/l) | 3572 ± 1295 | 2646 ± 1094 | 1856 ± 672 | 0.000 |
| Mean terminal estradiol levels (pg/ml) | 925 ± 1025 | 1654 ± 697 | 2744 ± 683 | 0.000 |

Significance levels are for the whole model using one-way ANOVA.

Where indicated by the signs (*, #, or $), intergroup variability was not found to be significant according to the following key: *No difference between groups 2 and 3, #no difference between groups 1 and 2, $no difference between groups 1 and 3. All other values denoted in bold had significant difference within group and for the whole model.
Determining poor response prior to IVF enrollment was the objective of this study since no accurate markers currently exist that can perform well on this front. Antral follicle count has been reported by many as a superior marker. However, it was not analyzed in this study, as a dedicated, objective, and uniform reporting of antral follicle count by the same observer on a high-resolution machine was not available universally for all patients.

There have been several studies on AMH as a clinical marker of ovarian reserve from over the world, but only two published abstracts from India, neither of which compare AMH with FSH in its predictive abilities and neither defines AMH cut-off levels for poor response. In this study, one of the few from India, AMH has been shown to be a better predictor of overall ovarian response and poor response compared to age and FSH as seen by AUCs for the three variables.

Van Rooij[38] was one of the firsts to describe a high degree of clinical correlation of AMH with OCR with a coefficient value of \( r = 0.57 \), corroborating very closely with the correlation coefficient value of \( r = 0.591 \) from this study.

Increasing FSH and age have previously been shown to be negative predictors of OCR. ROC analysis in this study, as in the study by Nelson et al.[29] and others,[28,30-35] reveals that they are both inferior predictors of ovarian response compared to AMH.[36,37]

The AMH cut-off value for poor response reported from various studies varies from 0.1 to 2 ng/ml, that amounts to almost a 20-fold variation.[28,29,33-35,38,39] Hence, a more definitive AMH cut-off value to determine absolute poor response was sought.

What one expects these cut-off values to do is to demarcate with nearly 100% accuracy a poor responder from a normal responder. More precisely, no woman with a potential for a good response ought to be classified as a poor responder since such a categorization could mean rejection from the IVF program. Why refuse a woman IVF when she has a fair chance of conception? That is the premise on which AMH cut-off values were calculated.

In the context of defining a poor response, disease positives can be taken as individuals with a poor ovarian response and disease negatives as individuals with average or hyperresponse. A true positive then is a poor responder and rightly so identified by the test. A true negative is a good responder and rightly so identified by the test. A false negative is a poor responder falsely identified by the test as a good responder. A false positive is a good responder wrongly identified by the test as a poor responder.

Speaking statistically, one would want the screening test to have zero or near-zero false positives. If one were to consider the following equation that establishes the relationship between false positivity rate and specificity,

\[
\text{False-positive rate} = 100 - \text{specificity},
\]

it can very simply be concluded that a test cut-off with a high specificity approaching 100% would achieve the objective of zero false positives. Looking at the sensitivity and specificity values that have been derived from the coordinates of the ROC curve for AMH [Table 3], it is easily seen that values of AMH between 0.5 and 3 pmol/l would give us the desired result.

But choosing a high specificity compromises the sensitivity and increases the numbers of individuals with a potential for poor response to be recruited for IVF, thus increasing cycle cancellation or poor OCR rates. Hence, looking at a test cut-off which has only a near 100% specificity is not enough. The test should be balanced with an acceptable level of sensitivity as well to have an acceptable number of false negatives.

Hence, re-looking at Table 3, the only level of AMH that maintains a high degree of specificity without much change in the sensitivity is a level of 2 pmol/l (=0.28 ng/ml). Value of 10 pmol/l takes the specificity too low, hence losing the objective of keeping false positives to a minimum. Values less than 2 pmol/l lead to a sudden sharp decline in sensitivity, hence increasing the numbers of absolute poor responders that would mistakenly be picked up for IVF. The sensitivity at 20%, although still low, actually translates into an absolute figure of 18 poor responders per hundred population recruited for IVF based on the following equation:

\[
\text{Total false negatives} = (100 - \text{sensitivity}) \times (\text{Prevalence of disease positives})
\]

\[
= (100 - 20) \times (45/198)
\]

\[
= 80 \times 0.23
\]

\[
= 18.4.
\]

Although 2 pmol/l appeared to be a reasonable cut-off of AMH levels for predicting poor response, there was a huge overlap between average and poor responders in the AMH range of 2–10 pmol/l. In a study by Meduri et al.,

The AMH cut-off levels (pmol/l) Sensitivity (%) Specificity (%)
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0.5 8 100
1 9.5 99
2 20 98
3 23 92.8
10 71 69
20 91 47
mean AMH levels, although low in women with premature ovarian failure as compared to the normal population, were still within detectable range in 40% of such women and within the normal range in a few patients, despite minimal to nil follicles on ovarian biopsy. This overlap hinders AMH as an absolute predictor of non-responder status to controlled ovarian stimulation based on a low plasma AMH value. Consequently, adjustment of patients’ expectations is required and consideration may be given to individualization of therapeutic strategy as follows.

In women with AMH levels of 2 pmol/l or less, cycle cancellation may be a good option. However, since at no value of AMH could we identify non-response, it can be said that with the available evidence, no woman can be excluded from the IVF program, but the information can be used for counseling regarding avoidance of repeated cycles of IVF if the first cycle confirms poor response. With AMH levels between 2 and 10 pmol/l, a suspicion of poor response still exists. Hence, a high starting dose of gonadotropins or alteration of stimulation protocol may be helpful.

CONCLUSIONS

AMH seems to be a better predictor of overall ovarian response and poor response compared to FSH and age, though it cannot be the absolute predictor. Levels of 2 pmol/l (=0.28 ng/ml) seem to be discriminatory for poor response.

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