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A study to assess the usefulness of ovarian reserve tests in predicting ovarian response in patients with unexplained infertility

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Abstract

Introduction: The assessment of ovarian reserve in women with unexplained infertility is needed for predicting response to controlled ovarian stimulation. This helps in appropriate pretreatment counselling and in modification of an individual's treatment protocol to maximize the potential response.

Aims and Objectives: 1. To determine the correlation of Follicle Stimulating Hormone (FSH), AntiMullerian Hormone (AMH) and Antral Follicle Count(AFC) with ovarian response in patients with unexplained infertility undergoing ovulation induction. 2. To determine the best parameter among the above in predicting response to ovarian stimulation.

Type of study: Prospective, correlational study.

Materials and Methods: Seventy women with unexplained infertility received treatment in the form of ovulation induction and timed intercourse/IUI. They had basal Serum FSH, Serum AMH assessment on Day 3 of the menstrual cycle. AFC was assessed with transvaginal sonography (TVS) on Day 3 of the cycle. The response to stimulation was measured in terms of the number of follicles >/= 16mm on TVS on the day of Inj HCG administration. >/= 3 follicles which were >/= 16 mm was considered a good response. The response was correlated to the levels of FSH, AMH and AFC.

Results and Conclusion: There were 50 good responders, ie; with >/= 3 follicles>/= 16 mm on the day of HCG. 20 women responded with < 3 follicles >/=16 mm on the day of HCG – the poor responders. There was significant statistical correlation between age among good and poor responders. AFC and AMH were found to correlate significantly with ovarian response with p value <0.001. AFC was as accurate as AMH in predicting response.

Basal FSH did not correlate with the ovarian response indicating its poor value as a predictor of ovarian reserve.

Keywords: Ovarian reserve, infertility, AntiMullerian hormone, antral follicle count

Introduction

Ovarian reserve is a term used to describe the functional potential of the ovary and reflects the number and quality of oocytes within it [1]. The assessment of ovarian reserve is needed for predicting the response to controlled ovarian stimulation. This helps in appropriate pretreatment counselling of the couple. It also helps the clinician in modification of an individual's treatment protocol to maximize her potential response.

The woman's age and serum FSH (Follicle Stimulating Hormone) level in the early follicular phase is one of the factors determining ovarian reserve. However Serum FSH has intercycle and intracycle variation due to a feedback loop between hormones of the pituitary and ovarian hormones. Also has a wide range (4-25 IU) in threshold values.

Serum Anti-Mullerian hormone (AMH) is produced by the granulosa cells of follicles right from the stage of the primordial follicle to the initial formation of the antrum. AMH levels do not change significantly throughout the menstrual cycle, thus being a more reliable marker and time independent parameter.

Table 1: AntiMullerian Hormone- Interpretation

Interpretation	AMH Blood Level
High (often PCOS)	Over 3.0 ng/ml
Normal	Over 1.0 ng/ml
Low Normal	0.7 - 0.9 ng/ml
Low	0.3 – 0.6 ng/ml
Very Low	Less than 0.3 ng/ml

The antral follicle count (AFC) has been widely used as another ovarian reserve test. Antral follicles are resting follicles that are found in the ovary at the beginning of each menstrual cycle. They are approximately 2 to 9 mm in size. In spite of inter observer and anatomical variations, it has been suggested that the ability of AFC to predict poor response might be better than basal FSH.
This study aims to determine the response to ovulation induction and its correlation to markers of ovarian reserve, ie; FSH, AFC and AMH.

Materials & Methods
Source of data and Sample Size: 70 patients attending the infertility clinic in the Department of OBG between January 2018 and June 2019 at ESICMC & PGIMSR diagnosed with unexplained infertility. The sample size has been calculated to be 66 (rounded off to 70) by considering 0.340 Spearman correlation value of AMH with ovarian response (Ismail Y *et al*.: 2015) at 5% level of significance to ensure at least 80% power.

Type of study: Prospective, correlational study.

Inclusion Criteria
Age 20-40 years
Women with unexplained primary infertility ie; seeking treatment after 1 year of unprotected intercourse.
Regular menstrual cycles
Normal uterine cavity and patent tubes as demonstrated by TVS and Hysterosalpingogram (HSG)
Normal semen parameters (WHO 2010 criteria)
Adequate visualisation of ovaries by TVS
Body Mass Index (BMI) 19-25 kg/m2

Exclusion criteria
Women with PCOS
H/O ovarian surgery, endometriosis
Abnormal uterine bleeding
Evidence of endocrine disorders
Those with ovarian cyst >10 mm on Day2/Day3 of the cycle as seen by TVS

Methodology
The present study included 70 women diagnosed with unexplained primary infertility, attending the infertility clinic in ESIC & PGIMSR, Bangalore.
Primary infertility is defined as women unable to conceive after unprotected intercourse for one year or more. Unexplained infertility is diagnosed in a couple where the female has regular cycles, normal uterus and patent fallopian tubes as demonstrated by ultrasound or HSG and the male has normal semen parameters according to WHO 2010 criteria.
A detailed menstrual, obstetric, coital and medical history was taken. Written informed consent was obtained. Ethical clearance was obtained from the institutional ethical clearance committee.
On the 3rd day of the menstrual cycle, all patients were investigated with TVS (transvaginal scan) to assess AFC. On the same day, a fasting venous sample was obtained for the measurement of basal serum FSH and Serum AMH.
Step up protocol for ovulation induction was followed ie, Clomiphene citrate 50 mg started on Day3 of cycle for 5 days orally (Day3 – Day7). Inj Human Menopausal Gonadotropin (HMG) was started and given on alternate days from Day 9 and followed up by TVS as to count the number and size of the follicles and the dose of HMG was adjusted accordingly. Inj Human Chorionic Gonadotropin 5000 IU was given when a dominant follicle of 18 – 20mm size was visualised on TVS.
The response to ovarian stimulation was measured in terms of the number of follicles >/= 16 mm on TVS on the day of HCG administration.
>/= 3 follicles of >/= 16 mm size was considered a good response. The response to stimulation was correlated to the levels of FSH, AMH and AFC. The patients were then advised to have timed intercourse or Intra Uterine insemination was done 36 hours after HCG administration.

Statistical Analysis
Data was entered in MS Excel and statistical analysis was done using STATA statistical software version 14 (StataCorpLCC, Lakeway Drive College Station, texas, USA). The continuous variables were summarized as mean with standard deviation (SD) or median with an inter-quartile range based on the distribution of data. The categorical variables were summarized as frequencies and proportions. ttest/Mann Whitney test was used to find the statistical significance of associationof continuous variables. Univariate analysis was done using logistic regression and Odds Ratio with (95% confidence interval) was calculated. A p - value less than 0.05 was considered statistically significant.

Results
In the present study, out of 70 women with unexplained infertility, who underwent ovulation induction, there were 50 (71.4%) good responders, ie; with >/= 3 follicles which were >/= 16 mm on the day of HCG. 20 (28.6%) women responded with < 3 follicles which were >/= 16 mm on the day of HCG – the poor responders. There were a total of 9 pregnancies (12.86%). 7 in good responders (10%) and 2 in poor responders (2.86%).

Table 2: The baseline characteristics of the patients are shown

	Good	Poor	Total
Response	50(71.4%)	20(28.6%)	70(100%)
Pregnancy	7 (10%)	2 (2.86%)	9 (12.86%)

The baseline characteristics of the patients are shown in Table 2.

Table 3: Baseline characteristics of patients

	Range	Mean +/- SD
Age (yrs)	21-40	30.02 +/- 4.51
BMI (kg/m2)	19-26.2	22.73 +/- 1.63
Duration of infertility(yrs)	1.5-19	6.31 +/- 3.91
FSH	2.3-15.5	8.12 +/- 3.13
AMH	0.33-9.02	2.95 +/- 1.88
AFC	2-14	8.07 +/- 3.21
Number of follicles on the day of HCG	0-8	3.51 +/- 1.78

Table 4 shows the correlation between ovarian reserve tests in good responders and poor responders. There is statistical correlation between age among good and poor responders. There is no significant statistical difference in BMI, duration of infertility among good and poor responders. However there is significant statistical difference in AMH and AFC and number of follicles on day of HCG between both the groups. Also the significance is more so with AFC than AMH in predicting response. There is no significant difference in FSH between the good and poor responders.

Table 4: Correlation between ovarian reserve tests in good and poor responders.

	Good Responders (N = 50)	Poor Responders (N = 20)	p value
AGE	28.6 +/- 4.1	33.4 +/- 3.7	<0.001 (S)
BMI	22.6 +/- 1.6	23.1 +/- 1.5	0.20 (NS)
Infertility Duration	6.6 +/- 3.7	8.1 +/- 3.9	0.14 (NS)
FSH	8.2 +/- 2.8	8.0 +/- 3.8	0.88(NS)
AMH	3.5 +/- 1.8	1.5 +/- 0.9	<0.001 (S)
TOTAL AFC	9.7 +/- 2.1	4.0 +/- 1.3	<0.001 (S)
No. of follicles on day of hcg	4.4 +/-1.3	1.4 +/- 0.7	<0.001 (S)

Table 5: Correlation between ovarian reserve tests

	AGE	FSH	AMH
FSH	r 0.272 P 0.022		
AMH	r – 0.422 *P*< 0.05	r - 0.134 P 0.267	
AFC	r – 0.455 *P*< 0.05	r 0.072 P 0.552	r 0.616 *P*< 0.001

Table 6: Correlation between ovarian reserve tests

Correlation parameters	Correlation coefficient (r)	Strength and direction of association
FSH and AGE	0.272	Weak positive correlation
AMH and AGE	-0.422	Moderate negative correlation
AFC and AGE	-0.455	Moderate negative correlation
AMH and FSH	-0.134	Weak negative correlation
AFC and FSH	0.072	No correlation
AFC and AMH	0.714	Strong positive correlation

Univariate analysis was done using logistic regression to find the association between the different variables and ovarian response (Table 7).

Table 7: Univariate analysis was done using logistic regression to find the association between the different variables and ovarian response

Group	Odds Ratio	(95% confidence interval) Lower Upper	p value
AGE	1.33	1.14 1.56	< 0.001
FSH	0.98	0.83 1.16	0.88
AMH	0.30	0.16 0.57	< 0.001
AFC	0.30	0.16 0.54	< 0.001

As age increases by 1 year, the odds of poor response increases by 1.3 times and this association is significant with $p < 0.001$. There is no association between FSH and ovarian response (Odds Ratio = 0.98). As AMH increases by 1ng/ml and AFC increases by 1, the odds of poor response decreases by 0.7 each and these associations were significant with $p < 0.001$ (Odds Ratio = 0.3).

Discussion

The present study included women who underwent ovulation induction for unexplained infertility and whose response was measured in terms of the number of follicles produced on the day of Inj HCG. Out of the 70 women chosen for the study, 50 women had good ovarian response and 20 had poor response.

There was a significant difference between age among good and poor responders ($p < 0.001$) correlating with the negative relationship between ovarian response to ovulation induction and female aging [2, 3]. No significant difference was found in the duration of infertility between good and poor responders. This did not correlate with expected longer duration in poor responders [4] but correlated with findings of a similar study [5].

FSH was not found to be a good predictor of ovarian response. This may be attributed to availability of newer markers such as AMH which proved to be a better indicator as studied by Buyuk *et al.* [6]. However, some studies indicate that FSH is better than female age in predicting ovarian response [7].

The mean AMH levels and AFC were significantly high in good responders compared to poor responders (Table 3) [3, 8] and statistically significant positive correlations were found for AMH and AFC with regard to ovarian response ($p < 0.001$). Similar observations were made in other studies [9].

When strength and direction of association between the ovarian reserve tests was analysed, a strong positive correlation was found between AMH and AFC (Table 6) (r=0.714) ($p < 0.001$) [10]. This observation showed that AFC was as good a predictor as AMH of ovarian response. AMH is a relatively expensive test and still not widely done everywhere whereas AFC counts are measured routinely by consultants due to the availability of ultrasound. Hence AFC alone can be used routinely and reliably where AMH cannot be estimated for the above reasons.

Table 6 also shows the strength of association between other tests of ovarian reserve. There was a moderate negative correlation between age and both AMH and AFC, and a weak positive correlation between age and FSH. However there was no correlation between FSH and both AMH and AFC (Table 6) [11, 12].

For age, the odds ratio was found to be above unity and was found to be significantly associated with outcome (p > 0.001). S.AMH and AFC had odds ratio lower than unity, and also had a significant association with the outcome ($P < 0.001$) [13].

Even though AMH and AFC are good predictors of ovarian reserve, they are screening tests and low ovarian response in poor responders could be associated mainly with a quantitative rather than qualitative decline in ovarian function. Hence they should not be used to deny treatment if the couple wishes to [14].

The small number of patients included in the study is considered one of the limitations of our study and further studies including more patients is needed. The associations found between ovarian reserve tests and ovarian response in this study (Table 7) cannot be considered in women with polycystic ovarian syndrome.

Conclusion

Both AFC and AMH are effective in predicting ovarian response to ovulation induction. They are useful tools which aid in counselling not only women with a high risk of producing a poor response to ovulation induction but also counselling women with decreased AMH and AFC regarding starting treatment without any further delay. They may also be helpful in individualising management and making dose adjustments of ovulation induction drugs prior to starting treatment itself. Basal FSH did not correlate with ovarian response indicating its poor value as a predictor of ovarian response.

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