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AMH and FSH as predictive markers of ovarian response

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Abstract
Background: Anti-Mullerian hormone (AMH), a glycoprotein, is a member of the transforming growth factor-β superfamily and helps in regulation of folliculogenesis and follicular atresia in the ovaries. Follicle stimulating hormone (FSH) is also a glycoprotein that stimulates the growth of ovarian follicles .Thus, they can be considered useful for prediction of ovarian response.
Aim: To determine whether AMH and FSH levels play a role as markers of ovarian response and to find the significance of one over the other.
Material and Methods: A total of 50 women with ovarian factor infertility were enrolled in the study. Blood samples were collected on Day 2 or 3 of cycle for measurement of serum AMH and FSH levels. First cycle of induction with 100mg clomiphene citrate was given and number of leading follicles (> or = 14mm diameter) were counted. Cases with less than 3 leading follicles were subjected to second cycle of induction where along with 100mg clomiphene citrate, 150 IU of Inj. HMG (human menopausal gonadotrophin) was given and number of leading follicles counted. Development of less than 3 follicles at the end of second cycle were considered as poor response.
Result: A total of 50 patients participated in the study. The mean difference of AMH between good responders and bad responders was 3.74±0.62 with a p- value of 0.030, which is statistically significant and the mean difference of FSH between both the groups was 4.16±0.28 with a p- value of 0.001, which highly significant.
Conclusion: Both AMH and FSH are good predictors of poor ovarian response. Further, FSH is better than AMH in predicting the ovarian pool.

Keywords: Anti-Mullerian hormone (AMH), Follicle stimulating hormone (FSH), infertility, ovarian response

Introduction
Infertility is defined as 1 year of unprotected intercourse without pregnancy. The main causes of infertility include: Ovulatory factor, male factor, tubal factor, uterine factor, pelvic factor and unexplained. Infertility has emerged as a serious health problem in India. Ovulatory factor accounts for up to 40% of all cases of female infertility [1]. First-line therapy for anovulatory infertility is usually clomiphene citrate (CC). However, a substantial proportion of women with anovulatory infertility fail to conceive following CC therapy. Such patients may benefit from gonadotrophin therapy to stimulate follicle development and induce ovulation. Failure to respond adequately to standard protocols is termed as poor response. According to Rotterdam ESHRE/ American society for Reproductive Medicine (ASRM), the minimum criteria to define poor ovarian response is as follows:

1. Either advanced maternal age more than 40 years.
2. Less than 3 oocytes retrieved with conventional stimulation protocol.
3. Abnormal ovarian reserve test.

Two episodes of poor response after maximum stimulation are sufficient to define patient as poor responder [2].
Thus, poor ovarian response can be identified by estimation of ovarian reserve, which is defined as estimate of oocytes remaining in the ovary that are capable of fertilization resulting in a healthy and successful pregnancy. Ovarian reserve can be predicted by various biophysical and biochemical markers. Assisted Reproduction Technology (ART) procedures are time consuming, expensive and require effort from both clinician and patient's side. It would be clinically and economically helpful if there were easy methods for prior assessment

of likelihood of an adequate ovarian response and prevent unnecessary complications. Thus, this study is planned with an aim to determine whether AMH and FSH levels play a role as markers of ovarian response and to find the significance of one over the other.

Methodology

This was a prospective observational study that included 50 infertile women. The study was carried out in the Department of Obstetrics and Gynaecology in collaboration with Department of Biochemistry and, AIMSR, Bathinda. Study was hospital based. Members of the study group were selected consecutively as and when they presented to hospital applying inclusion and exclusion criteria from Febuary 2016 to June 2017.

i) Inclusion criteria

- Apparently healthy infertile women having ovulatory factor infertility.
- Patients with both ovaries well visualized on transvaginalsonography.

ii) Exclusion criteria

- Age less than 21years or more than 40 years.
- Patients suffering from acute infections, PID, Endometriosis, active tuberculosis, acute liver disease, hypersensitivity to drugs used and immunocompromised individuals.
- Previous history of ovarian surgery.
- History of exposure to cytotoxic drugs or pelvic radiation therapy.
- Patients with tubal factor infertility.
- Patients with severe male factor infertility.

iii) Method: All women visiting infertility OPD in Department of Obstetrics and Gynaecology were screened for inclusion and exclusion criteria and enrolled in the study. Blood samples were collected on Day 2 or 3 of cycle for measurement of serum FSH and serum AMH. First cycle of induction with 100mg clomiphene citrate was given and number of leading follicles (> or=14mm diameter) were counted. Cases with less than 3 leading follicles were subjected to second cycle of induction where along with 100mg clomiphene citrate, 150 IU of Inj. HMG (human menopausal gonadotrophin) was given and number of leading follicles was counted. Development of less than 3 follicles at the end of second cycle was considered as poor response.

iv) Sample collection: On the morning of day 2 or 3 of menstrual cycle, 8ml of venous blood was withdrawn from cubital vein in plain vacuutainers, centrifused at 3,500rpm and stored at -4 degree Celsius. Analysis of serumFSH (using kit purchased from Alare, TOSHO, Japan on fully auto analyzer from TOSHO, Japan), serum AMH (using ELISA kit from Ansh Labs, USA) was done.

Results

Patient characteristics

The study group comprising of fifty patients had the following characteristics:

Table 1: Patient characteristics

N = 50	Mean ± SD	Range
Age	28.38±4.81 years	19 – 40 years
BMI	23.84 ± 2.33 kg/m^2	17.03 – 30.26 kg/m^2

BMI: body mass index

The age of patients ranges from 19- 40 years with mean of 28.38±4.81 years. The calculated mean body mass index was 23.84±2.33 kg/m^2 with lowest BMI of 17.03 and highest BMI of 30.26 kg.

For evaluation of this study we have used the groups A and B as described below:

Out of a total 50 patients enrolled in the study and evaluated for outcome at first cycle, 20(40%) showed good response and were classified as group A; and 30 (60%) who showed poor response were classified as group B. This has been represented in table 2.

Table 2: Observations at the end of first cycle

Groups	No. of Patients (n)	Percentage (%)
Group A (good responders)	20	40
Group B (bad responders)	30	60
Total (N)	50	100

The 30 patients from the poor response group (group B) where further observed in second cycle. At the end of second cycle all 30 patients were reclassified in group A or group B. Hence, the cumulative outcome of two cycles showed, a total of 29(58%) to be good responders and remaining 21 (42%) to be poor responders as represented in table 3.

Table 3: Observations at the end of second cycle

Groups	No. of Patients (n)	Percentage (%)
Group A (good responders)	29	58
Group B (bad responders)	21	42
Total (N)	50	100

Anti Mullerian Hormone

Table 4: AMH distribution according response

S. No.	AMH (ng/ml)	Group A		Group B		N (%)
		No. of Patients (n)	Percentage (%)	No. of Patients(n)	Percentage (%)	
1.	1-5.99	5	17.24	8	38.10	13 (55.34)
2.	6-10.99	8	27.59	9	42.86	17 (70.45)
3.	11-15.99	7	24.14	1	4.76	8 (28.9)
4.	16-20.99	8	27.59	1	4.76	9 (32.35)
5.	21-25.99	0	0	2	9.52	2 (9.52)
6.	26-30.99	1	3.45	0	0	1 (3.45)
	Total (N)	29	100	21	100	50

AMH: Anti-Mullerian Hormone

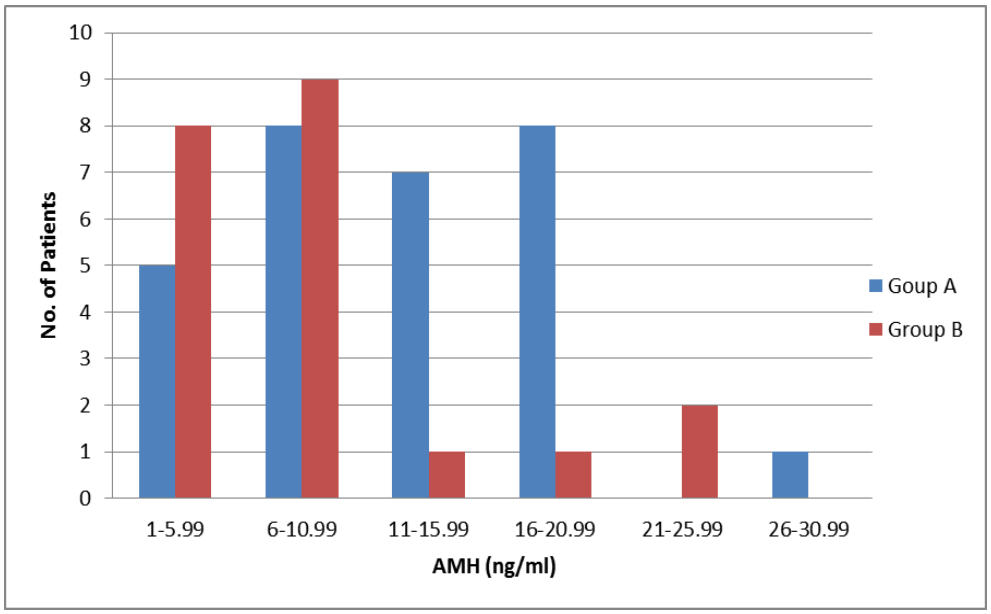

Fig 1: AMH distribution according to response

In table 4 and figure 1, among good responders 27.59% patients had AMH of 6 to 10.99ng/ml and 27.59% patients had AMH of16 to 20.99ng/ml, whereas among bad responders, the maximum number of patients (42.86%) had AMH of 6 to 10.99ng/ml.

Table 5: Calculation of mean AMH distribution

Group	Mean±SD	Mean Difference	t-value	p value	Sig.
A	12.45±6.18	3.74±0.62	2.237	0.030	S
B	8.71±5.56				

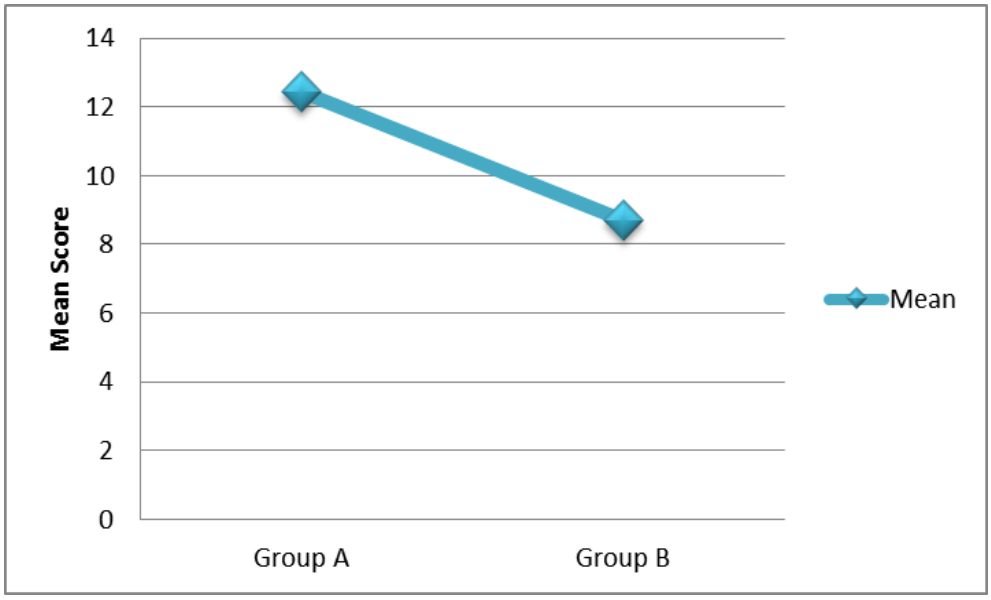

Fig 2: Mean AMH Distribution

In table 5 and figure 2, the mean AMH in patients as good responders was 12.45±6.18SD, whereas the mean AMH in bad responders was 8.71±5.56SD. The mean difference between the two groups was 3.74 ± 0.62 with a p- value of 0.030 which was statistically significant.

Follicle Stimulating Hormone

Table 6: FSH distribution according response

S. No.	FSH (IU/L)	Group A		Group B		N (%)
		No. of Patients (n)	Percentage (%)	No. of Patients (n)	Percentage (%)	
1.	1-5	13	44.83	0	0	13 (44.83)
2.	6-10	12	41.38	11	52.38	23 (93.76)
3.	11-15	3	10.34	8	38.10	11 (48.44)
4.	16-20	0	0	1	4.76	1 (4.76)
5.	21-25	1	3.45	1	4.76	2 (8.21)
	Total (N)	29	100	21	100	50

FSH: Follicle Stimulating Hormone

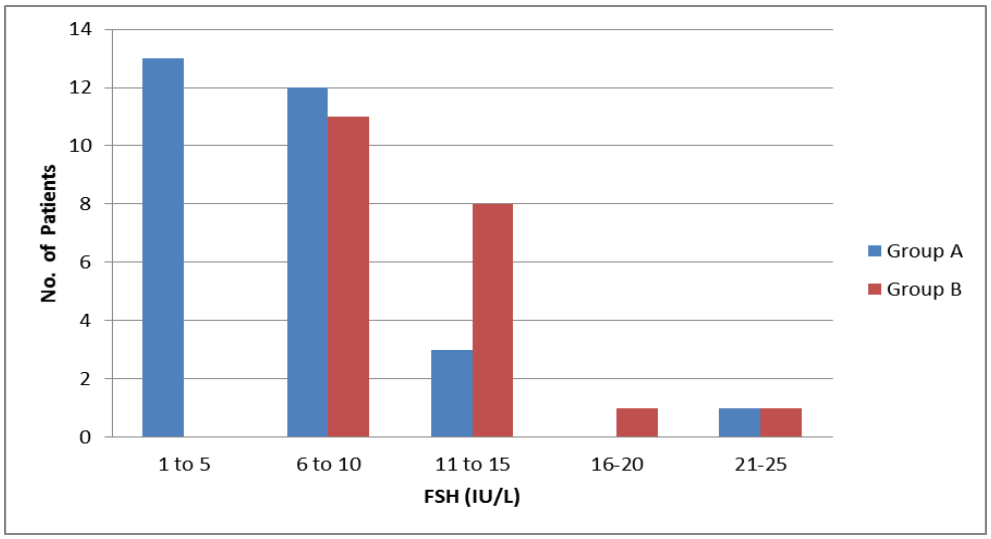

Fig 3: FSH distribution according to response

In table no. 6 and figure no. 3, among good responders, maximum number of patients (44.83%) had FSH of 1 to 5 IU/L and among bad responders, the maximum number of patients(52.38%) had FSH of 6to 10 IU/L.

Table 7: Calculation of mean FSH distribution

Group	Mean±SD	Mean Difference	t-value	p value	Sig.
A	7.13±4.04	4.16±0.28	3.443	0.001	HS
B	11.29±4.32				

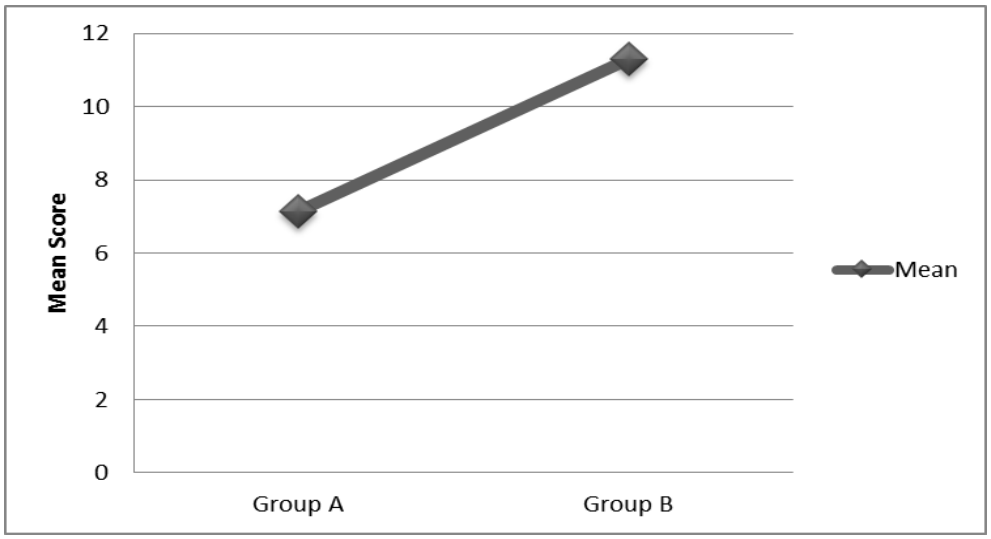

Fig 4: Mean FSH Distribution

In table no. 7 and figure no. 4, the mean FSH in patients as good responders was 7.13± 4.04 SD, whereas the mean FSH in bad responders was 11.29± 4.32 SD. The mean difference between the two groups was 4.16 ± 0.28 with a p-value of 0.001 which was statistically highly significant.

Discussion

Assisted reproduction technology has revolutionized the treatment of infertility and is being increasingly used. Attempts have been made by various researchers to determine certain markers of ovarian reserve, which could predict a successful outcome to ovulation induction in infertile women. This will be beneficial in optimizing the planned therapeutic intervention, and thus, minimize the emotional and financial strains imposed upon couples seeking fertility treatment. Through this study, biochemical markers had been identified, and the significance of these markers in the prediction of ovarian response to stimulation were demonstrated.

In the present study, patients with age 19 to 40 years were included. Maximum number of patients were aged between 26 and 30 years (n=18) followed by those aged 21–25 years (n=14), 31–35 years (n=12), 35- 40 years (n=4) and 16-20 years (n=2). Mean age of the good responders was found to be 26.97±4.37 years as compared to that of the poor responders which had a mean age of 30.33±4.80 years. This difference was found to be statistically significant with p-value of 0.015. Thus, age of the infertile women was found to be a significant determinant of poor ovarian response to ovarian stimulation and these results are similar to the study conducted by Jaiswar S. P *et al.* (2015) [1] with mean age of 27.6±4.3 years in good responders and 30.4±5.4 in poor responders. Similar study conducted by Tsung-Hsien Lee *et al.* (2009) [2] on the impact of female age on ovarian reserve markers to predict the outcomes of assisted reproduction technology cycles showed that advancing age had a strong co- relation with ovarian reserve.

Maximum number of patients who were good responders had normal BMI (18.50- 22.99kg/m^2), with mean of 23.19±2.14 kg/m^2. The maximum number of patients who were poor responders were obese (>25kg/m^2), with mean of 24.74±2.34 kg/m^2. The p- value was 0.014 which is statistically significant. Thus, BMI of the infertile women was found to be a significant determinant of poor ovarian response to ovarian stimulation. This result does not match the studies conducted earlier by Laszlo F. J. M. M. Bancsi (2002) [3] and Tsung-Hsien Lee *et al.* (2009) [2] who found that there is no relation of ovarian reserve with BMI but were consistent with a study done byJaiswar S. P *et al* (2015) [1] which showed that BMI is significant for predicting poor responders.

Serum AMH has been found to be a significant predictor of poor ovarian response. The mean value of serum AMH was found to be 12.45±6.18 ng/ml in good responders, while the mean value in poor responders was found to be 8.71±5.56 ng/ml, with a p- value of 0.030 which is statistically significant. Thus, higher the AMH, more are the chances of being a good responder. These results are consistent with earlier reports of De Vet A *et al.* (2002) [4], that AMH is significant marker of ovarian response to stimulation and that it is a marker of ovarian aging. Similarly in 2013, Singh N *et al.* [5] found that there is a significant correlation between day-2 serum AMH levels and the oocytes retrieval count in women undergoing ovulation induction for IVF, and that AMH is a good marker as the negative predictive values for the success of ART.

Serum FSH concentrations were higher in poor responders as compared with the good responders. Mean serum FSH values in good responders was 7.13±4.04 IU/L, while the poor responders had the mean value of 11.29±4.32 IU/L. The p-value was 0.001 which suggests that FSH has high significance to ovarian reserve. This finding co- relates well with other study conducted previously which mention that FSH is a marker of ovarian reserve but in present study it suggests that FSH is the best predictive marker for ovarian response to stimulation as compared to other markers, i.e. age, BMI, AFC and AMH.

Van Rooij (2002) [6] and co- workers conducted studies and concluded that AMH is a more useful serum marker than any of the known serum markers for assessment of ovarian reserve. In 2009, Luciano *et al.* [7], conducted a study on 165 women undergoing ovarian stimulation for in vitro fertilization and found that AMH levels and AFC were markedly raised in the high responders and decreased in the poor responders. Compared with FSH and AFC, AMH performed better in the prediction of excessive response to ovarian stimulation. In 2012, Satwik R *et al.* [8], conducted a study on Anti-mullerian hormone cut-off values for predicting poor ovarian response to exogenous ovarian stimulation in *in-vitro* fertilization and concluded that AMH is better predictor of overall ovarian response compared to FSH and age.

Conclusion

Both AMH and FSH are good predictors of poor ovarian response. Further, FSH is better than AMH in predicting the ovarian pool.

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