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Original Research Article

A Study of the Status of Ovarian Reserve in Infertile Women Attending Tertiary Care Centre

Kalpana Singh[1], Shubhanti Kumari[2], Kumari Shashi[3], Bhawana Tiwary[4], Huma Nishat[5], Sangeeta Kumari[6]

[1]Additional Professor and Head, Department of Reproductive Medicine, IGIMS, Patna, India.

[2]Assistant Professor, Department of Reproductive Medicine, IGIMS, Patna, India.

[3]Senior Resident, Department of Reproductive Medicine, IGIMS, Patna, India.

[4]Assistant Professor, Department of Reproductive Medicine, IGIMS, Patna, India.

[5]Assistant Professor, Department of Reproductive Medicine, IGIMS, Patna, India.

[6]Scientist I, Department of Reproductive Medicine, IGIMS, Patna, India

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Corresponding author: Dr. Shubhanti Kumari

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Abstract

Background: As infertility has been not only a medical but a psychosocial problem, it necessitates the complete evaluation of ovarian reserve in an infertile couple. Infertility may be caused by various factors like tubal, uterine, hormonal, age-related factors, ovarian like endometriosis, polycystic ovarian syndrome, premature ovarian failure and decreased ovarian reserve in elderly patients. WHO data suggest that worldwide about 48 million couples and 186 million individuals have to deal with infertility. The various tests include hormonal assays e.g., basal FSH, Inhibin B, AMH, LH/FSH ratio and ultrasonographic evaluation of AFC. Of all AFC and AMH have proven to the most accurate in estimating the ovarian status in infertile women. **Objective:** To assess the ovarian reserve status in infertile women by different markers for ovarian reserve. **Materials and Methods:** It is a hospital based prospective study, done in the department of Reproductive Medicine, IGIMS, Patna in 100 infertile women for one year (April 2018-April 2019), **Results:** In our study, ovarian reserve decreased with increasing age and of all markers for ovarian reserve, AMH alone or along with AFC is the most accurate method. **Conclusion:** In our study we found a linear co relation between increasing age and AMH. Day 2 AFC and AMH together prove to a better indicator of ovarian status than AMH alone in infertile women.

Keywords: Follicle Stimulating Hormone, Antimullerian Hormone, Antral Follicle Count, Infertility, Age, Ovarian Reserve, Gonadotropin Releasing-Hormone (Gnrh) Agonist, Ultrasonography.

Introduction

Infertility is one of the most important health issues worldwide, affecting approximately 8%–10% of couples[1]. Of 60–80 million couples suffering from infertility every year worldwide, probably between 15 and 20 million (25%) are in India alone[2,3]. According to a report by the World Health Organization (WHO), one in every four couples in developing countries is affected by infertility. The

magnitude of the problem calls for urgent action, particularly when the majority of cases of infertility is avoidable.

Infertility is divided into primary and secondary infertility. Primary infertility is defined as the "Inability to conceive after one year of regular unprotected intercourse (*i.e.*- sexually active, non-contracepting, and non-lactating) among women 15 to 49 yr old". Secondary infertility refers to the inability to conceive following a previous pregnancy. Worldwide, most infertile couples suffer from primary infertility[4].

The term "ovarian reserve" has traditionally been used to describe a woman's reproductive potential– specifically, the number and quality of oocytes she possesses[5,6]. However commonly used ovarian reserve markers serve as a proxy for oocyte quantity but are considered poor predictors of oocyte quality.

Therefore, modern usage of the term ovarian reserve refers to the quantity of remaining oocytes rather than oocyte quality, for which age still remains the best predictor. Diminished ovarian response describes women with ovarian ageing and is generally characterized by early menopause or premature ovarian failure[7-8].

Ovarian reserve is a complex clinical phenomenon influenced by age, genetics, and environmental variables[9]. The development of new methods to identify women with decreased ovarian reserve is clinically important. Decreased ovarian reserve (DOR) is defined as a decrease in the number of quality & quantity of oocytes. According to 2011 Bologna-ESHRE criteria for poor responders, at least two of the following three features must be present: – Advanced maternal age (≥40 years) or any other risk factor for POR – A previous POR (≤3 oocytes with a conventional stimulation protocol) – An abnormal ovarian reserve test (i.e., AFC< 5–7 follicles or AMH< 0.5 – 1.1 ng/mL).

With the understanding that age alone is an inadequate predictor of the ovarian reserve, the use of predictive markers that reflect the reproductive status of a woman is remarkable and important. In an effort to predict the status of ovarian reserve, markers described in the literature include basal follicle-stimulating hormone (FSH), basal estradiol (measured on day 2 or day 3 of menstrual cycle), serum antimullerian hormone (AMH) and antral follicle count (AFC) assessed by transvaginal ultrasound.

Other tests include inhibin B, clomiphene citrate challenge test (CCCT), gonadotropin releasing-hormone (GnRH) agonist stimulation test), measurement of ovarian volume and ovarian stromal blood flow. Most of these measures, however, have poor predictive value often because they are indirect measures of ovarian reserve or have substantial intracycle or intercycle variability.[10,11]

Basal follicle-stimulating hormone(fsh)

Basal follicular phase FSH is an indirect assessment of ovarian reserve and is based on the feedback inhibition of FSH pituitary secretion by ovarian hormones. Serum FSH, measured in early follicular phase (day 3–5 of the menstrual cycle) together with Estradiol, has been widely used but it is only an indirect marker of ovarian reserve and its blood concentrations rise only when ovarian reserve is severely compromised[12]. Basal FSH level is increased with advancing age by reduced Inhibin-mediated feedback towards the pituitary gland.

Day 3 FSH has been the most used test of ovarian reserve and has been the standard way of determining ovarian reserve, providing greatest accuracy[13].High level of serum FSH (>12 or >15 mIU/mL) on days 2 or 3 is an accurate prediction of poor response[14].

Antimullerian hormone (amh)

AMH is produced by follicles which are gonadotropin-independent and therefore

remains relatively consistent within and between menstrual cycles. It is considered to be more reliable marker for the prediction of ovarian response and reproductive potential.

AMH can estimate the quantity and activity of retrievable follicles in early stages of maturation. Its expression is maintained until the follicles reach about 6 mm in diameter. When antral follicles are selected for dominance, follicular growth is controlled by FSH action[15].

Low AMH is generally associated with fewer follicles retrieval in ivf cycles and poor oocyte and embryo quality. It has a better predictive value for stimulation response in patients with poor ovarian reserve than patients with normal ovarian reseve. AMH >3.5 ng/ml is commonly associated with over response reflecting greater risk for ovarian hyperstimulation syndrome[16].

AMH also has the advantage of reduced variability of its serum concentrations along the menstrual cycle compared to FSH, inhibin B, and estradiol.

Antral follicle count (afc):

AFC by ultrasonography on day 2 or 3 of the menstrual cycle has been shown to be an excellent predictor of ovarian reserve and response with significant superiority in relation to other markers. AFC is counted as sum of all follicles having adequate phology as described for a healthy follicle (i.e., 2-9 mm size range of well-defined anechoic cysts with smooth margins and absence of internal septations or nodularity)[17].

A low AFC is associated with poor ovarian response to ovarian stimulation during IVF and generally shows an age-related decline [18-20]. In terms of OHSS prediction, both AFC and AMH demonstrate strong predictive value for predicting those at greatest risk for OHSS.

Estradiol

Basal estradiol (E2) levels provides additional useful information for the evaluation of ovarian reserve. Early rise in serum E2 is an indicator of the advanced follicular development and early selection of a dominant follicle. As an ovarian reserve test, basal estradiol level has little value but may provide additional information in the interpretation of basal FSH[21].

Maternal age

Age is considered to be the single most important factor in determining quality and quantity of ovarian status and significantly decrease as a woman advances in her age.

The decline in a woman’s ovarian reserve with time is irreversible and the rate at which women lose primordial follicles varies considerably[22].

The qualitative aspect is best expressed by female age. A young woman with a poor ovarian response to ovarian hyperstimulation may have a reduced quantitative ovarian reserve, but as the quality aspect of her ovarian reserve is still good, she will still have reasonable pregnancy Outcome.

Aims and objectives:

The objective of this study was to study the status of the ovarian reserve in infertile women attending the tertiary care centre.

Study design

Hospital based prospective study.

Material and method:

This prospective study was conducted on 100 women in reproductive age group who attended out- patient clinic of Reproductive Medicine department of Indira Gandhi Institute of Medical Sciences (IGIMS), Patna. From April 2018 to April 2019. All data were collected after taking informed consent from the participants and detail history taking, general and systemic examination of the participants was done. Of the common markers considered for ovarian

reserve testing, basal follicle stimulating hormone (FSH), and anti-mullerian hormone (AMH) was done on day 2 of the menstrual cycle.Baseline transvaginal ultrasound was carried out on the subjects on the day 2-3 of menstrual cycle for the measurement of antral follicle count (AFC).

Inclusion criteria:

All female patients of reproductive age who visited outpatient clinic in the department of Reproductive Medicine were considered as cases except those with exclusion criteria.

Patients having normal ultrasound of pelvis with visualisation of both ovaries.

Exclusion criteria:

All the females who did not give consent for participation in study.

Females with premature ovarian failure.

All infertile women with a history of surgical treatment on the ovary for ovarian cysts, endometriosis, any pelvic surgery, pelvic inflammatory disease or using any hormonal treatments for last three months.

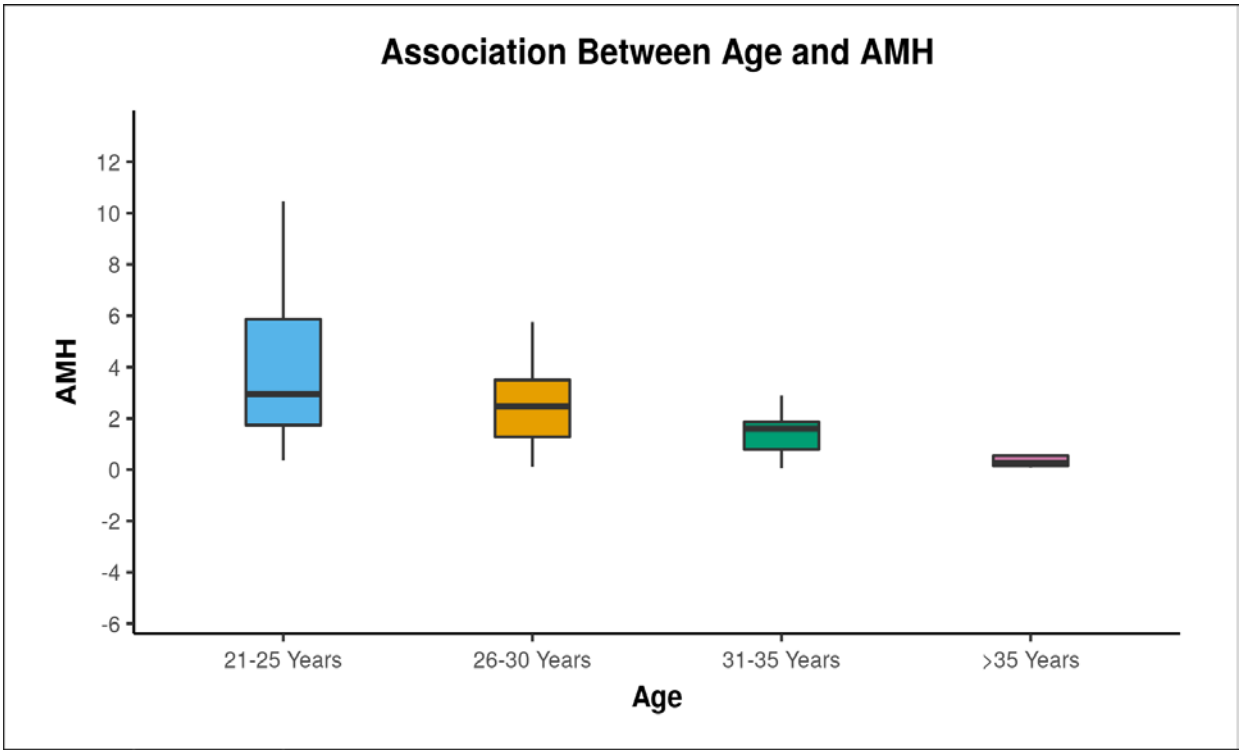
Result

Table 1: Comparison of the 4 Subgroups of the Variable Age in Terms of AMH (n = 100)

AMH	Age				Kruskal Wallis Test	
	21-25 Years	26-30 Years	31-35 Years	>35 Years	$\chi 2$	p value
Mean (SD)	3.95 (3.20)	2.75 (2.11)	1.74 (1.65)	0.58 (0.89)	24.178	<0.001
Median (IQR)	2.95 (1.74-5.86)	2.47 (1.27-3.5)	1.6 (0.79-1.87)	0.27 (0.16-0.55)		
Range	0.37 - 12.48	0.12 - 9.57	0.06 - 7.72	0.09 - 2.9		

Pair wise Comparison of Subcategories of Age	Adjusted P Value
>35 Years - 21-25 Years	<0.001
>35 Years - 26-30 Years	0.002
21-25 Years - 26-30 Years	0.648
>35 Years - 31-35 Years	0.279
21-25 Years - 31-35 Years	0.013
26-30 Years - 31-35 Years	0.306

Post-Hoc pairwise tests for Kruskal-Wallis test performed using Dunn Test method with Sidak correction.



The variable AMH was not normally distributed in the 4 subgroups of the variable Age. Thus, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons.

The mean (SD) of AMH in the Age: 21-25 Years group was 3.95 (3.20). The mean (SD) of AMH in the Age: 26-30 Years group was 2.75 (2.11). The mean (SD) of AMH in the Age: 31-35 Years group was 1.74 (1.65). The mean (SD) of AMH in the Age: >35 Years group was 0.58 (0.89). The median (IQR) of AMH in the Age: 21-25 Years group was 2.95 (1.74-5.86). The median (IQR) of AMH in the Age: 26-30 Years group was 2.47 (1.27-3.5). The median (IQR) of AMH in the Age: 31-35 Years group was 1.6 (0.79-1.87). The median (IQR) of AMH in the Age: >35 Years group was 0.27 (0.16-0.55). The AMH in the Age: 21-25 Years ranged from 0.37 - 12.48. The AMH in the Age: 26-30 Years ranged from 0.12 - 9.57. The AMH in the Age: 31-35 Years ranged from 0.06 - 7.72. The AMH in the Age: >35 Years ranged from 0.09 - 2.9.

There was a significant difference between the 4 groups in terms of AMH ($\chi 2$ = 24.178, p = <0.001), with the median AMH being highest in the Age: 21-25 Years group.

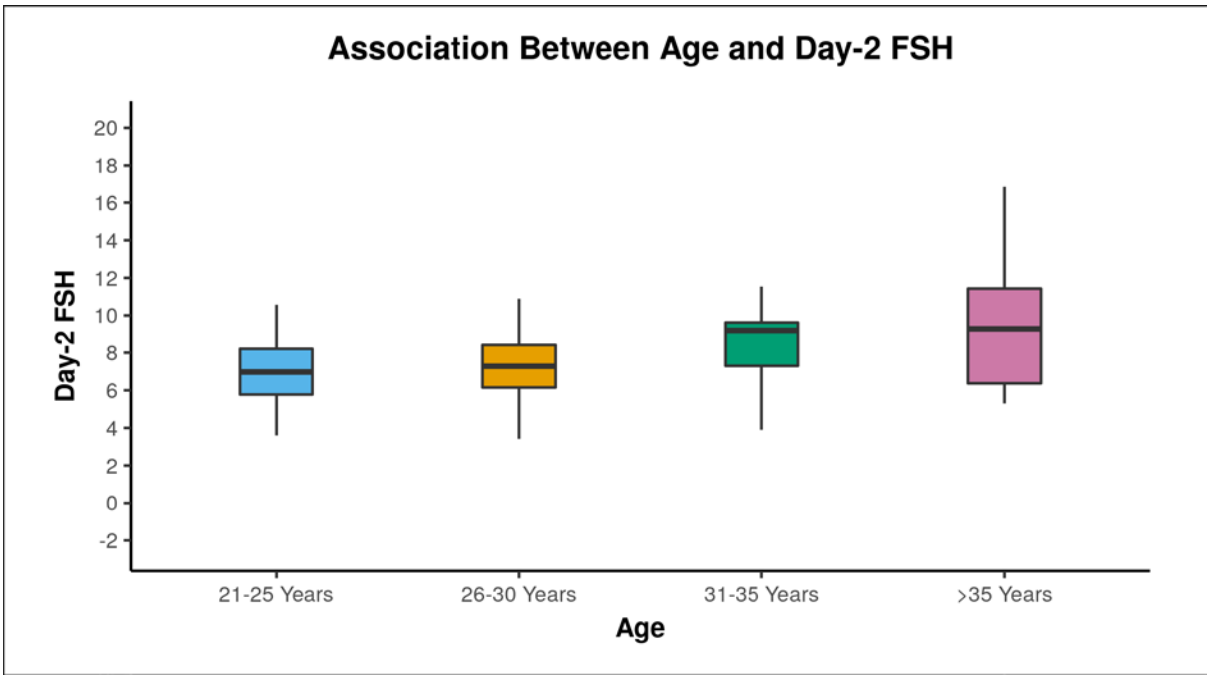
The Box-and-Whisker plot below depicts the distribution of AMH in the 4 groups. The middle horizontal line represents the median AMH, the upper and lower bounds of the box represent the 75th and the 25th centile of AMH respectively, and the upper and lower extent of the whiskers represent the Tukey limits for AMH in each of the groups.

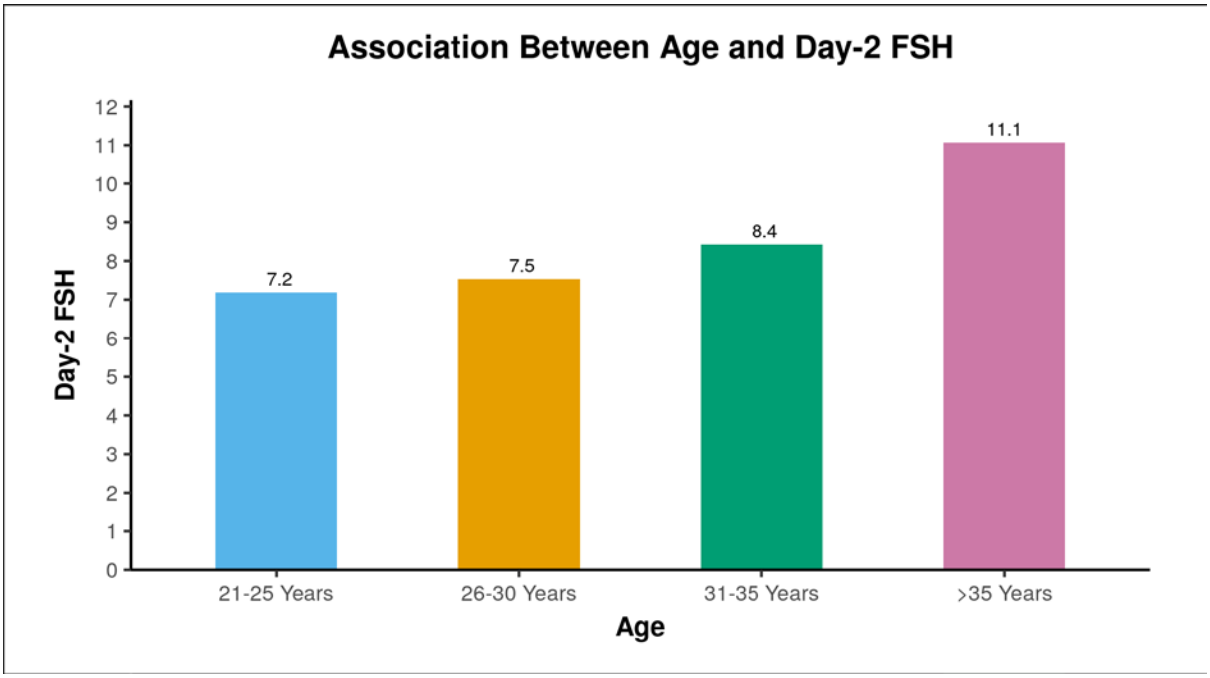
Table 2: Comparison of the 4 Subgroups of the Variable Age in Terms of Day-2 FSH (n = 100)

Day-2 FSH	Age				Kruskal Wallis Test	
	21-25 Years	26-30 Years	31-35 Years	>35 Years	$\chi 2$	p value
Mean (SD)	7.19 (2.30)	7.52 (2.63)	8.42 (2.60)	11.06(6.62)	6.698	0.082
Median (IQR)	6.97 (5.77-8.2)	7.28 (6.15-8.41)	9.2 (7.3-9.62)	9.29 (6.37-11.43)		
Range	2.06 - 13.57	2.25 - 14.7	2.74 - 14.25	5.3 - 25.79		

Pairwise Comparison of Subcategories of Age	Adjusted P Value
>35 Years - 21-25 Years	0.337
>35 Years - 26-30 Years	0.631
21-25 Years - 26-30 Years	0.989
>35 Years - 31-35 Years	1.000
21-25 Years - 31-35 Years	0.178
26-30 Years - 31-35 Years	0.498

Post-Hoc pairwise tests for Kruskal-Wallis test performed using Dunn Test method with Sidak correction.





The variable Day-2 FSH was not normally distributed in the 4 subgroups of the variable Age. Thus, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons.

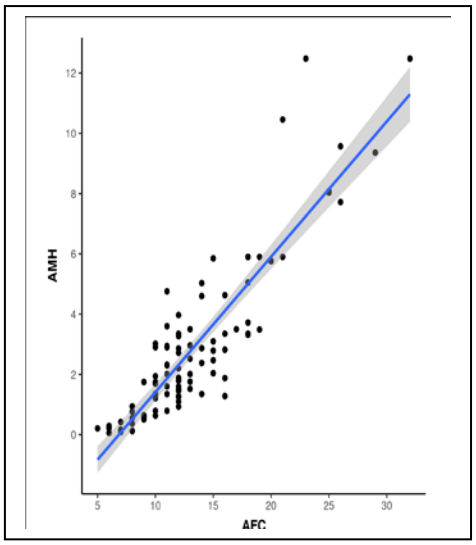
The mean (SD) of Day-2 FSH in the Age: 21-25 Years group was 7.19 (2.30). The mean (SD) of Day-2 FSH in the Age: 26-30 Years group was 7.52 (2.63). The mean (SD) of Day-2 FSH in the Age: 31-35 Years group was 8.42 (2.60). The mean (SD) of Day-2 FSH in the Age: >35 Years group was 11.06 (6.62). The median (IQR) of Day-2 FSH in the Age: 21-25 Years group was 6.97 (5.77-8.2). The median (IQR) of Day-2 FSH in the Age: 26-30 Years group was 7.28 (6.15-8.41). The median (IQR) of Day-2 FSH in the Age: 31-35 Years group was 9.2 (7.3-9.62). The median (IQR) of Day-2 FSH in the Age: >35 Years group was 9.29 (6.37-11.43). The Day-2 FSH in the Age: 21-25 Years ranged from 2.06 - 13.57. The Day-2 FSH in the Age: 26-30 Years ranged from 2.25 - 14.7. The Day-2 FSH in the Age: 31-35 Years ranged from 2.74 - 14.25. The Day-2 FSH in the Age: >35 Years ranged from 5.3 - 25.79.

There was no significant difference between the groups in terms of Day-2 FSH ($\chi 2 = 6.698$, $p = 0.082$).

The Box-and-Whisker plot below depicts the distribution of Day-2 FSH in the 4 groups. The middle horizontal line represents the median Day-2 FSH, the upper and lower bounds of the box represent the 75th and the 25th centile of Day-2 FSH respectively, and the upper and lower extent of the whiskers represent the Tukey limits for Day-2 FSH in each of the groups.

Table 3: Correlation between AFC and AMH (n = 100)

Correlation	Spearman Correlation Coefficient	P Value
AFC vs AMH	0.840	<0.001



The above scatterplot depicts the correlation between AFC and AMH. Individual points represent individual cases. The blue trend line represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trend line.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a strong positive correlation between AFC and AMH, and this correlation was statistically significant (rho = 0.84, p = <0.001).

Discussion:

Ovarian reserve tests and prognostic markers are indirect measurement of quantity and quality of the remaining oocytes in both ovaries at a given age[23].In present study, it was seen that mean FSH level approximately increased with increasing age and this was attributed to reduced ovarian reserve.

The Serum AMH is an increasingly popular method for the assessment of ovarian reserve. In present study, the AMH level was inversely correlated with age and the peak or the maximum value of AMH was found in 21 to 25 yrs., and this was approximately similar to studies done by Kelsey et al who reported it at 24.5 years [24]. These obvious fluctuations could be explained by varying ethnicity, environmental factors, or nutritional status.

In present study, AMH values strongly declined with age whereas FSH levels were moderately increased. De Vet et al. also suggested that changes in serum AMH levels have been shown to occur relatively early in the sequence of events associated with ovarian aging. AMH value can change under some storage or laboratory assay conditions. In addition, clinical cut-off values vary from one lab to another lab [25]. Because of measurement variability of AMH, the European Society of Human Reproduction and Embryology (ESHRE) has stated that improved assay validity and an international standard for AMH are needed so that this biomarker of ovarian reserve can be utilised at its best. But for predicting high and poor response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests[26,27].

In present study the co relation between age and day 3 FSH was age was not linear. Although we found increased day 2 FSH with increasing age in most patients, some women 35 years and above still had normal value of FSH. In contrast, few

younger patients had elevated day 2 FSH which can be explained by the fact that decreased ovarian reserve can occur over a range of ages. As explained by Lambalkand de Koning in their study [28] changes in basal FSH level can be attributed to many variables. AMH was found to be a better biomarker of ovarian reserve than the day 2 FSH particularly with normal FSH levels.

Both AFC and AMH level have been used since years as better markers of ovarian reserve and response during controlled ovarian hyperstimulation compared with other traditional methods e.g., age and basal FSH level. Various previous published studies have shown similarities about the co relation between AMH and antral follicle count(AFC)[29] as ours in which we found that AFC decreased with the increment of age and along with AMH,it is a promising predictor of ovarian reserve and assessment of reproductive potential in a women with infertility[30].

Conclusion

Accurate and reliable markers of ovarian reserve are needed in a infertile couple are for optimization of results of infertility treatment by proper dosing of medications for stimulations, method to opt and to monitor response of treatment. In our study we found decreasing trend of ovarian reserve with increasing age. Even though AFC and AMH are good predictor of ovarian status independently, both have shown increase accuracy in estimation of ovarian reserve and a parallel co relation with each other.

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