Int J Pharm Bio Sci 2014 Jan; 5(1): (B) 1074 - 1080

Research Article **Biochemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

ENDOCRINE MARKERS AND DECLINE IN REPRODUCTIVE POTENTIAL OF WOMEN

BUSHRA FIZA[*, 1, 2], RATI MATHUR[2], MAHEEP SINHA[1] AND PUSHPENDRA SARASWAT[1]

[1]Mahatma Gandhi Medical College & Hospital, Jaipur, India-302022
[2]S.M.S. Medical College, J.L.N. Marg, Jaipur, India-302004

ABSTRACT

As the chronological age increases, there is a physiological decline in reproductive potential of women. Moreover, the chronological age of women may not reflect the biological age of her ovaries. Various endocrine markers have been used to assess the ovarian reserve. The changing pattern of the endocrine markers; follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and anti-Mullerian hormone (AMH) with the increasing age was observed to find out which of these best correlates with advancing reproductive age. The present study reveals that ovarian aging in women of reproductive age may not always coincide with their chronological age and some of the hormones may serve as distinct markers of ovarian aging.

KEYWORDS: **Endocrine Markers, Reproductive Potential, Ovarian aging, Anti-Mullerian Hormone, AMH**

BUSHRA FIZA
Mahatma Gandhi Medical College & Hospital, Jaipur, India-302022

INTRODUCTION

With increasing age, there is a decline in the reproductive potential of women. "Ovarian reserve is the number and quality of oocytes within the ovaries. As a woman ages, her ovarian reserve declines [1,2]". Diminished ovarian reserve has been identified as a leading cause of infertility. Most women with diminished ovarian reserve may still have regular menstrual cycle which makes them totally unaware of their reproductive potential. Therefore, the chronological age of a woman may not reflect the biological age of her ovaries. Various endocrine markers have been used to assess the ovarian reserve. In women over 35 years of age, an increase in serum follicle stimulating hormone (FSH) levels has been observed [3]. In addition, the changes in serum estradiol (E2) levels in women of advanced reproductive age have been contradictory [4, 5]. Serum anti-Mullerian hormone (AMH), a new marker of ovarian reserve has been recently introduced. AMH is produced by the granulose cells of preantral and antral follicles and its primary function is to inhibit the initiation of primordial follicle growth [6, 7]. Serum AMH has been reported to decline with age and also related strongly to the ovarian response following ovarian hyper-stimulation [8-12]. The aim of the present study was to determine the changing pattern of the endocrine markers viz. AMH, FSH, LH and E2 with the growing age and to evaluate which of these best correlates with the advancing reproductive age.

MATERIALS AND METHODS

A total of 316 infertile females visited the infertility clinic during September 2011 to February 2012; Jaipur Fertility Centre of Mahatma Gandhi Medical College & Hospital, Jaipur. These patients were subjected to standardized initial screening which included complete history, physical examination, routine clinical investigations, hormonal and immunoassays and ultrasonography (USG). After initial screening and permission from the Institutional Ethics Committee; 150 females were selected for study. The criteria for inclusion were age between 20 – 46 years, regular menstrual cycle (21-35 days) and normal ovarian morphology as confirmed by USG. Patients with irregular menstrual cycle, polycystic ovary (PCO), genital tuberculosis, and bad obstetric history or on hormonal therapy were excluded. The selected 150 females were grouped into five groups: < 25 years (n=28), 25-30 years (n=34), 30-35 years (n=31), 35-40 years (n=27) and > 40 years (n=30) and subjected to baseline study. On day 3, the blood samples were collected by venipuncture and determined for serum luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol (E_2) levels using VIDAS instrument and kits (Biomerieux, France). Serum AMH levels were determined using an Ultrasensitive enzyme linked immunosorbent assay (ELISA) (Beckman-Coulter Gen II kits). The levels of hormones were presented as mean, SD. One way ANOVA was applied to assess whether there is a significant variation in the levels of these hormones in the different age groups. A p value of $\leq$ 0.05 was considered statistically significant. Linear correlation of the four hormones i.e. LH, FSH, E_2 and AMH with age was also applied and correlation coefficients (r) were calculated with slop.

RESULTS

The endocrine data obtained from the females in the five groups has been presented as mean and SD in Table I. It is obvious from the data reveals in Table I that the serum AMH levels showed a continuous decrease with the increasing age (p less than 0.05). On the contrary, the serum FSH levels showed a significantly increasing pattern with the growing reproductive age (p less than 0.05). Serum E_2 levels also showed a continuous increase in the first three groups [i.e. < 25 years (n=28), 25-30 years (n=34), 30-35 years (n=31)] but thereafter [i.e. > 35 years (n=27)] the values were almost same. Hence, the overall changes were statistically significant, though the degree of freedom was very low. Further, the values of serum LH showed a disturbing pattern and the overall changes though significant but the degree of freedom

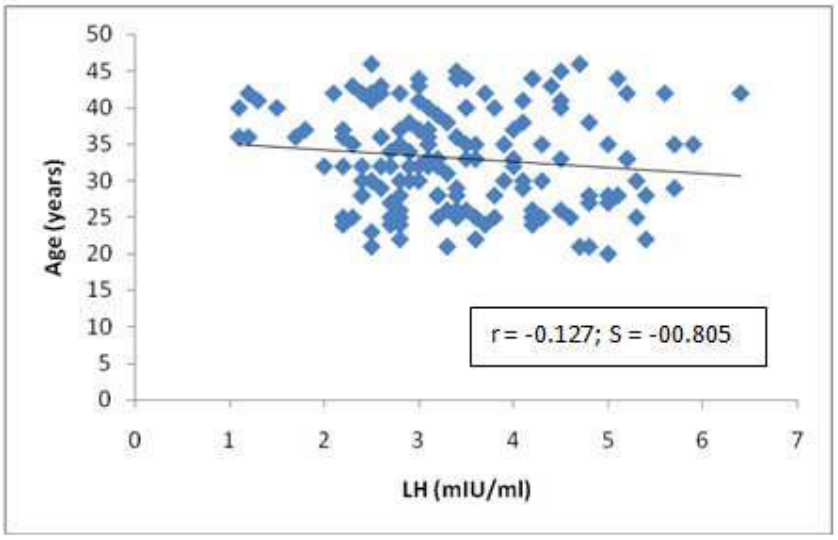
was very low. On comparison of the degrees of freedom for these four hormones; it was highest for serum AMH followed by Serum FSH, and lowest for E2 and LH respectively. The correlation of the hormones with age was also studied and graphically represented (Graph 1-4); it was highest with a negative slope between age and serum AMH that shows AMH is negatively correlated with the growing reproductive age in women. Similarly, serum FSH also showed a significant correlation with the increasing age in women but the slop was positive. On the other hand, the correlation coefficient for serum E_2 and LH was very low and the slope did not indicate a significant correlation with age. The study, therefore, confirms that of these four hormones; serum AMH is the most reliable marker of ovarian aging followed by serum FSH.

Table 1
Day 3 Baseline hormone levels in the different age groups

Age Groups (years)	(< 25)	(25-30)	(30-35)	(35-40)	(> 40)	F	p
AMH (ng/ml)	2.24 ± 0.68	2.08 ± 0.79	1.36 ± 0.54	1.07 ± 0.50	0.51 ± 0.44	41.39	0.000
FSH (mIU/ml)	5.14 ± 1.69	5.25 ± 1.01	6.43 ± 1.33	8.46 ± 2.69	10.75 ± 3.50	35.22	0.000
E_2 (pg/ml)	35.27 ± 7.62	38.70 ± 9.03	45.65 ± 11.01	45.40 ± 13.07	43.56 ± 16.56	4.32	0.002
LH (mIU/ml)	3.61 ± 0.97	3.76 ± 1.01	3.53 ± 1.03	2.87 ± 1.01	3.44 ± 1.25	2.95	0.022

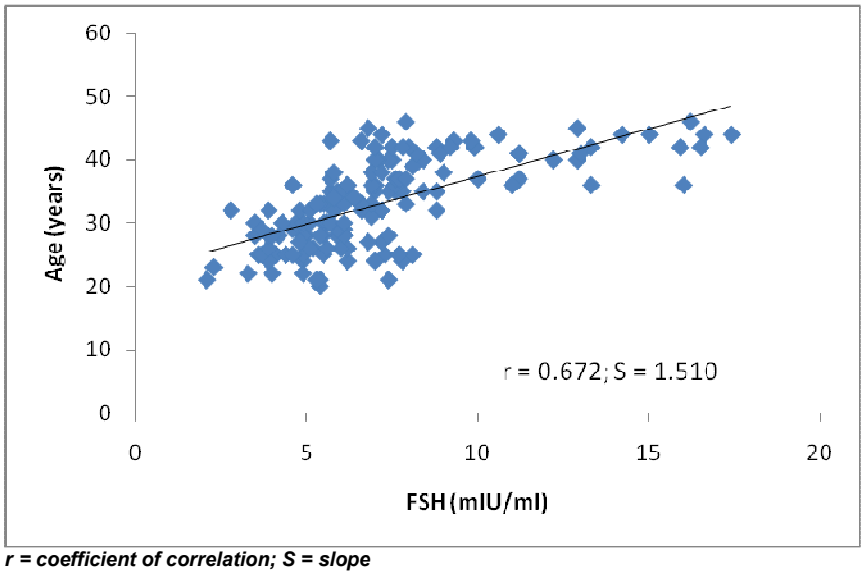
- ***F – Degree of freedom***
- ***p values as obtained on applying One Way ANOVA.***

Graph 1
Correlation between Age and serum LH levels



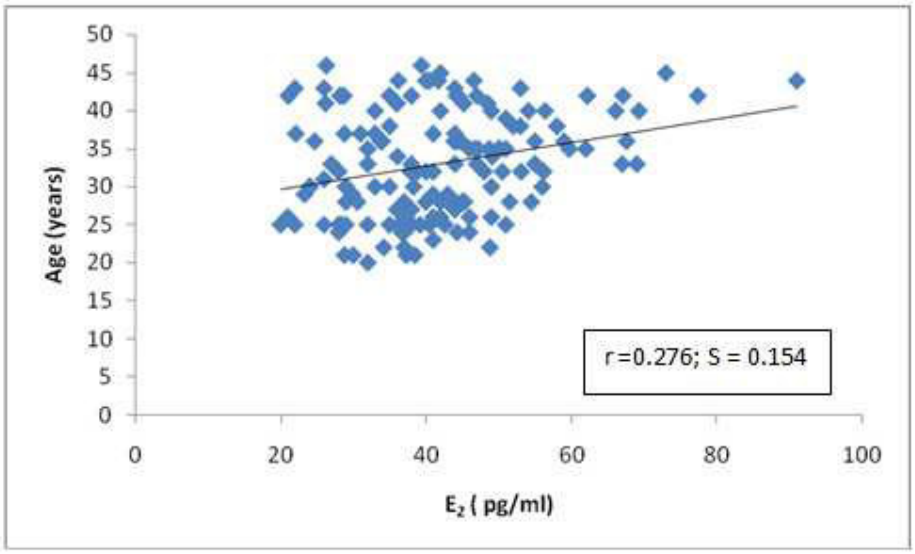
r = coefficient of correlation; S = slope

Graph 2
Correlation between Age and serum FSH levels



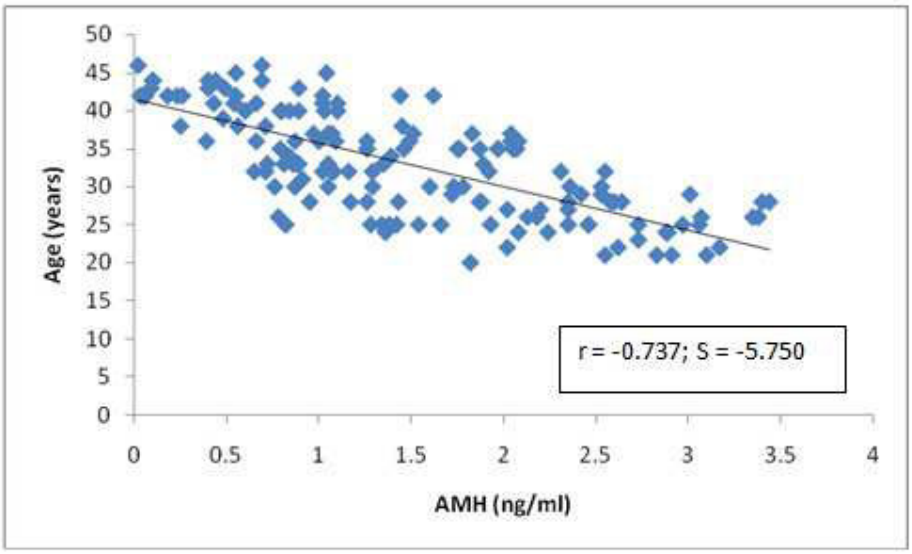
r = coefficient of correlation; S = slope

Graph 3
Correlation between Age and serum E_2 levels



r = coefficient of correlation; S = slope

Graph 4
Correlation between Age and serum AMH levels



r = coefficient of correlation; S = slope

DISCUSSION

Repeated clinical studies have demonstrated that certain endocrine markers correlate more strongly to antral follicle count and ovarian response to ovulation induction than the chronological age of women. Nowadays, various hormone levels specially LH, FSH, E2 and recently AMH are estimated for baseline study to assess the ovarian response in assisted reproductive technology (ART). The aim of the present study was to assess the correlation of these endocrine markers with age in women with normal ovarian morphology and regular menstrual cycle. Age specific reference values for these markers would provide a framework for expected values that could improve the potential regarding expectation and consideration of treatment options for infertility. The study was exclusive as age groups of five years interval were considered and the endocrine data was subjected to one way ANOVA. Of the four hormones studied; AMH was found to be most strongly correlated with age and showed a negative slope. These findings were similar as previous studies[1; 14-15].The study showed a rapid fall in serum AMH levels by 30 years of age that was similar to the results of previous study[1]. Besides this, serum FSH levels showed a positive correlation with increasing age while coefficient of correlation was lower than that for AMH versus age. A steep rise was reported beyond 35 years of age and these findings were similar to the previous studies[1, 3], while some studies are contrary to the present findings that they have shown no correlation between serum FSH and age until the age of 40 years[2, 13].

In the present study; serum E2 levels showed a rise in the younger age groups i.e. < 30 years, beyond which it showed almost static pattern. Previous studies have shown both an increase and a decline in the serum E2 levels with increasing age[4, 5]. Hence, women have been reported to maintain a regular ovulatory pattern and normal E2 levels for years after they become infertile. Therefore, E2 should not be considered as a reliable marker of ovarian aging. The values for serum LH did not show a distinct pattern in the age groups. The levels were almost similar in the younger age groups i.e. up to 35 years of age. A sharp fall was noted in the 35 -40 years age group, beyond which the serum LH levels increased again. On applying one way ANOVA the changes were significant but the degree of freedom was low and as such no correlation of serum LH with increasing age was observed. Our findings were contradictory to the previous study that showed an increase in the levels of serum LH 40 years of age[16]. The variation in serum LH levels in relation to the increasing age has not been studied

much, so the estimation of serum LH may not be considered as a marker of ovarian aging.

CONCLUSION

The present study reveals that the ovarian aging in women of reproductive age may not always coincide with their chronological age and some of the hormones may serve as distinct markers of ovarian aging. The study further confirms that serum AMH and FSH are more reliable markers of ovarian aging. Levels of these hormones in women of reproductive age may be helpful in assessing their reproductive potential and may also guide in the treatment of infertility.

REFERENCES

1. Tremellen KP, Kolo M, Gilmore A, Lekamge DN, Anti-mullerian hormone as a marker of ovarian reserve, Aust. and New Zealand J Obst & Gynaecol, 45:20-24,(2005).
2. van Rooij IA, Broekmans FJ, Scheffer GJ, Looman CW, Habbema JD, de Jong FH, Fauser BJ, Themmen AP, te Velde ER, Serum antimüllerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study, Fertil Steril, 83(4): 979-987,(2005).
3. Sherman BM, West JH, Korenman SG, The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women, J Clin Endocrinol Metab, 42(4):629–636,(1976).
4. Klein NA, Battaglia DE, Fujimoto VY, Davis GS, Bremner WJ, Soules MR, Reproductive aging: accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women, J Clin Endocrinol Metab, 81(3):1038–1045, (1996).
5. MacNaughton J, Banah M, McCloud P, Hee J, Burger H, Age related changes in follicle stimulating hormone, luteinizing hormone, oestradiol and immunoreactive inhibin in women of reproductive age, Clin Endocrinol (Oxf), 36(4):339–345,(1992).
6. Durlinger AL, Visser JA, Themmen AP, Regulation of ovarian function: the role of anti-Mullerian hormone, Reproduction, 124:601–609, (2002).
7. Rey R, Sabourin JC, Venara M, Long WQ, Jaubert F, Zeller WP, et al., Anti-Mullerian hormone is a specific marker of sertoli- and granulose cell origin in gonadal tumors, Hum Pathol, 31(10):1202– 1208,(2000).
8. de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC, Anti-Mullerian hormone serum levels: a putative marker for ovarian aging, Fertil Steril, 77(2):357–362,(2002).
9. Seifer DB, MacLaughlin DT, Christian BP, Feng B, Shelden RM, Early follicular serum mullerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles, Fertil Steril, 77(3):468 –471,(2002).
10. Van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, Jong FH, et al., Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve, Hum Reprod, 17(12):3065–3071,(2002).
11. Fanchin R, Schonauer LM, Righini C, Guibourdenche J, Frydman R, Taieb J, Serum anti-Mullerian hormone is more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on day 3, Hum Reprod,18(2):323–327,(2003).
12. Fanchin R, Schonauer LM, Righini C, Guibourdenche J, Frydman R, Taieb J, Serum anti-Mullerian hormone dynamics during controlled ovarian hyperstimulation, Hum Reprod,18(2):328–332,(2003).
13. Schipper I, de Jong FH, Fauser BC, Lack of correlation between maximum early follicular phase serum follicle stimulating hormone concentrations and menstrual cycle characteristics in women under the age of 35 years, Hum Reprod, 13(6): 1442-1448, (1998).

14. Nelson SM, Messow MC, Wallace AM, Fleming R, McConnachie A, Nomogram for the decline in serum anti-mullerian hormone: population study of 9,061infertility patients, Fertil Steril, 95(2): 736-741, (2011).
15. Seifer DB, Baker VL, Leader B, Age specific serum anti-mullerian hormone values for 17,120 women presenting to fertility centers within the United States, Fertil Steril, 95(2): 747-750, (2011).
16. Reame NE, Kelche RP, Beitins IZ, Yu MY, Zawacki CM, Padmanabhan V, Age effects of follicle-stimulating hormone and pulsatile luteinizing hormone secretion across the menstrual cycle of premenopausal women, J Clin Endocrinol Metab, 81(4): 1512-1518,(1996).