Original Article

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Age-Related Value of Anti-Mullerian Hormone

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ABSTRACT

Background: There is a correlation between anti-mullerian hormone (AMH) and the age when it becomes undetectable during menopause. The AMH immunoassay has been widely estimated in clinical practice to assist in reproduction and infertility treatment.

Objective: To investigate the normal level of serum anti-mullerian hormone (AMH) in relation to women's age in Basra.

Patients and Methods: Cross-sectional study was carried out in Basra Maternity and Child Hospital from January 2018 to September 2019. Serum AMH levels were estimated for 975 women aged 15–50 years. They were classified into 7 age groups:15–20, 20–25, 25–30, 30–35, 35–40, 40–45 and 45–50 years. Serum AMH and FSH levels were determined by commercial enzyme-linked immunoassay.

Results: Negative relationship was noticed between AMH concentration and age. The mean AMH levels for the age groups 1, 2, 3, 4, 5, 6 and 7 were 4.9 ng/ml, 4.25ng/ml, 3.27 ng/ml, 2.43ng/ml, 2.17ng/ml, 1.95ng/ml and 0.9ng/ml respectively.

Conclusions: This study recorded normal levels of AMH in women in Basra. These levels can be considered for the medical treatment of infertile women.

Keywords: age, anti-mullerian hormone, FSH.

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INTRODUCTION

Anti-mullerian hormone (AMH) plays an important role in male sex differentiation, as its production by the embryonic testis induces the reduction of mullerian ducts.[1]

Deficient production of AMH or dysfunction of its receptor results in differentiation of the mullerian duct into oviducts, uterus, and vagina in genetic male embryos.[2]

During the female life, until menopause, it is produced by granulosa cells of primary, secondary, preantral follicles and early antral follicles until they reach the size 4–8mm.[3] AMH expression is almost absent in follicles of more than 8 mm in size.[4]

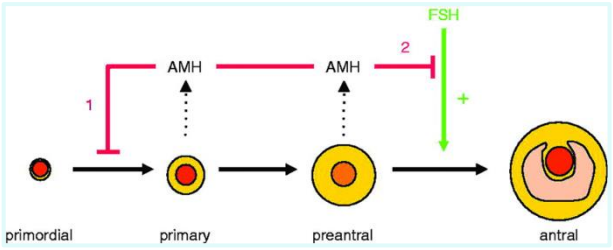

Figure 1: Model of AMH action in the ovary.

The progressing stages of folliculogenesis are depicted in Figure 1. AMH is produced by the small growing (primary and preantral) follicles in the postnatal ovary and has two sites of action. It inhibits initial follicle recruitment[1] and inhibits FSH-dependent growth and selection of preantral and small antral follicles.[5]

There are two major actions for AMH in the ovary. One is the inhibition of primary involvement of primary follicles from primordial follicles, and consequently, the second is the sensitivity of antral follicles to follicle-stimulating hormone during cycle recruitment[6] so that the inhibition of follicular storage of the ovary can be prevented.

In addition, the anti-mullerian hormone is not formed in follicle-stimulating hormone-dependent (antral) follicles and also in atretic follicles. The primary reserve for serum AMH comes from antral follicles since they have a higher number of granulosa cells along with good blood supply. The hormone passes in the blood and its level can be measured.[7]

The pituitary produces the gonadotropin hormones LH and FSH after stimulation of gonadotropin-releasing hormone (GnRH) from the hypothalamus. LH production is closely controlled by GnRH, while the production of FSH is co-regulated by hypothalamic GnRH and other factors as inhibins and activins. When the level of serum estradiol begins to increase in the mid-follicular phase, there is a fast decrease in pituitary FSH secretion which is co-mediated by a high level of serum inhibin B.[6]

The sensitivity of growing follicles to FSH depends on the expression of anti-mullerian hormone receptors. So, out of the initially recruited follicle unit, only those with lower AMH expression become sensitive to the follicle-stimulating hormone of which usually one is permitted for dominance. Therefore, AMH acts as an autocrine factor that regulates the dominant follicle selection.[8]

On the other hand, AMH is not formed in follicle-stimulating hormone-dependent (antral) follicles or atretic follicles. The origin of the serum anti-mullerian hormone is the antral follicles because they have granulosa cells along with good blood flow. The hormone passes in the blood and its level can be measured.[9]

It has been indicated that there is a close association between the size of the primordial follicles and the number of antral follicles.[10] Due to age, AMH levels diminish and FSH

serum levels decrease, which leads to a low number of antral follicles.

A lower level of serum AMH was observed among obese women, which in turn led to low ovarian reserve. It can be indicated that impaired granulosa cell hormone production and defect in ovulation may occur among obese women.[11] Therefore, AMH has been recorded as the optimal indicator for the status of ovarian reserve.[12]

PATIENTS AND METHODS

A cross-sectional study was carried out in Basra Maternity and Child Hospital from January 2018 till September 2019. The study involved 975 women with ages ranged from 15–50 years. They were classified into seven age groups as 15–20, >20–25, >25–30, >30–35, >35–40, >40–45, and >45–50 years.

The following conditions were excluded:
1. Polycystic ovarian disease
2. Ovarian surgery
3. History of radiotherapy or chemotherapy
4. Women used contraceptive therapy or any medical therapy for the induction of ovulation.

Anti-mullerian hormone assay:

Blood samples were collected 2–3 days of the cycle. After centrifugation, serum AMH values were estimated through the ELIZA method using AMH /MIS EIA kit, which is two immunological steps sandwich-type assay with a range from 0.14ng/ml to 21ng/ml. The lower levels below 0.14ng/ml were considered as the zero level.[13]

Statistical analysis:

The correlation between AMH and various variables was done by using SPSS 24 and Pearson's correlation was used as well.

RESULTS

The study involved 975 healthy women. The characteristic features for all the subjects are illustrated in (Table 1).

Table 1: The general characteristics for different age groups

Variable	15-20Y	>20-25Y	>25-30Y	>30-35Y	>35-40Y	>40-45Y	>40-50Y
No. of cases	135	140	145	125	145	135	**130**
Age(years) Mean ± SD	18 ± 0.1	22 ± 0.5	27± 0.2	32 ± 1.2	37 ± 0.1	41 ± 0.2	**47 ± 1**
BMI	20 ± 0.1	21 ± 0.5	22 ± 0.3	23 ± 0.2	21 ± 1	25 ± 1.3	**29 ± 3.2**
FSH iu/ml	7.5 ± 0.2	7.7 ±0.3	9.4 ± 0.7	9.9 ± 0.4	12.1 ± 4.5	15.9 ± 1.5	**17.3 ± 1.8**

The mean age group of 975 women was 34.4 + 5.2. Serum FSH was 8.4+ 0.2.

Serum AMH was obtained for all the women groups, and the mean, median, and SD values were obtained for each group (Table 2). The AMH levels were inversely related to age.

Table 2: Serum AMH levels (ng/ml) among different age groups.

Age	Number	Range	Mean +SD	Yearly average decrement
15-20	135	4.6-15.2	4.9+2.6	-
>20-25	140	3.9-14.5	4.25+1.5	**0.7**
>25-30	145	2.9-10.21	3.27+2.1	**1.2**
>30-35	125	1.83-8.4	2.43+2.5	**1.13**
>35-40	145	1.21-5.71	2.17+3.0	**0.66**
>40-45	135	0.631.23	1.95+2.5	**0.52**
>45-50	130	0.13-0.9	0.9+3.1	**0.35**

The range as well as the mean of AMH values decreased gradually and were correlated with older ages.

The average yearly decreases in the mean serum AMH value is 0.2 mg /ml/year after the 35 years of age.

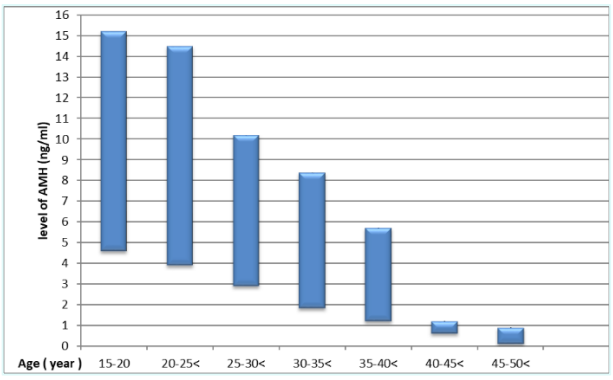

Figure 2: Graphical comparison of AMH value in relation to age in 5 years interval.

DISCUSSION

The AMH immunoassay has been widely used in daily clinical practice. It is widely performed during assisted reproduction and infertility treatment.[11] This cross-sectional study for Iraqi women from adolescence to menopause presents a trend norm gram of serum AMH in Basra.

It has described the relationship of AMH values with age and proved that this hormone is induced in the 36th week of pregnancy and increases during puberty and remains constant until levels decrease after 25 years. At the age of 25 years, there was an inverse relationship between AMH with age, which becomes unrecovered during menopause.[12] Thus, serum AMH concentration indicates the presence of growing follicles, which are produced during reproductive time.[11] Accordingly, serum AMH could be applied as an optimal ovarian reserve marker.

La Marca et al.[13] study had recorded that the inter-cycle and intra-cycle differences of serum AMH value is low enough to permit the various timing of AMH estimation during the menstrual cycle. Thus, it has been stated that AMH levels are valuable and suitable more than other serum ovarian reserve methods, such as inhibin B and FSH.

The present study represents serum AMH value in females in Basra regardless of fertility status, which confirms that serum AMH concentrations decrease with age. Similarly, Seifer et al.[14] have examined age-specific serum AMH levels for 17,120 women of the age 24-50 in the United States. This study has shown that serum AMH values correlated negatively with age. However, this study depends on the result of women who have a history of infertility only and excludes the

general population. It should be stated in the work, that age-specific means were lower than the results obtained in the present investigation.

Barad et al.[15] have reported the age-specific reference value of AMH among 792 infertile women in the United States within 5 age groups. Half of the women had lowered ovarian reserve. Even so, that research has presented lower AMH concentrations than our work.

Nevertheless, the results of the present research are in agreement with a study done in Italy among 277 women with a normal cycle.[16]

Many studies have observed that serum AMH indicates the pattern of developing follicles However, it is the best marker for an indication of retrieved oocysts.[17]

Serum AMH testing can be carried out as pre-operative and post-operative means for ovarian surgery in younger women. Thus, it is a useful marker for ovarian reserve after surgery.[18]

Hagen et al.[19] have observed in their study that healthy female children have increasing AMH levels during early childhood, and thereafter stable AMH concentration until early adulthood. In addition, up to 10% of women at reproductive age are affected by PCOS which is characterized by an increased AMH level.[19] In any case, women with a regular cycle were included in the present study while PCOS women were excluded.

The variation of AMH values may indicate the range in reproductive capacity and ovarian activity. Indeed it has been noticed that the age of menopause was more accurately predicted by serum AMH concentration than by chronological age.[20] It may be proposed that at any age women with AMH at a higher than normal level will enter menopause at a later age compared to women with AMH value at the lower than normal range.[21]

Women with regular cycles have remained inconclusive on the levels of serum AMH and FSH,[22] in contrast to the present study where serum AMH and FSH level in women after the age of 35 years were negatively correlated. In addition, the inverse relation between AMH and age was stronger than that between FSH and age, suggesting that AMH is the optimal marker for the age of the ovary than FSH.[23]

CONCLUSION

It can be concluded that this study indicated the normal value of serum AMH in Basra, which can be considered for the medical treatment of infertile women.

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