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**COLLEGE OF MEDICINE**

**DEPARTEMENT OF OBSTETRIC AND GYNECOLOGY**

***Age related level of anti mullerian hormone (AMH)***

***Presented by***

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﴿ قَالَ رَبِّ أَنَّى يَكُونُ لِي غُلَامٌ وَكَانَتِ امْرَأَتِي عَاقِرًا وَقَدْ بَلَغْتُ مِنَ الْكِبَرِ عِتِيًّا \* قَالَ كَذَلِكَ قَالَ رَبُّكَ هُوَ عَلَيَّ هَيِّنٌ وَقَدْ خَلَقْتُكَ مِنْ قَبْلُ وَلَمْ تَكُ شَيْئًا ﴾ [مريم: 8 – 9



**CERTIFICATION:**

***I certify that this thesis was prepared by the candidate Doaa Faraj Noor, under my supervision and submitted as the requirement for the degree of Diploma in Obstetrics and Gynecology.***

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**Dedication**

*To my dear supervisor*

 *Dr.Maysoon Shareif, Dr .Ghufran Jaafar*

*for their kind support*

 *and encouragement.*

*To my family*

*who waiting my success.*

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***List of Abbreviations :***

|  |  |
| --- | --- |
| AMH  | Anti mullerian hormone |
| AFC  | Antral follicular count |
| FSH | Follicular stimulating hormone |
| MIS | Mullerian inhibitory substance |
| LH  | Luteinizing hormone |
| GnRH | Gonadotropin releasing hormone |
| PG  | Prostaglandin |
| TGF | Transforming Growth Factor |
| PCOS  | Polycystic ovary syndrome |
| BMI | Body mass index |

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**Abstract:-**

**Objective :-**

 To determine the serum level of AMH values in women in Basra in different age groups .

 **Methods :-**

 Cross –sectional study was conducted in Basra maternity and child hospital during period between first of January 2018 till the first of September 2019 .

 The serum AMH levels were evaluated in a total 975 women ,their age was range between 15-50 year ,women were classified in to 7 categorized by age 15-20 y ,≥20-25 y ,≥25 -30 y, ≥30-35 y ,≥35-40 y ,≥40-45y ,≥45-50 year .

 Measurement of serum AMH and FSH was measured by commercial enzyme linked immunoassay with certain exclusion criteria for the women who included in the study .

**Result:**-

 The serum AMH levels correlated negatively with age ,the mean AMH level of each age group were 4.9 ng/ml ,4.25ng/ml ,3.27 ng/ml , 2.43ng/ml ,2.17ng/ml ,1.95ng/ml ,0.9ng/ml respectively .

**Conclusion:-**

 This study determined local reference values AMH in women in Basra, the value can be applied to clinical evaluation and treatment infertile women.

**Introduction**

**Ovarian cycle**

 The ovary of premenopausal women composed of a central dense collagenous stroma and thin outer cortex. Thousands of primordial follicles in the cortex containing a germ cell surrounded by one layer of granulosa and theca cells. The arrest in the germ cell occurs at the diplotene stage of prophase of the first meiotic division1. The early stages of follicle development in the human are independent of gonadotropins2. Once a developing follicle reaches the pre-antral stage of development, further progression to the antral and preovulatory stages appear to be absolutely dependent upon the presence of gonadotropins.

 Early antral follicles secret glycoprotein including antimullerian hormone (AMH), also called mullerian inhibitory substance (MIS) and inhibin B3. elevation of circulating concentration of follicle stimulating hormone (FSH) seen in the early follicular phase of ovarian cycle allows a limited number of pre-antral follicles to reach the stage of maturity ,only one "lead follicle " will acquired significant aromatase enzyme activity within its granulosa cells4 ,leading to increased synthesis and secretion of oestradiol from androgenic precursor , the 'tow –cell ,tow gonadotropin ' hypothesis specifies the need for both LH to stimulate production of precursor androgens ,particularly androstendione ,by the theca cell layer ,with FSH driving aromatization to oestradiol within the adjacent granulosa cell layer. 5

 The pituitary secretes the gonadotropin hormones LH and FSH in response to pulses of gonadotropin releasing hormone (GnRH) from the hypothalamus, which travel to the anterior pituitary via the hypothalamo-hypophyseal portal tract. LH secretion appears to be closely regulated by GnRH pulsatility, while secretion of FSH is co-regulated by hypothalamic GnRH and other factors which act directly on the pituitary, possibly including the inhibins and activins, Once the concentration of serum oestradiol begins to rise in the mid-follicular phase, there is a rapid suppression of pituitary FSH production by negative feedback ,suppression of pituitary FSH secretion in the follicular phase co-mediated by rising serum concentrations of inhibin B6. The result is progression to atresia for all but the dominant follicle, leading to mono-ovulation7.

**The LH surge and ovulation:**

 Final maturation of the oocyte only occurs after initiation of the LH surge. This ensures that the oocyte is mature and ready for fertilization when released from the follicle. This occurs in response to the rapid rise in estradiol during the latter days of the follicular phase of the ovarian cycle, it is also preceded by a rise in serum concentration of progesterone, and The LH surge initiates final maturation of the oocyte with completion of meiosis and extrusion of the first polar body3, 7. Also induces an inflammatory type reaction at the apex of the follicle adjacent. A process of new blood vessel formation, with associated release of prostaglandins (PGs) and cytokines leads to rupture of the follicle wall and ovulation about 38 h after the initiation of the LH surge. The ‘empty’ follicle rapidly fills with blood and the theca and granulose cell layers of the follicle wall luteinize, with formation of the corpus luteum, A rapid synthesis of progesterone, along with oestradiol, follows.These concentrations rise still further if pregnancy follows8.

**Anti Mullerian Hormone :-**

 Since 1940, when A.Jost pointed to a protein substance formed in testes of mammals including man and different from testosterone, responsible for regression of mullerian ducts .it was named Mullerian inhibiting substance .it lasted almost 40 years before the protein was isolated and characterized, including the gene which coded for it9. Anti Mullerin Hormone (AMH) also known as Mullerian Inhibiting Substance (MIS) is a homodimeric glycoprotein linked by disulfide bonds and a molecular weight of 140Da .the hormone belongs to the Transforming Growth Factor (TGF-B) super family. The gene encoding AMH is located in the short arm of chromosome 19 .AMH action is exerted through two receptors: type1 receptor (AMHRI) and type2 receptor (AMHRII) which are present on the AMH target organs (gonads and mullerian ducts) 10.

 Anti Mullerian Hormone (AMH) play important role in the male sex differentiation as its production by the embryonic testis induce the regression of mullerian ducts11 .Deficient production of anti mullerian hormone or dysfunction of its receptor, result in differentiation of mullerian duct into oviducts, uterus and upper third of the vagina in genetic male embryos 12. During the female life until menopause it's secreted by granulosa cells of primary, secondary, preantral follicles and early antral follicles until they reach size 4-8 mm 13. Anti mullerian hormone expression disappears in follicles of increasing size almost lost in follicles larger than 8mm14.



Figure (1);

"Model of AMH action in the ovary. Progressing stages of folliculogenesis are depicted. 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 "15.

 Anti Mullerian Hormone has 2 main mechanisms of action in the ovary ; inhibition of initial recruitment of primary follicles from primordial follicles ,and inhibition sensitivity of antral follicles to follicle –stimulation hormone during cycle recruitment 16,thus preventing too early depletion of the ovarian follicular reserve .Both in vivo and in vitro experiments have indicated that the transition from primordial into growing follicles becomes enhanced by the absence of Anti Mullerian Hormone17. Sensitivity of growing follicles to FSH depend on expression of Anti Mullerian Hormone receptors , So ,out of the initial recruited follicle unit ,only those with lower Anti Mullerian Hormone expression become sensitive to Follicle Stimulating Hormone of which usually one is permitted for dominance .therefore Anti Mullerian hormone acts as autocrine factor that regulate the dominant follicle selection 18.

 On the other hand, Anti mullerian hormone is not formed in Follicle Stimulating hormone –dependent (antral) follicles and also in atretic follicles. Early antral follicles are the primary source of serum Anti mullerian hormone because they have higher number of granulosa cells compared with other follicles and have a better blood supply. The hormone passes in the blood and its level can be measured 19. The number of early antral follicles is directly related to the total size of the primordial follicles pool 20, with the decrease in the number of antral follicles that occurs with age, Anti Mullerian Hormone serum levels diminish .Therefore, Anti Mullerian Hormone as been suggested as ideal marker of assessing ovarian reserve 21.

***OVARIAN RESERVE***

 Is a term that is used to determine the capacity of the ovary to provide egg cells that are capable of fertilization resulting in a healthy and successful pregnancy .with advanced maternal age the number of egg cell that can be successfully recruited for a possible pregnancy declines, constituting a major factor in the inverse correlation between age and female fertility 22.

During fetal life, germ cells populate the ovary and become surrounded by somatic cells, forming the so called primordial follicles23. At birth, about 1 million oocytes are present, this number decrease during child hood, resulting in primordial follicle pool of 300 -500 follicles at menarche 24. Throughout life, follicles leave the primordial follicle pool to enter the growing pool. Folliculogenesis is the maturation of the ovarian follicle, a densely packed shell of somatic cells that contains an immature oocyte. Folliculogenesis describes the progression of a number of small primordial follicles into large pre ovulatory follicles that enter the menstrual cycle 25. The majority of these growing follicles will be lost as a result of atresia ,unless they are rescued by Follicular Stimulating Hormone( FSH) .This rescue by Follicular Stimulating Hormone (FSH) starts after puberty when the pituitary –gonadal endocrine axis has been activated .Among the cohort of rescue follicles ,only one follicle is selected to become the dominant follicle , which will ovulated under the influence of luteinizing hormone (LH)26. This process continues throughout life until the primordial follicle pool is exhausted and as a consequence , growing follicles are no longer present in the ovary ,resulting in menopause27 .

 In the years preceding menopause ,fertility already decreases and menstrual cycle irregular .this menopausal transition period precedes menopause by a fixed time interval 28,29 .

 In the western world ,menopause is reached at a median age of 51 years old .however ,there is a considerable individual variation in the age of menopause and subsequently ,also in the age of sub fertility 29,30 .Hence ,chronological age is a poor indicator of reproductive aging ,and thus of the ovarian reserve .While there is no known direct method for assessing the ovarian reserve of individual women 31 .indirect determination of ovarian reserve is important in the treatment of infertility 32.

 Most widely used ovarian reserve testes are Follicle Stimulating Hormone ( FSH) ,Anti Mullerian Hormone (AMH) ,and antral follicle count (AFC) .diminishing ovarian reserve is a phenomenon noted in women during mid to late thirties and at times earlier , reflecting the declining follicular pool and oocyte quality 33.

 Anti mullerian hormone (AMH) levels strongly correlated with basal antral follicle count measured by trans vaginal ultra sound 34. Unlike other biochemical markers ,it can be measured on any day of the cycle 35,36 ,and dose not exhibit inter cycle variability 37.Various threshold values 0.2 -1.2 ng\ml , have been used to identify poor responder with 80 -87 % sensitivity and 64 -93 % specificity 38,39. On the top of the age related decline in Anti Mullerian Hormone ,significant fluctuation has been reported for a number of condition and this to be taken into account when interpreting values in clinical practice 40 .

 **Factors affecting level of AMH**

1-Age: there is decrease in AMH with advancing age therefore serum AMH level may be considered as the best marker for aging of ovary and transition to menopause41.

2-It is increased in PCOS: female with PCOS show increase development of antral follicles in comparison with normal one42,43.

3-The relationship between BMI and AMH level is inversed44.

4-Ethnicity and race: it is found to be higher in Caucasians compared to Afro-American and Hispanics42.

5-Recent data has shown serum AMH level in oral contraceptive users lower 30-50%; whether used orally, vaginally or transdermal compared with those returned to natural cycle after stopped hormonal contraceptive44 .

**AMH VALUES:**

 Serum Anti Mullerian hormone level are in the literature usually given in the mass unit (ng/ml OR mg/L) ,or usage of international system of unit (pmol/l) .the converting factor is (pmol/L )= 7.14 \*(ng/ml) 45,46,47.

|  |  |
| --- | --- |
| 1-3 ng /ml | Normal  |
| 0.7-1 ng/ml | LOW NORMAL |
| 0.3-0.7 ng/ml | LOW |
| Less than 0.3 ng /ml | VERY LOW |
| More than 3 ng/ml | HIGH  |

Table (1) above show AMH interpretation guideline 48 .

**Aim of the study:-**

 To determine the level of serum AMH in relation to different age group in women in Basra .

**Patient ,material and method :-**

**1- Study population**

 Cross sectional study was conducted in Basra Maternity And Child hospital in Basra city during the period between first of January 2018 till the first of September 2019 .

The study include women with their age range between 15-50 years .

The exclusion criteria include the following conditions :-

 1-women with polycystic ovarian disease .

 2-wommen with previous history of ovarian surgery .

 3-women with history of radiotherapy or chemotherapy .

 4-women used contraceptive therapy or any medical therapy for induction of ovulation .

The studied women were divided into the following groups in regards to women's age ,

1- 15-20year 2-≥20-25year

3-≥25-30 year 4-≥30-35year

5-≥35-40year 6-≥40-45year.

7-≥45-50 year.

**2-Antimulerian hormone assay :**

 In the second and third day of a spontaneous menstrual cycle the blood samples were obtained by venipuncture . The serum AMH levels were measured by enzyme immunoassay using on AMH /MIS EIA kit ,which is a two immunological step sandwich type assay was from 0.14ng/ml to 21ng/ml. serum AMH values below the reported clinical level of measurement (0.14ng /ml) were treated as zero value for analysis .

**3-Statistical analysis :**

 Was performed using statistical package of social sciences (SPSS) 24 to determine the correlation between AMH and other variable , the data was analyzed by Pearson's correlation.

**Result:-**

 A total 975 healthy women were included in the study .

Table 1: the basal characteristics of each age group .

 Age groups

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ≥45-50Y | ≥40-45Y | ≥35-40Y | ≥30-35Y | ≥25-30Y | ≥20-25Y | 15-20Y | Variable |
| 135 | 140 | 145 | 135 | 145 | 140 | 135 | No. of cases  |
| 47 + 1 | 41 + 0.2 | 37 + 0.1 | 32 + 1.2 | 27 + 0.2 | 22 + 0.5 | 18 + 0.1 | Mean year +SD |
| 29 + 3.2 | 25 + 1.3 | 21 + 1 | 23 + 0.2 | 22 + 0.3 | 21 + 0.5  | 20 + 0.1 | BMI |
| 17.3 + 1.8  | 15.9 + 1.5  | 12.1 + 4.5 | 9.9 + 0.4 | 9.4 + 0.7 | 7.7 +0.3 | 7.5 + 0.2 | FSH mIu/ml |

The mean age group of 975 women was 34.4 + .

The mean level of serum FSH was 8.4+ 0.2.

 Table 2

Age specific mean and SD for serum AMH levels (ng/ml).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Yearly average decrement | Mean +SD | Range  | Number  | Age  |
| - | 4.9+2.6 | 4.6-15.2 | 135 | 15-20 |
| 0.7 | 4.25+1.5 | 3.9-14.5 | 140 | ≥20-25 |
| 1.2 | 3.27+2.1 | 2.9-10.21 | 145 | ≥25-30 |
| 1.13 | 2.43+2.5 | 1.83-8.4 | 135 | ≥30-35 |
| 0.66 | 2.17+3 | 1.21-5.71 | 145 | ≥35-40 |
| 0.52 | 1.95+2.5 | 0.631.23 | 140 | ≥40-45 |
| 0.35 | 0.9+3.1 | 0.13-0.9 | 135 | ≥45-50 |

 Serum AMH was obtained for all the women groups ,the mean and SD values were obtained for each group ,table 2 .

The AMH levels was inversely correlated with age .

Both range and mean with SD of AMH values decreased steadily in a manner highly correlated with advancing age .

The average yearly decrease in the mean serum AMH value was 0.2 mg /ml/year after 35 year.

Age (year)

Graphical comparison of AMH value in regard to age in 5 years interval .

**Discussion:**  The AMH immunoassay has been widely estimated in daily clinical practice ,and its widely performed during assisted reproduction and infertility treatment49.This cross –sectional study of Iraqi women from adolescence to menopause present a trend normogram of serum AMH in Basra .

 A large number of studies have described the correlation of serum AMH levels with age who proved that this hormone appears in the 36th week of gestation and increase continuously through puberty and remain constant until levels decrease after 25 year ,from age 25 there was an inverse correlation between AMH and age ,which becomes undetectable when menopause occur50. Thus ,serum AMH levels are considered to reflect the number of small growing follicles and are reduced through reproductive life49.

 Accordingly ,many studies have suggested that the serum AMH could be a novel ovarian reserve test. La Marca et al , study had confirmed that the inter cycle and intra cycle variability of serum AMH level is very low enough in fact to allow random timing of AMH measurement during the menstrual cycle . Hence ,it has been suggested that AMH values are more convenient and more effective than other serum ovarian reserve tests like FSH and inhibin B51.

 The present study represent serum AMH reference value in female in Basra regardless of fertility state which confirm that serum AMH levels decline with increasing age .However few studies reported reference levels for serum AMH values .recently Seifer et al 52 have examined age –specific serum AMH values for 17,120 women of reproductive age from 24 to 50 years old presenting to fertility centers with in the United States ,this study showed that the serum AMH levels decreased steadily with increasing age ,however this study depend on result of women with history of infertility only and thus were not representative of the general population ,in that study ,the age- specific mean were somewhat lower than our study .

 Barad DH et al ,in their study performed in the United States reported age –specific reference value of AMH which had been examined in 792 infertile women with in five age groups ,more than half in that study population had diminished ovarian reserve and premature ovarian failure ,that study presented lower mean and median AMH values than the our study53 .

 In Italy ,La Marca et al , evaluated a cohort of 277 women that had regular menstruation patterns they excluded women affected by confounding factors such as PCOS or a history of ovarian surgery .those with a given age group in that study had similar median AMH levels like in our study54 . In assisted reproductive technology ,several studies have demonstrated that serum AMH levels accurately reflect the total developing follicular cohort and predict ovarian response to controlled ovarian stimulation . In addition ,there have been many studies demonstrating that serum AMH is better marker in predicting the number of retrieved oocytes than the other serum marker55 .

 Serum AMH testing may also be performed as pre-operative and post-operative evaluation of ovarian surgery in younger women ,it was suggested that serum AMH is useful marker for evaluation reserve after ovarian surgery56 .

 Hagen CP et al , observed in his study that healthy female children have increasing AMH levels during early childhood and thereafter stable AMH concentration until early adulthood ,Also Hagen et al observed in his study ,in the general population up to 10% of women of reproductive age are affected by PCOS which in characterized by increased AMH level 57.

 In the our study only women with regular cycle were included and PCOS women were excluded .The variation of AMH levels may reflect the range in reproduction capacity and age of menopause which shows a similar large variation in normal women ranging from 40 to 60 year ,Indeed it has been shown that the age of menopause was more accurately predicted by serum AMH concentration than by chronological age58. It suggesting that AMH is capable of predicting age at menopause for a given women ,it may proposed that at any age women with AMH at upper limit of the normal range will enter menopause at a later age compared with women with AMH levels at the lower limit of normal range59 .

 Recent studies on women with regular cycles have remained in conclusive on the relation between serum AMH levels and FSH levels 60,in our study serum AMH and FSH level in women after 35 year old were negatively correlated .

 In addition ,the inverse correlation between AMH and age was stronger than that between FSH and age suggesting that AMH is a more accurate marker of ovarian aging than FSH 61.

**Conclusion:-**

1-it was the first study in Basra to document age specific AMH value .

2-there is inverse relation between age and AMH which will help in prediction of menopause and iatrogenic premature ovarian failure .

3-this study determined reference values of serum AMH in Basra .Which can be applied to clinical .evaluation and treatment of infertile women .

**Recommendations** :-

Future studies about age –specific reference value of AMH considering body mass index ,smoking ,race and ethnic group .

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جامعة البصرة

كلية الطب

قسم النسائية و التوليد

**صلة العمر بعامل AMH) )**

**antimullerian hormpne**

اعداد

 *د. دعاء فرج نور*

*بكاليوريوس طب و جراحة عامة*

دراسة مقدمة الى جامعة البصرة /كلية الطب/قسم النسائية والتوليد

ضمن متطلبات نيل شهادة الدبلوم العالي في النسائية والتوليد

اشراف

أ.د.ميسون شريف أ.د.غفران جعفر

استشارية النسائية والتوليد استشارية النسائية والتوليد

 العراق 2019

**الخلاصة**

**الهدف من الدراسة:**

لتحديد مستوى هورمون AMH في الدم عند النساء في البصرة بأعمار مختلفة .

**طريقة العمل:**

دراسة اجريت في البصرة مستشفى البصرة للنسائية والولادة من تاريخ /1/2018 1 ولغاية 1/9/2019.

تم قياس نسبة عامل AMH في الدم لمجموع 975 من النساء اللاتي تتراوح اعمارهن بين 15-50 سنة ,قسمت الى 7 مجاميع حسب العمر

 (1) 15-20سنة (2) ≥20-25 سنة

 (3) 30- 25≤ سنة (4)35 -30 ≤ سنة (5)40- 35 ≤ سنة (6)45-40 ≤ سنة (7)50-45 ≤ سنة

قياس هورمون AMH و FSH بالطريقة الانزيمية المرتبطة , بعد استثناء بعض النساء بخصائص معينة .

**النتائج :**

مستوى AMH في الدم يتناسب عكسيا مع العمر .متوسط مستوى AMH

لكل فئة عمرية هو , 4.25ng/ml ,4.9ng/ml ,3.27 ng/ml2.

,2.43ng/ml ,2.17ng/ml ,1.95ng/ml 0.9ng/ml على التوالي .

 **الاستنتاج :**

هذه الدراسة تحدد القيمة المحلية لهرمون AMH للنساء في البصرة ,النتائج ممكن ان تستخدم في تشخيص و علاج العقم .