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RELATIONSHIP BETWEEN OBESITY AND ANTI MULLERIAN HORMONE IN WOMEN ABOVE (35) YEARS OLD

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ABSTRACT

Objective: To study the relationship between obesity and anti mullerian hormone as a serum marker of ovarian reserve in women above age 35 years. **Methods:** This study was conducted in the infertility center in Basrah Maternity and Child Hospital. One hundred women included in the study which were divided into 2 age groups of late pre-menopausal phase; 50 women (obese) (group A) had a Body Mass Index (BMI) more than 30 kg /m^2 and the other 50 women (non-obese) (group B) had BMI less than 30 kg /m^2. Anti mullerian hormone was measured by ELIZA method. **Results:** The obese women group(A) had a mean age of (39.9±2.7) years and non obese women group (B) had a mean age of (39±2.7) years. The anti mullerian Hormone level in group A(Obese) was (1.4±0.4) which it was significantly lower as compared to group B (non-Obese) (2.4±0.4) {P<0.01}. Body Mass Index is also negatively correlated with serum anti -mullerian hormone. **Conclusion:** Obese women have lower anti mullerian hormone levels compared to non obese women in the late reproductive years indicating that obesity is likely to have an affect on ovarian reserve in the pre-menopausal age group.

KEYWORDS: Anti Mullerian, Obesity, Infertility.

INTRODUCTION

Anti-mullerian hormone, also known as mullerian inhibiting substance. The hormone belongs to the Transforming Growth Factor-B (TGF-B) super family. Anti mullerian hormone has 2 main mechanisms of action in the ovary: inhibition of initial recruitment of primary follicles from primordial follicles, and inhibition the sensitivity of antral follicles to follicle-stimulating hormone during cyclical recruitment [1], Thus, preventing too early depletion of the ovarian follicular reserve.

Early antral follicles are the primary source of serum anti-mullerian hormone because they have higher numbers of granulosa cells compared with other follicles and have a better blood supply. The number of early antral follicles is directly related to the total size of the primordial follicles pool.[2] The decrease in the number of antral follicles that occurs with age, anti Mullerian hormone serum levels also diminish. Therefore, anti Mullerian hormone has been suggested as ideal marker of assessing ovarian reserve.[3]

Most widely used ovarian reserve testes are follicle stimulating hormone (FSH), anti- mullerian hormone and antral follicle count. 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.[4]

Obesity continues to be epidemic throughout the world with a proximately two thirds of adults being either over weight (BMI>25Kg/M^2) or obese (BMI>30Kg/M^2).[5] Contributions of obesity to infertility and to poor *in vitro* fertilization (IVF) outcomes are well recognized. Furthermore, obese women have been shown to have impaired response to ovarian stimulation and significantly lower live births after IVF.[6] Indeed ,obesity is associated with ovarian intra follicular alteration at multiple cellular levels including steroidogenic metabolic and inflammatory pathways [7]

Fat cells synthesize leptin and then adiponectin which they regulate the female reproductive system at all levels of the hypothalamic –pituitary- ovarian axis. Granulosa cells in the ovaries have receptors for both adiponectin and leptin.[8,9] Recent data have revealed that adiponectin causes an increase in Insulin-Like Growth Factor-1(ILGF_1) induced steroid release by human granulose cells while leptin inhibit this effect.[9,10] Therefore, alteration in these adipokines in the context of obesity may counteract the sensitivity effect of locally produced growth factors on granulose cell. Additionally, there is *in vitro* evidence that leptin may have a function on steroidogenesis.[11]

Thus, the aim of this study is to investigate the effect of obesity on the ovarian reserve among women during late

reproductive age by estimating the serum level of anti mullerian hormone as serum marker of ovarian reserve.

Patients and Methods

This study was conducted in the infertility center in Basrah Maternity and Child Hospital during the period between October 2013 till October2015. All women who involved in the study accepted participation.

Fifty women with Body Mass Index (BMI) of 30-35kg/m^2 regarded as obese group (A). fifty women after matching in regard to age with group A, their body mass index (BMI less than30kg/m^2) as group B (non–obese women).

The inclusion criteria included all women in the early transition phase of the late premenopausal state. According to the staging system for reproductive aging in women this phase is characterized by regular menstrual cycles between 22 and 35 days, with variability in cycle length 7 days in either direction compared with patients baseline and observed for at least two cycles with intact uterus and ovaries and to have had regular menstrual cycles for the previous three months.

The exclusion criteria were current use of hormone or drugs that may have an affect on ovarian function, smoking, pregnancy, lactation, hysterectomy, previous ovarian surgery, polycystic ovarian syndrome and endometriosis.

All women underwent a comprehensive history and thorough physical examination. BMI was calculated by measuring height and weight using the same scale. Blood samples were withdrawn from the patients on the cycle day 2, 3, 4, 5 of the menstrual cycle. Blood samples were centrifuged for 15 minutes and the separated sera were stored at -20^o C until assayed by ELIUZA method. Linear regression analysis was used to measure the association between BMI and anti mullerian hormone.

RESULTS

The women in group A (obese women) had a mean Body Mass Index (BMI) of (35.8±3.8kg/ m^2) with a range of 31 - 49kg/ m^2. The women in group (B) (non obese women) had a mean BMI of (25.5±1.6kg/ m^2) with a range of 23 - 29kg/ m^2. The relationship was significantly significant ($p<0.01$).

The mean age in the obese group was 39.9 years with a range of 36 - 45 years old. The mean age in the non obese group was 39.7 years with a range of 36 - 45 years old. There was no significant difference between two groups regarding age.

Anti mullerian hormone level in group (A) was (1.4±0.4ng/ml) which was significantly lower as compared to group (B) (2.4± 0.4ng/ml).

Body Mass Index is also correlated with serum anti mullerian hormone level which was significantly negative.

Table. 1: Anti mullerian hormone in relation to obese and non-obese women.

Parameters	Group(A) Obese N=50	Group(B) Non – obese N=50
Age (years)	39.9	39.7
Body Mass Index (Kg/ m^2)	35.8±3.8	25.5±1.6
Anti mullerian hormone (ng/ml)	1.4±0.4	2.4±0.4

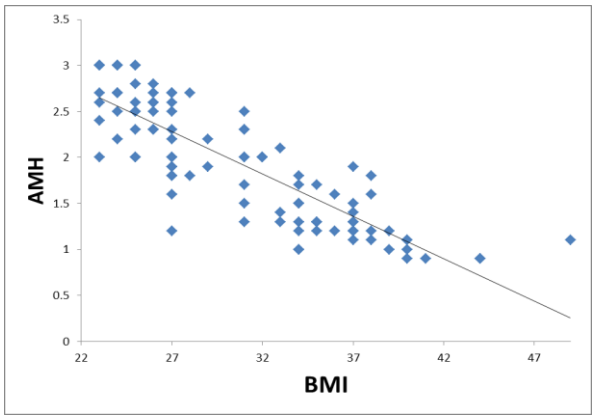

Figure. 1: Correlation between Anti mullerian hormone (AMH) levels (ng/ml) and Body Mass Index (BMI) (Kg/ m^2).

DISCUSSION

The result of this study showed that decreased ovarian reserve is not the direct cause of lowered anti mullerian hormone in obese, regular cycling, late –reproductive – aged women. [12]

In published data, serum and ovarian measures of decreased ovarian reserve do not show consistent changes with body size. One explanation for this lack of consistency is that these measures are not ideal surrogates of ovarian reserve. Alternatively, body size may alter hormone production at the level of the ovary , increase sequestration or elimination of serum hormones. For example the observation that adiponectin modulates ovarian steroid genesis in conjunction with insulin and gonadotropins provides indirect evidence that obesity alters ovarian hormonal synthesis. These data suggest that lower anti mullerian hormone levels in obese, late reproductive women result from physiologic processes other than decreased ovarian reserve.[13]

A negative effect of obesity on Anti Mullerian Hormone levels have been found in relation to ovarian reserve.[14] In reproductive age women, serum anti mullerian

hormone levels do not appear to fluctuate during oral contraception use, but anti mullerian hormone levels were significantly lower in obese women. Lower Levels do not appear to be due to differences in gonadotropin levels or ovarian activity.[15]

The Anti Mullerian Hormone level was positively related to the 2-5mm size follicle number but not to 6-9mm size follicle number at ultra sonogram in polycystic ovary syndrome. That would suggest the increase of anti mullerian hormone serum level in polycystic ovary syndrome is the consequence of the androgen –induced excess in small antral (2-5) mm size follicle numbers and that each follicle produces a normal amount of anti mullerian hormone.[16]

It has been demonstrated that serum anti mullerian hormone level do not change significantly throughout the menstrual cycle.[17] It is produced by follicles and thus serum levels may be used as a marker for ovarian reserve, representing the quantity and quality of the ovarian follicle pool.[18]

It has been observed that the concentration of anti mullerian hormone decreased over time in young normo ovulatory women whereas other markers as the number of antral follicles, inhibin B and FSH did not changes.[19] Over weight and obese fertile women without any signs of hyper androgenism have lower FSH, luteinizing hormone (LH), Inhibin B and estradiol levels in the early follicular phase (day 2- day 5 of menstrual cycle). Also, there is a possible direct inhibitory effect of body mass on the gonadotropin and estradiol production, independently of age, insulin {concentration and sensitivity} and other hormones. In contrast, the number of ovary follicles do not seems to be influenced by insulin and BMI in these patients.[20]

In over weight and obese women with polycystic ovary syndrome and reproductive dysfunction the effect of weight loss and calories restriction result in improvement in reproductive function but no changes in the anti mullerian hormone level.[21] It has been documented that lower level of anti mullerian hormone in obese late reproductive age women result from physiological processes other than decreased ovarian reserve.[22,23] Furthermore, Samir et al [24] showed that obesity has no association with levels of serum FSH, anti mullerian hormone, blood glucose or antral follicle count indicating that obesity is unlikely to have an effect on ovarian reserve in the premenopausal age group.[24]

Zaidi and his colleagues [25] showed that ovarian volume decreases with an increase in the BMI, indicating the possible decrease in fertility which reveal the effect of age rather than BMI. However, overian volume did not differ by body size according to another study.[23] The different findings could be related to different population characteristics and different techniques used to measure and calculate the ovarian volume which is less accurate among obese women because of restricted ultrasound imaging.

In a study conducted in Tehran where 115 fertile women were included of different age group (25-45) years, they found that antral follicle count had the best correlation with age, followed by total ovarian volume, FSH and FSH/LH. The correlation of ovarian reserve markers with age is more significant. Hence, it is a better predictor for ovarian response than BMI.[26] In Multivariate analysis, after adjustment of age, it has been found no association between BMI and ovarian reserve.

Anti Mullerian hormone is highly predictive for timing of menopause Using age and anti mullerian hormone ,the age range in which menopause will subsequently occur can be individually calculated.[27]

Several studies findings clearly showed that anti mullerian hormone and age are strange and independent predictors of time to menopause than either variable alone. The study also has confirmed great relationship between smokers and menopause age, but obesity had no significant association with time to menopause.[27]

Two studies have shown that obese women have lower ovarian reserve than normal weight women. This is reflected by their lower serum anti-mullerian hormone level (up to 77% lower), suggesting that obesity may impair granulosa cell hormone production.[28,29] In addition, obese women have elevated serum and follicular fluid leptin levels and suppressed serum and follicular fluid adiponectin levels.[8]

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