Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2014; 2(3D):1114-1118 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2014.v02i03.050

Research Article

To Study the Relationship between Obesity and Anti-Mullerian Hormone: As a Serum Marker of Ovarian Reserve In premenopausal Women

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Abstract: This study was performed with an objective to study the relationship between obesity and AMH as a serum marker of ovarian reserve in premenopausal women. We performed a cross-sectional comparative study of two age-matched groups of late premenopausal participants: 50 participants ("non-obese") had a BMI < 30 kg/m^2, and the other 50 participants ("obese") had a BMI of 30 to 35 kg/m^2.The obese women had a mean age of 42.7 years and the non-obese women had a mean age of 43.1 years. Blood samples were collected from all participants and anthropometric measurements were calculated. The blood samples were assayed for antimüllerian hormone (AMH). The AMH level in group A (Obese) was 1.2 $\pm$ 0.2 ng/ml which was significantly lower as compared to group B (Non-Obese)1.7 $\pm$ 0.5 ng/ml ($p< 0.01$).BMI is also significantly correlated with serum AMH level ($r = - 0.531$, $p< 0.01$). In conclusion, there was significant difference in serum levels of AMH between obese and non-obese women indicating that obesity is likely to affect ovarian reserve in the premenopausal age group.
Keywords: Premenopausal, Anti-Mullerianhormone (AMH), Obesity, Body Mass Index (BMI), Women, Ovarian reserve

INTRODUCTION

Anti-Müllerian hormone also known as AMH is a protein that in humans is encoded by the AMH gene [1]. It inhibits the development of the Müllerian ducts (paramesonephric ducts) in the male embryo [2]. It has also been called Müllerian inhibiting factor (MIF), Müllerian inhibiting hormone (MIH), and Müllerian-inhibiting substance (MIS). It is named after Johannes Peter Müller.

AMH is a protein hormone structurally related to inhibin and activin and is a member of the transforming growth factor-β (TGF-β) family. It is a homodimeric glycoprotein linked by disulfide bonds and a molecular weight of 140kDa [3].

In healthy females AMH is either just detectable or undetectable in cord blood at birth and then shows a marked rise by three months of age; while still detectable it falls until four years of age before rising linearly until eight years of age remaining fairly constant from mid-childhood to early adulthood - it does not change significantly during puberty; from 25 years of age AMH declines to undetectable levels at menopause [4].

AMH is expressed by granulosa cells of the ovary during the reproductive years and controls the formation of primary follicles by inhibiting excessive follicular recruitment by Follicular Stimulating Hormone (FSH). Therefore it has a role in folliculogenesis and some authorities suggest it is a measure of certain aspects of ovarian function, useful in assessing conditions such as polycystic ovary syndrome and premature ovarian failure [5-7].

In a global survey it was found that more than 30% of women in the group aged 25 to 44 years are overweight (BMI 25 to 30 kg/m^2), and 20% are obese [8].

Obese women have increased incidence of conditions such as diabetes mellitus, hypertension, cardiovascular disease, pancreatitis, and musculoskeletal diseases and also obese women are more likely to havereproductive problems [9].

Obese women are known to be at higher risk of menstrual dysfunction and an ovulation, possibly due to altered secretion of pulsatile gonadotropin releasing hormone (GnRH) [10]. Obese women those having regular menstrual cycles also found to have reduced fecundity [11].

The term "ovarian reserve" refers to the quantity and quality of a woman's current reservoir of oocytes. It is closely associated with reproductive potential and can be used to determine woman's reproductive age indirectly [12].

In women who are undergoing assisted reproductive technology and are obese or overweight has been associated with a need for higher doses of gonadotropins, increased cycle cancellation rates, and fewer oocytes retrieved than in women of normal weight [13]. Lower rates of pregnancy and live birth have also been reported in these women with higher miscarriage rates [13, 14]. However, other studies have not found any negative effect of obesity on assisted reproductive technology (ART) out-come [15, 16].

Various tests have been performed over the last twenty years for assessing ovarian reserve and to determine follicle number and quality and also to predict the outcome of assisted reproduction procedures [17].

The earliest and most useful parameters used for evaluation of ovarian reserve include woman's age and assays of serum FSH in the early follicular phase [18, 19]. For evaluation of ovarian reserve, including ovarian volume various ultra-sound parameters are also used [20, 21] and the antral follicle count, with varying degrees of reliability [22, 23].

Recently, serum antimüllerian hormone levels have been introduced as a novel measure of ovarian reserve. La Marca *et al*. showed that serum AMH levels, unlike other ovarian reserve tests, do not change significantly throughout the menstrual cycle [24]. Other studies have also confirmed that the intercycle and intracycle variability of serum AMH levels is very low enough, to allow random timing of AMH measurement during the menstrual cycle. Hence, it has been suggested that serum AMH values are more convenient and more effective than other serum ovarian reserve tests like FSH and inhibin B or estradiol [6].

AMH is a product of the granulosa cells in preantral and antral follicles [25]. Serum AMH levels decline with age and are correlated with the number of antralfollicles and the ovarian response to hyperstimulation [26, 27]. Few studies have evaluated the effect of obesity on ovarian reserve. Some studies have identified lower serum AMH levels inobese women than in non-obese women [28, 29].

We conducted the present study to examine the effect of obesity on ovarian reserve in women in the late reproductive age group. We assessed the effect of obesity on serum marker AMH for determining ovarian reserve.

MATERIALS AND METHODS

This study was conducted in the Department of Obstetrics and Gynecology, PGIMS Rohtak between June 2013 and June 2014. All participating women gave written informed consent before beginning the study. We included 50 participants with a BMI of 30 to 35 kg/m^2 (group A, obese women) and 50 age-matched participants with BMI < 30 kg/m^2 (group B, non-obese women) serving as control group.

All the women were 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 of between 22 and 35 days, with variability in cycle length 7 days in either direction compared with patient's baseline and observed for at least two cycles [30].

To meet the inclusion criteria women had to be in the late premenopausal stage with an intact uterus and ovaries and to have had regular menstrual cycles for the previous three months.

Exclusion criteria were current use of hormones or drugs that may affect ovarian function, smoking, pregnancy, lactation, hysterectomy, previous ovarian surgery, clinical or ultrasound criteria suggesting polycystic ovarian syndrome or endometriosis, or any medical condition that might affect ovarian function.

All participating women underwent a comprehensive history and thorough physical examination and calculation of BMI, assays of AMH. For calculation of BMI, height and weight were measured using the same scale for all participants. Blood samples were withdrawn from the antecubital vein on cycle day 2, 3, 4, or 5 of the menstrual cycle in all women. All samples were centrifuged at 2000 g for 15 minutes. Serum was separated and stored at –20 °C until assayed.

Serum levels of AMH were determined by a The Ultra Sensitive Anti-Mullerian hormone/ Mullerian inhibiting substance (US AMH/MIS) enzyme linked immunuosorbent assay (ELISA).

RESULTS

The 50 women in group A (obese women) had a mean BMI of 32.5 ± 1.2 kg/m^2, with a range of 30.4 to 34.6 kg/m^2, and thenon-obese women had a mean BMI of 25.5 ± 2.2 kg/m^2, with a range of 22.1 to 29.2 kg/m^2. The mean age in the obese group was 42.7 years with a range of 37 to 45 years. The mean age in the non-obese group was 43.1 years with a range of 37 to 45 years. The mean BMI in the obese group (32.5 ± 1.2 kg/m^2) was significantly higher than that of the non-obese group (25.5 ± 2.2 kg/m^2) ($P < 0.01$). There was no significant difference between the two groups regarding age.

The AMH level in group A was 1.2 ± 0.2 ng/ml which was significantly lower as compared to group B 1.7 ± 0.5ng/ml ($p< 0.01$). These data are shown in the table 1.

BMI is also significantly correlated with serum AMH level ($r= - 0.531$, $p< 0.01$). Fig. 1 demonstrates the correlation between serum AMH and BMI.

Table 1: BMI and AMH Levels

Parameter	Group A	Group B
Age	50	50
BMI (kg/m^2)	32.5 ± 1.2	25.5 ± 2.2
AMH (ng/ml)	1.2 ± 0.2	1.7 ± 0.5

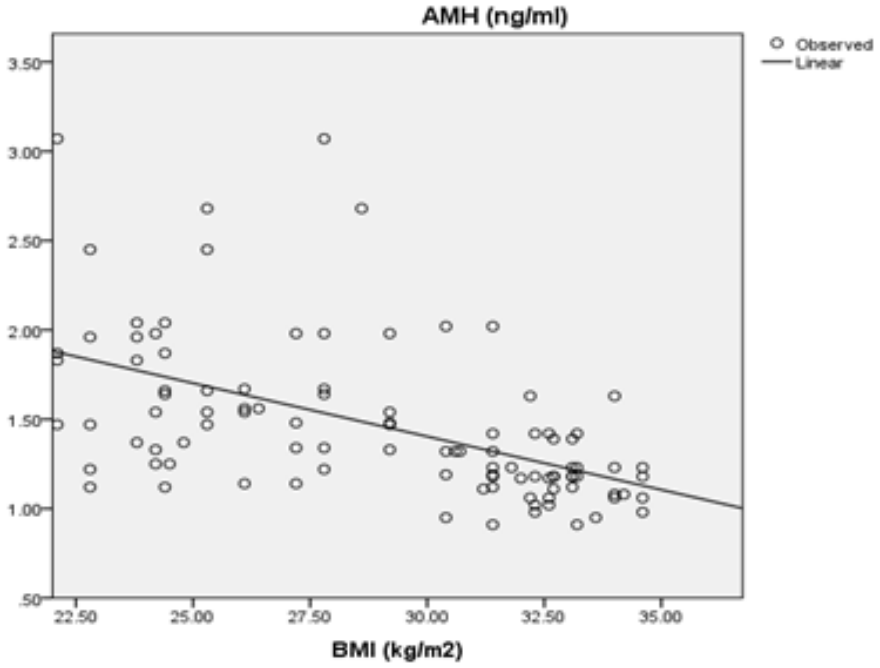

Fig. 1: Correlation between serum AMH and BMI

DISCUSSION

During the menopausal transition changes has been reported in the body fat and its distribution but the health-related implications for these body composition changes are ill-defined [31]. It remains to be determined if the change in body fat will affect the endocrine milieu of women in the late reproductive age.

Our study was designed to explore the effect of obesity on serum AMH (which denotes a marker of ovarian reserve) in late reproductive age women, because of a possible effect of obesity on folliculogenesis [32, 33]. Several studies have suggested a negative effect of obesity on parameters of ovarian reserve.

Other investigators reported lower levels of AMH in obese women compared with normal weight women in the late reproductive age [28, 29].

Our results showed significant difference in serum levels of AMH between obese and non-obese women. There was a significant correlation between BMI and serum AMH level. Accordingly, we are suggesting that obesity may have effect on ovarian reserve in late reproductive age women. The fact that our results showed effect of obesity on serum AMH levels, is similar to many other studies [29].

Our study group of obese women was limited to women with a BMI between 30 and 35 kg/m^2. We did not include morbidly obese patients because we thought that this specific group of women may have a different endocrine profile that may not apply to women with lesser obesity.

Our study showed a significant effect of obesity on AMH (a marker of ovarian reserve), which has been suggested by other investigators who have also reported lower levels of AMH in obese women compared with normal weight women in the late reproductive age [29].

Freeman *et al*. recently provided Effect of Obesity on Parameters of Ovarian Reserve in Premenopausal Women 28 and suggested a negative effect of obesity on AMH levels. In a study of women with polycystic ovary syndrome by Pigny *et al*. [34], the AMH levels were lower in obese than non-obese women, though not

statistically significant. These data may support our findings. However, these studies documented that obesity had no effect on ovarian follicle count. They suggested that lower levels of AMH in obese late reproductive age women result from physiologic processes other than decreased ovarian reserve [28, 29, 33].

In addition to these, several studies have suggested a negative effect of obesity on other than serum AMH. De Pergola *et al*. suggested that overweight and obese fertile women, in comparison with women of normal weight have lower serum levels of FSH, LH, inhibin B and estradiol in the early follicular phase [33]. This may support lower level of AMH in obese women.

CONCLUSION

We conclude that there is a significant decrease in serum AMH level with increase in BMI in late premenopausal women. Serum AMH levels correlated negatively with BMI. AMH being a marker of ovarian reserve and BMI being a marker of obesity, our study shows, there exists a significant effect of obesity on ovarian reserve among premenopausal women. However, this should be verified by larger studies with clear distinctions between normal, overweight, obese, and morbidly obese women, and between groups of different age and menopausal status.

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