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Relation of Anthropometric Measures and Insulin Resistance with Antimullerian Hormone in Premenopausal Women

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Research Article

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Abstract

Background: It has been suggested that obesity is associated with decreased level of antimullerian hormone (AMH) which considered as a good marker of ovarian reserve.

Aim: The aim is to evaluate the association between obesity and AMH and whether there is relation of the anthropometric measures and insulin resistance with the level of AMH in Egyptian premenopausal women.

Subjects and Methods: Eighty premenopausal women with BMI more than 30 (obese group) and 80 age-matched healthy lean women (control group). BMI, waist circumference (WC), blood pressure (BP) were measured. Fasting blood glucose (FBS), fasting insulin (FI), insulin resistance (HOMA-IR), high sensitive C-reactive protein (hs-CRP) and AMH were analyzed.

Results: AMH levels in obese group were significantly lower than control group. There were significant negative correlations between each of BMI, WC, FBG, hs-CRP, FI and HOMA-IR with AMH ($r = -0.214, -0.226, 0.141, -0.264, -0.241$ and -0.258 respectively) (all p values ≤ 0.05). With forward stepwise linear regression analysis we found that HOMA-IR was significantly and independently related to AMH; (B = - 0.172; 95% CI -0.273: -0.071).Furthermore, HOMA-IR was confirmed to be an independent predictor of AMH after adjustment of age and BMI; (B = - 0.173; 95% CI – 0.274; - 0.072) and also by adjustment of age and WC; (B= -0.135 95%CI -0.268; -0.001).

Conclusion: Obesity and insulin resistance are associated with decreased ovarian reserve among Egyptian premenopausal women.

Keywords: Anti-mullerian hormone; Obesity; Ovarian Reserve; Premenopausal Women

Introduction

Obesity is a worldwide epidemic problem with higher prevalence rate in women [1]. It is associated with the risk of cardiovascular disorders [2], diabetes mellitus [3], stroke [4] and other co morbidities. Moreover, obesity has an impact on reproductive health in women, where it is linked to low rate of pregnancy [5-8] and poorer outcomes in vitro fertilization (IVF) [9]. Moreover, in comparison to lean women, those with obesity have decreased responses to medications of fertility, fewer number of oocytes retrieved [10], and higher risk of

maternal and infant complications [11].

Antimullerian hormone (AMH) is a peptide hormone related structurally to inhibin hormone and considered as a member of the transforming growth factor-beta family [12]. It is also known as mullarian inhibiting factor which has a role in sex differentiation in male, while in females it is secreted postnatal by the ovarian follicles, hence It has an important role in folliculogenesis [13,14]. It is unlike other ovarian tests not change significantly throughout menstrual cycle14), otherwise it is decreased with aging [13]. Some authorities suggest its measurement to assess premature ovarian failure and polycystic ovary syndrome [13,14], moreover, AMH appears to be a strongest and earlier predictor of number of oocytes retrieved during IVF cycle outcome [15].

It has been suggested that obesity is a factor that reduces AMH, however, there are conflicting results concerning this issue as some studies have been reported an inverse relation between obesity and AMH [16-19], while others have failed to clarify such association [20-22]. Because of epidemic prevalence of obesity in Egyptian women and the discrepancies in literatures concerning the association between obesity and AMH, the aim of our study is to investigate the relation between obesity and AMH and whether there is correlation of obesity related components such as BMI, WC, FBG, hs-CRP and insulin resistance with AMH levels among Egyptian premenopausal women.

Methods

Subjects

A total of 160women were included in this study at the age of reproduction (25 to 35); 80 with BMI more than 30 (obese group) and 80 lean females (control group). Obese premenopausal women were recruited from Obesity Clinics in Diabetes and Endocrinology Unit at Specialized Medical Hospital, Mansoura University, Faculty of Medicine, Mansoura City, Egypt, during the period from November 2016 to December 2017. Healthy controls were recruited from the same locality and with the same exclusion criteria of the study group. Informed consents were obtained from all women before they participated in the study, which was approved by the ethical committee of our institution. The inclusion criteria were premenopausal women with regular menstrual cycles for previous three months. Exclusion criteria were current use of OCPS or drugs that may affect ovulation, smoking, pregnancy, lactation, thyroid disorders, previous ovarian or uterine surgery and clinical or ultrasonic criteria of polycystic ovary.

Medical History and Physical Examination

All participants were subjected to thorough history taking and clinical examination. Anthropometric measures including height, weight, body mass index (BMI) and waist circumference (WC) were obtained using standardized techniques; height was measured to the nearest 0.5 cm, body weight was measured to the nearest 0.1 kg, BMI was calculated as weight in kilograms divided by height in meters squared (kg/m2), WC was measured at the highest point of the iliac crest. Blood pressure was taken in the sitting position after 10 minutes rest using a random-zero sphygmomanometer.

Biochemical Assay

Fasting serum samples were used for FBG level measurements according to the method of Trinder [23]. Determination of serum insulin was performed using ELISA kit, according to the method of Hwang, et al. [24]. The kit was provided from Diagnostic System Laboratories. Inc. Corporate Headquarters, 445 Medical center Blvd. Webster, Texas 77598-4217 USA.

Insulin sensitivity in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated with the following formula: fasting plasma glucose (mmol/L) ×fasting serum insulin (μU/mL) divided by 22, as described by Matthews, et al. [25] high HOMA scores denotes insulin resistance. The plasma samples were stored at -20C until used for the followings: Quantitative determination of hs-CRP was performed according to the method of Muller, et al. [26] using kits purchased from spin react, S.A. (Saint Estere de bas, Spain).

Hormonal Assay

Serum AMH was measured using the pico AMH ELISA (lower limit of detection 0.0016 ng/mL, 1 ng/mL 5 7.14 pmol/L) (Ansh Labs, Webster, TX). Samples were run at a 1/10 dilution, then neat for the samples that were low. AMH values that were below the lower limit of detection (n 5 3) were assigned a value of 0.0011 ng/mL using an established formula [27]. The AMH ELISA has intra- and inters assay coefficients of variation (CVs) of 6.9% and 6.5%, respectively.

Statistical Analysis

All analysis were done using SPSS version 20 for windows. A tailed P value less than 0.05 was considered significant. Continuous data presented as mean ± SD. Comparative analysis between two study groups was done using Student *st*- test. All correlations were done using person correlation test. Association between clinical

and biochemical parameters of obesity and AMH was done using forward stepwise linear regression analysis using predictors that found to be significantly related to AMH in correlation tests. Association between each of FBG, FI and HOMA-IR with AMH was done in other linear regression models after adjustment of age, BMI and WC.

Results

Table 1 illustrates that BMI, WC, hs-CRP, FI and HOMA-IR were significantly higher in obese group than control. While AMH level was found to be significantly lower in obese women than the non- obese (p value <0.05). There was a significant negative correlation between each of BMI, WC, hs-CRP, FI and HOMA-IR as predictors and AMH as an outcome (all p value <0.05), Table 2.

By using BMI, WC, hs-CRP, FI and HOMA-IR as outcome, forward stepwise linear progression analysis showed that only HOMA-IR was significantly and independently related to AMH (B 95%CI)=3.4(-1.2-.3) P value=0.001. Table 3 demonstrates that there is no significant association between FBG and AMH even after adjustment of age and body fat components (BMI and WC), (all p values≤ 0.05). There is a significant negative association between FI and AMH after adjustment of age and BMI; however this association became insignificant after adjustment of WC (p value ≥ 0.05). HOMA-IR is found to be a significant negative predictor of AMH after adjustment of age and body fat parameters (either BMI or WC), (p value ≤0.005).

Parameters	Obese group NO =80	Control group NO =40	P Value
Age (years)	31.1 ± 4.5	31.1 ±3.1	0.569
S.B.P. (mmHg)	115.8 ± 14.2	117.3 ± 15.2	0.281
D.B.P. (mmHg)	75.6 ± 9.0	74.4 ± 9.5	0.444
BMI (kg/m2)	36.1 ± 3.3	21.7 ± 1.8	<0.001
W C	104.2 ± 14.5	86.3 ± 5.5	<0.001
F.B.G mg/dl	99.3 ± 15.1	95.6 ± 9.3	0.067
hs-CRP	3.6±1.1	2.3±0.7	<0.001
FI (miu/l)	11.9 ± 3.6	6.7 ± 1.2	<0.001
HOMA-IR	1.9 ± 0.8	1.5 ± 0.3	<0.001
AMH(ng/ml)	2.6+0.7	3.2+0.8	< 0.001

Table 1: Characteristics of study groups
Values expressed as means±SD.
*p significant < 0.05.

Predictors	r	P
BMI (kg/m2)	-0.214	0.007
W C	-0.226	0.004
FBG (mg/dl)	-0.141	0.075
hs-CRP	-0.264	0.001
FI	-0.241	0.002
HOMA	-0.258	0.001

Table 2: Correlation between AMH and other variables
P≤ 0.05, significant correlation

Predictors	B (95% CI)	P value
F B G - Mode 1 - Mode 2 - Mode 3	 - 0.008 (- 0.01b:0.001) - 0.007(- 0.016:0.001) - 0.005 (- 0.014:003)	 0.075 0.078 0.211
FI - Mode 1 - Mode 2	 - 0.043 (- 0.07: - 0.0016) - 0.043(- 0.071:-0.016)	 0.002 0.002

- Mode 3	- 0.031 (- 0.067:- 0.005)	0.088
HOMA		
- Mode 1	- 0.172 (- 0.273:- 0.071)	0.001
- Mode 2	- 0.173(- 0.274:- 0.072)	0.001
- Mode 3	- 0.135(- 0.268:- 0.001)	0.048

Table 3: Association between metabolic parameters and AMH
- Mode 1; adjusted for age
- Mode 2; adjusted for age and BMI
- Mode 3; adjusted for age and WC

Discussion

This cross-sectional study was designed to investigate the association between obesity and AMH, a marker of ovarian reserve, and whether various anthropometric measures are correlated with its level.

The main finding in our study was a significantly lower AMH level in the study group of obese premenopausal women than those with normal weight (control group). The results also demonstrate a significant negative correlation between BMI, WC, hs-CRP, FI and HOMA-IR as predictors and AMH as an outcome (all p value <0.05), however, HOMA-IR only is found to be a significant negative predictor of AMH after adjustment of age and body fat parameters (either BMI or WC), (p value ≤0.005).

Many studies supported the effect of increased BMI on AMH as freeman et al. who showed that level of AMH decline more than 65%in obese women [28], also this result parallel those of Skalbaetal and Buyuk et al. who found a significant negative relationship between BMI and level of AMH [29,30]. Moreover, De Pergola, et al. [31] suggested that overweight and obese fertile women have lower serum levels of FSH, LH, inhibin and estradiol in the early follicular phase and this may support the finding of lower levels of AMH. In addition, some researches demonstrated improvement in reproductive function which was associated with significant decrease in level of AMH following 6 months treatment with metformin for weight loss [32].

Our finding as regard relation between BMI and AMH was in contrast to Sahmay, et al. [33] who showed negative but insignificant relation between BMI and AMH levels. Nardo, et al. and Halawaty, et al. have reported insignificant relationship were found between BMI and circulating AMH level in a cross-sectional study that included 100 premenopausal women [34,35]. Indeed, the association between obesity and AMH primarily derived from studies of women at reproduction with polycystic ovary syndrome (PCOS), where it was found that AMH levels did not appear to vary significantly by body size [36,37]. However, among control women without PCOS, BMI was inversely associated with AMH levels.

The mechanism underlying the inverse relationship between obesity and AMH is not entirely clear, a number of theories have been proposed to further explain this relationship. It is possible that insulin resistance in individuals with obesity acts on granulosa cells and consequently alters AMH concentration [38]. There may also be lipotoxic effects on the granulosa cells [39]. It is also suggested that leptin and adiponectin are involved in modulating ovarian function as these adipokines play a role in reproductive processes by way of the hypothalamic-pituitary-ovarian axis [38]. Another possibility is that AMH may be metabolized, stored, and cleared in a different way among subjects with obesity [39].

In our study, the etiology for lower AMH levels among the obese group could not be explored; however we support the suggestion that obesity may create an altered follicular environment. Furthermore, this study demonstrate a significant negative correlation between obesity related parameters; BMI, WC, hs-CRP, FI and HOMA-IR as predictors and AMH as an outcome, however, HOMA-IR only is found to be a significant negative predictor of AMH after adjustment of age and BMI and WC.

Current reports about the relation between insulin resistance and AMH levels are conflicting and heterogeneous especially during the premenopausal age, with some indicating presence and others absence of a correlation between both of them. Published studies of insulin resistance and CRP and ovarian markers are largely limited to investigations of PCOS [29].

In line with our findings, Verit, et al. [40] showed that increased CRP levels and decreased insulin sensitivity were associated with diminished ovarian reserve as determined by antral follicle count (AFC) and estrogen level. The mechanisms by which insulin resistance exerts its effect on AMH have not yet been clarified, but because

of AMH is mainly produced in granulosa cells of preantral follicles and small antral follicles making it reasonable to hypothesis that abnormal insulin action is associated with granulosa cell dysfunction and decreased AMH [35]. Overall our findings raise the possibility that high BMI and insulin resistance might be direct determinant of functional ovarian reserve as assessed by AMH during the reproductive years in obese premenopausal women.

Limitations of study

The cross-sectional design is considered a limitation as it is only allowed for assessment of associations, thus the relationship of BM and other obesity related components with AMH in reproductive age should be further investigated to gain additional insight into the long-term effects of obesity on AMH.

Conclusion

This study of premenopausal Egyptian obese women demonstrated that AMH is significantly lower in such population than those with normal weight and insulin resistance is the only independent predictor to AMH.As it has been suggested that AMH is a strong indicator of ovarian function, our findings might indicate that folliculogenesis and/or ovarian reserve may be affected in premenopausal Egyptian women with obesity. However, more investigation is needed to attain clarifications of such relationship.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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