The Anti-Mullerian Hormone Levels In Polycystic Ovary Syndrome And Its Relation To Body Mass Index

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ABSTRACT :

BACKGROUND:

Anti-mullerian hormone level reflects the ovarian follicular reserve and considered as sensitive marker of ovarian aging. Although the ultimate pathogenesis of polycystic ovary syndrom remains obscure, the distinictive feature is a failure of follicular maturation resulting in anovulation and accumulation of pre-antral and small antral follicles which contribute significantly to the production of anti-mullerian hormone.

OBJECTIVE:

To evaluate the anti-mullerian hormone levels in polycystic ovary syndrome women and to explore its relation with body mass index.

STUDY DESIGN:

Cross section study.

Setting: Department of Gynecology and Obstetrics at Al-Elwiya Maternity Teaching Hospital.

MATERIALS AND METHODS:

One hunderd women suffering from polycystic ovary syndrom (18-37 years old) were included in the study and arranged in three groups according to their body mass index: first group, 30 of them, were having normal body weight (body mass index 18.5 to 24.9kg/m^2) and second group, 59 participants with body mass index 25 to 29.9kg/m^2 and third group, 11 women, their body mass index ≥ 30kg/m^2. Blood sample was collected from them after taking a detailed history and assessment according to the questioner form and the results were compared among the groups.

RESULTS:

Increase in body mass index is found to be accompanied with decrease in anti-mullerian hormone levels ($P < 0.05$), with mean anti-mullerian hormone level significantly decreases as body mass shifts up from normal to overweight to obesity (8.5, 6.4 & 4.4 ng/mL respectively) ($P < 0.05$). Anti-mullerian hormone level did not significantly correlate with age of those women ($P > 0.05$).

CONCLUSION:

An inverse correlation had been found between anti-mullerian hormone levels and body mass index in women with polycystic ovary syndrome.

KEYWORDS: Anti-mullerian hormone, Body mass index, polycystic ovary syndrome.

INTRDUCTION:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women with a prevalence between 6 and 10%[(1)]. The etiology of Insulin resistance and the hyperinsulinemic state present in most women with PCOS appears to play a central role in PCOS development and is considered to be the cause rather than the result of hyperandrogenism [(4)].

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the syndrome remains obscure[(2)], but there is strong evidence that it can, to a large degree, be classified as a gentic disease [(3)].

Since AMH levels reflect the number of developing follicles, their measurement may be used as a marker of ovarian follicle impairment in polycystic ovary syndrome. Women with PCOS have two to six-fold greater number of follicles (primary, secondary and antral) in their ovaries, and the follicular development is halted when follicular diameter is 6-9mm, that is just before the selection of the dominant follicle [(1)].

Women with PCOS, serum and follicular AMH levels are higher than in healthy women. AMH

measurements have been offered a relative high specificity and sensetivity as a diagnostic marker for PCOS (92% and 67% respectively)[5]. The role of AMH in the disturbed folliculogenesis of PCOS may be related to its effect locally; while its the role in the gonadotropin dysregulation of PCOS is not very clear [6]

There are very few studies evaluating the impact of obesity and weight loss on AMH levels, the existing studies concerning mostly overweight and obese women with PCOS . The inverse correlation between BMI and AMH levels has not been fully explained. Three hypotheses have been proposed: a) obesity may affect the catabolism of AMH, b) obesity could reduce the ovarian potential, and c) obesity may be related to ovarian dysfunction.(7,8)

AIM OF THE STUDY:

Is to find the correlation between body mass index and anti-mullerian hormone levels in those women.

PATIENT AND METHODS:

A prospective study is carried out at AL-Elwiya Maternity Teaching Hospital and 0ne hundered women aged from 18 to 37 years suffering from polycystic ovary syndrome were selected while attending the Gynaecology Clinic of Hospital seeking for medical advice because they were suffering from infertility or other manifistation of the disease i.e. menstural irregularity and hirsutism. They were already diagnosed to have PCOS according to their medical reports and they were further assessed to confirm diagnosis according to the Rotterdam criteria. They were arranged according to their body mass index into three groups:

- Group one which included; 30 women who were normal healthy weight (BMI from 18.5 to 24.9 kg/m^2).
- Group two which included; 59 women who were overweight (BMI from 25-29.9 kg/m^2).
- Group three which included; 11 women who were obese (BMI $\geq$ 30kg/m^2). Participants with class I (BMI 30-34.9 kg/m^2) and class II (BMI 35-39.9 kg/m^2). Obesity was included in one group because of small number of participants. There were no participants in this study with class III obesity (BMI $\geq$ 40 kg/m^2).

The study was approved by the Obstetrics and Gynecology committee of Arabic Board for Health Specialization.

Verbal consent was obtained from the participants before any interference and blood samples collection.

Inclusion criteria

Polycystic ovary syndrome according to Rotterdam criteria.

Exclusion criteria:

1. Smokers
2. Previous ovarian surgery.
3. Any recent hormonal therapy.
4. Evident medical diseases according to their detailed history.

The study protocol included a questionnaire form designed to include age, menstrual cycle pattern, fertility status, hair growth and distribution, weight, height, acne, endocrine abnormalities (hormonal profile), medical history, surgical history and ultrasound details.

Complete general examination was done for the participants including vital signs. Hirsutism was assessed according to the Ferriman-Gallwey score, also anthropometrics measurements (weight, height) for calculation of BMI. BMI was calculated as $\mathbf{BMI} = \frac{\text{weight in kg}}{\text{square of height in meters}}$.

Height and weight were measured using the same scale for all participants. Height was measured without shoes; weight was measured in light clothings. Vaginal ultrasound for married women while abdominal ultrasound was done for unmarried girls for features of polycystic ovary syndrom. A blood sample was taken from the participants to measure AMH level.

two of three of the following criteria should be present to diagnose a women with PCOS (Rotterdam criteria 2003):

- Ovulatory dysfunction such as oligomenorrhea or amenorrhea.
- Clinical (hirsutism/acne) or biochemical evidence of hyperandrogenism.
- Polycystic ovary on ultrasound scan defined as presence of 12 or more cysts (2-9mm) in size in one or both ovaries with enlarged ovaries (>10mm) [9].

Five ml of venous blood sample was taken from each women any day of menstrual cycle since AMH level remains stable throughout the menstrual cycle. The blood sample was centrifuged at 3000 RPM for 15 minutes and the serum obtained in properly labeled sterilized tubes and stored at -8 ˚C till analyzed. AMH was measured using enzyme-linked-immunosorbent sensetive assay kit (AMH ELISA) results expressed in ng/ml. All assessment steps were performed by instrument automatically.

Statistical analysis

Data first were entered into excel file, transferred then for statistical analysis into a file of statistical package for social sciences version 22 (SPSS v22). Continuous variables presented as means with standard deviation and discrete variables presented as numbers and percentages. Testing with Pearson's correlation coefficient (r) was used to detect the significant correlations between two continuous variables. T test & ANOVA were used as to detect the significance of difference in means of independent samples.

Chi-square test for independence used to test the significance of association between discrete variables. Level of significance was set at P value of 0.05.

RESULTS:

This study enrolled 100 women diagnosed to have polycystic ovary syndrome (PCOS). Age of sampled patients varied from 18 to 35 years. Mean age was found to be 25.23±3.79 years (Table 1). Majority (81%) fallen in the age 21-30 years. Body mass index (BMI) varied from 20.50-36.00 Kg/m^2 and the mean BMI for the whole sample was 26.21±2.89 Kg/m^2. Normal body weight was observed in 30 (30%) of sampled patients, and overweight was found in around 59 (59%), while obesity was a characteristic of only 11 (11%) of the sample (Table 4, Figure 3). Anti-mullarian hormone (AMH) level varied in studied sample from 2.50 to 10.50 ng/mL and the mean reading for the whole sample was 6.83±1.96 ng/mL.

Table 1: Characteristics of sampled PCOS patients.

Variable	Value
Age Group; n (%)	
18-20 y	8 (8.0)%
21-25 y	50 (50.0)%
26-30 y	31 (31.0)%
31-35 y	11 (11.0)%
Min-Max (y)	18-35
Mean ±SD (y)	25.23±3.79
BMI Category; n(%)	
Normal weight	30 (30.0)%
Over weight	59(59.0)%
Obese	11(11.0)%
Min-Max (Kg/m^2)	20.50-36.00
Mean ±SD (Kg/m^2)	26.21±2.89
AMH Level (ng/mL)	
Min-Max	2.50-10.50
Mean ±SD	6.83±1.96

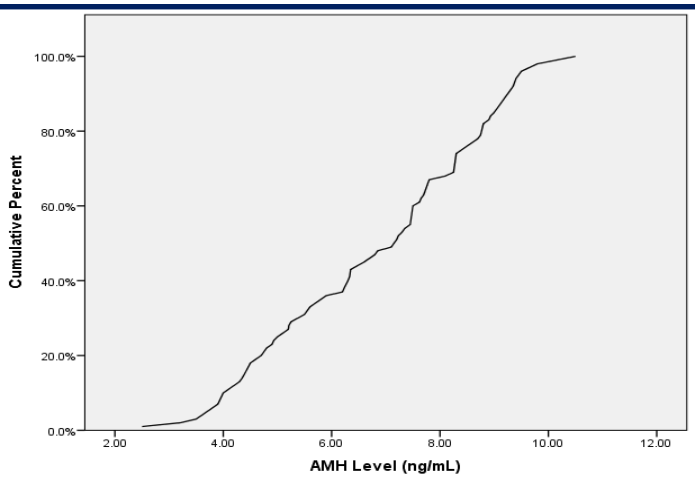

Figure 1: observed levels of AMH in sampled women

This figure expresses the observed readings of AMH and shows that none had a level above 11 ng/mL, around 48% of patients were having a level ≤ 7 ng/mL, and 25% were having AMH level ≤ 5 ng/mL.

Table 2: Correlations between age, BMI and AMH level.

Correlation between variables	Pearson's correlation coefficient (r)	P value
Age(y) with BMI(Kg/m2)	-0.042	0.680
Age(y) with AMH(ng/mL)	-0.151	0.134
AMH(ng/mL) with BMI(Kg/m2)	-0.708	<0.001

There was no significant correlation between age and BMI in studied PCOS sample (P > 0.05). Age did not correlate significantly with AMH in studied PCOS sample (P> 0.05). The correlation between AMH and BMI was found to be significant (P<0.05) and this correlation found to be inverse, i.e. AMH level decreases if BMI increase and increases if BMI decrease. (Figure 2)

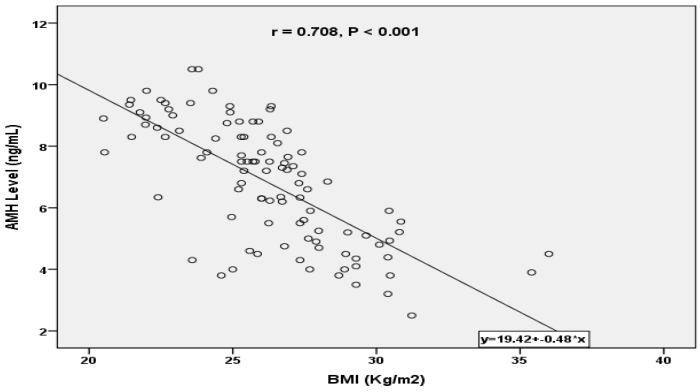

Figure 2: Correlation between BMI and AMH level.

A regression equation was estimated for the relation between BMI and AMH (Figure 2) and showed that AMH will decrease by 0.48 ng/mL for each extra 1 Kg/m^2 in BMI unit. This quation as well predicts roughly the level of AMH when the BMI is known,e.g. for a BMI of 30 Kg/m2, the AMH level =19.4- (0.48*30) = 19.4-14.4= 5 ng/mL.

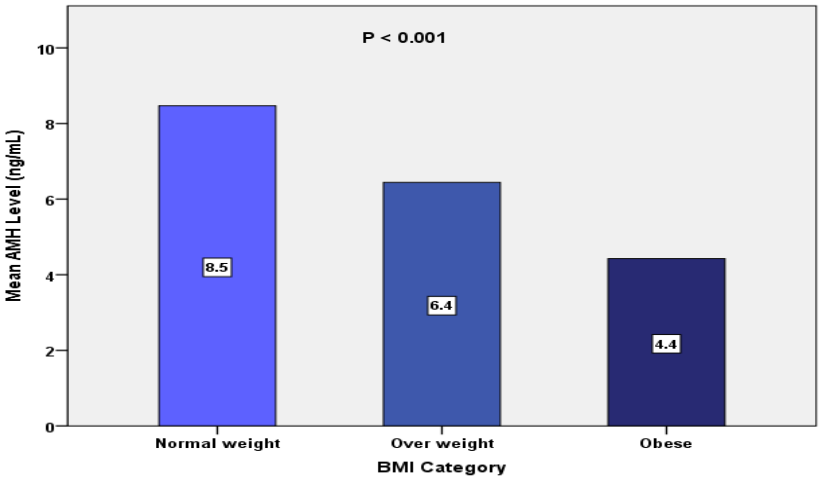

Figure 3: Mean AMH level in PCOS women according to the BMI category.

Figure 3 shows that the mean level of AMH significantly (P<0.05) decreases as BMI shifts up from normal weight to overweight to obese, it shifts down from 8.5 to 6.4 to 4.4 ng/mL respectively. For farther assessment of the relation between age groups and mean AMH level, and this study found there is no significant variation in mean AMH level between age groups (P > 0.05, Figure 4)

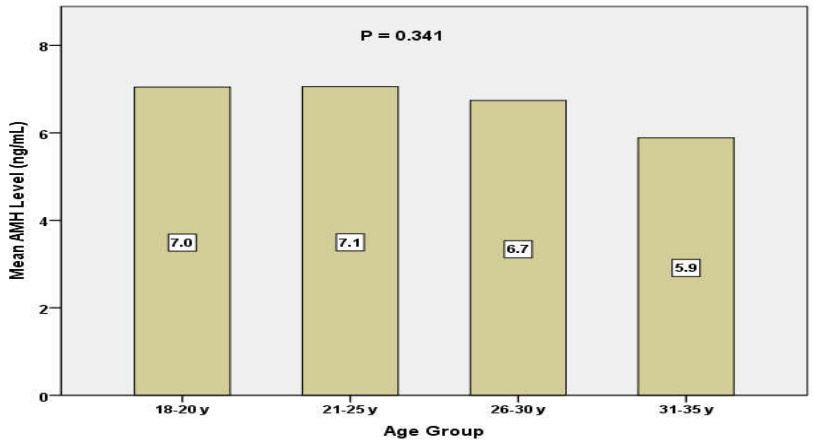

Figure 4: Mean AMH levels in each age group of sampled PCOS women.

DISCUSSION:

Polycystic ovary syndrome is characterized by increased number of follicles at all growing stages particularly in the pre-antral and small antral stage, those which primarily produce AMH[1]. In this study, more than half of the participants showed AMH level higher than 7ng/ml. AMH levels are positively correlated with individual features of PCOS, including LH concentrations, testosterone, mean ovarian volume and the number of ovarian follicles so the AMH level can help to demarcate between women with PCOS compared with women with polycystic ovarian morphology alone.

Thus, not only is AMH elevated in women with PCOS but it also correlates with the severity of PCOS [10]. Increased serum AMH levels in PCOS also reflect an intrinsic dysregulation of granulosa cells, in which AMH, itself, involved since an over expression of the AMH receptor type 2 has also been demonstrated [11].

Although obesity is known to be linked to polycystic ovary disease since its historical explanation by Stein-Leventhal. It appeared later not a major criteria of the disease but weight reduction and diet adjustment has a pretty good effect on disease symptoms. When AMH introduced to be one of the hormonal profile criteria of the disease, its rise in PCOS is logically explained on bases of follicular number in PCOS but its relation with body fat is a place of mystery which may be disclosed in future [6]

In this study there is a significant inverse correlation clearly appeared between serum AMH levels and BMI ($P < 0.05$) in PCOS patients at their different ages.

Similar results were discovered by Ellen W. Freeman et al, who reported that obese women had significantly lower mean AMH levels over the 8-year interval compared to the non-obese women (0.459 ng/ml; CI 0.28, 0.75 and 0.566 ng/ml; CI 0.34, 0.94, respectively; P=0.016). [12]

Furthermore Mei-Jou Chen et al, who studied 99 women with PCOS he found that AMH had a significant negative association with BMI [13] and Athanasia Piouka et al, also found that AMH levels were significantly lower in obese and overweight women compared with healthy weighted PCOS women.[14]

Alice S. Park et al, in his study found that oligomenorrheic girls had serum AMH levels (5.33 ± 0.47 ng/ml) that were significantly greater than the normal adolescents (3.05 ± 0.31 ng/ml) and adults (2.33 ± 0.22 ng/ml), but similar to values seen in the PCOS adolescents (5.28 ± 0.26 ng/ml) and adults (6.36 ± 0.47 ng/ml). Obese adolescents and PCOS women had significantly lower AMH levels compared to lean controls ($P < 0.02$). [15]

Kriseman M. et al, he studied anti-mullerian hormone levels in obese non PCOS women, found no association between AMH and BMI (r-0.04, $P > 0.05$) while found a significant and inverse correlation between BMI and AMH levels in women with PCOS (r-0.31, $P < 0.01$).[16]

On the other hand, Yong Siow et al, his study on 31 young girls (12–18 years old) with PCOS and 17 girls (12–19 years old) with normal menstrual cycles. Serum AMH levels in PCOS girls were significantly higher compared with normal girls, but level of AMH remained significantly elevated in PCOS girls irrespective of BMI status, probably this because of small study group [17].

On the contrary, Huseyin Cengiz et al, said that serum AMH did not differ between obese and non-obese adolescent patients with PCOS [18], probably because he studied only adolescent girls with PCOS or because other unclear factors and its result does not match with this study. When applying regression equation, we found that AMH level will decrease by 0.48ng/ml for extra 1 kg/m^2 in BMI unit, a fascinat result which may have a very good role in pridicting AMH level in obese patient, but further studies needed to support this finding.

A negative correlation between body fat percent and serum AMH levels was Er Luo et al, who discribed for the first highlight the importance of further investigation into the role of body fat percent, especially in body fat-related AMH change as it relates to the underlying pathogenesis of PCOS(19)

Regarding age and AMH levels no relation between age and AMH level was found. This is probably because all the participants included are before age of forty and the bulk of them at their mid reproductive age which did not allow adequate age effect on the result. This seen also in Pigny et al, study who reported no relation between age and AMH level in PCOS patients [20].

While Terhi Piltonen et al, who included forty-four healthy women (aged 21–44 years old) and 65 women with previously diagnosed PCOS (aged 16–44 years old), in his study, AMH levels found to be gradually decrease with age both in healthy women and in women with PCOS [21]. Ellen W. Freeman et al, found that the association between AMH and age is highly significant ($P <0.001$). [12]

Furthermore, Ariana K. Jawad and Mahabad S. Ali, included 70 anovulatory normogonadotrophic women and 30 cases control group (normal ovulatory women) age of women was 15-40 years old. They found that there was negative correlation between women's age and AMH level both in control and patient group. [22]

CONCLUSION:

Anti-mullerian hormone level shows an inverse correlation with body mass index in women with polycystic ovary syndrome.

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