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Comparison of Antimullerian Hormone Level Between Women with Polycystic Ovary Syndrome and Normal Ovulatory Infertile Women of Reproductive Age

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Abstract

Background Polycystic ovary syndrome (PCOS) is the most common cause of chronic anovulation and hyperandrogenism in young women. This syndrome is characterized by an increase in the number of small antral follicles that are between 5-8 mm in size. Antemüllerian hormone (AMH) is secreted mostly by this type of follicle and when it is much too high, the production of a healthy egg every cycle can be halted as it works by reducing the receptors of the ovary to follicle stimulating hormone (FSH).

Objective To compare the AMH level between women presented with PCOS with its level in normal ovulatory infertile women and to determine its correlation with the clinical, hormonal and ultrasonographic parameters in both groups.

Methods This is a prospective cross-sectional study done at Um-Albaneen Infertility Center in Al-Imamein Al-Kadhimein Medical City from march 2015 to January 2016. One hundred infertile women were recruited in this study, 50 women with PCOS and 50 women have other factors of infertility apart from PCOS and ovulatory dysfunction. Sera were taken from all the participants at day (2-3) of menstrual cycle and were investigated for AMH, FSH, luteinizing hormone (LH), androstenedione, testosterone and estradiol (E2) levels. The number of early antral follicles (2-9 mm in diameter) was estimated by transvaginal ultrasound scanning.

Results Level was significantly higher in PCOS women (42.6±23.8) compared to the normal ovulatory infertile women (16±7.5), P-value <0.001. There was positive correlation between AMH and LH, testosterone, androstenedione, number of antral follicles (antral follicle count) and ovarian volume. However, the correlation was negative with age, body mass index, estradiol, and FSH.

Conclusion AMH strongly correlated with testosterone level and the number of small antral follicles in PCOS women, so it can be considered as a good diagnostic marker for PCOS.

Keywords Antimullerian hormone, PCOS.

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List of abbreviation: AML = Antemüllerian hormone, BMI = Body mass index, E2 = estradiol, FSH = Follicle stimulating hormone, LH = Luteinizing hormone, PCOS = Polycystic ovary syndrome,

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among females. PCOS is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it

can, to a large degree, be classified as a genetic disease [1]. The condition was first described in 1935 by American gynecologists Irving F. Stein, Sr. and Michael L. Leventhal, from whom its original name of Stein-Leventhal syndrome is taken [2]. PCOS produces symptoms in approximately 5-8% of women of reproductive age group. It is thought to be one of the leading causes of female subfertility and the most frequent endocrine problem in women of reproductive age [3].

Diagnostic Criteria of PCOS

•Rotterdam

In 2003, a consensus workshop sponsored by the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) in Rotterdam indicated that PCOS to be present if any 2 out of 3 criteria are met [4]:

- Oligoovulation and/or anovulation.
- Excess androgen activity (clinical or biochemical).
- Polycystic ovaries (by gynecologic ultrasound) ≥12 follicles of 2-9 mm and/or enlarged ovarian volume of ≥10 mL in one or both ovaries.

•Androgen Excess PCOS Society.

In 2006, the Androgen Excess PCOS Society suggested a tightening of the diagnostic criteria to all of [5]:

- Excess androgen activity.
- Oligoovulation/anovulation and/or polycystic ovaries.
- Other entities are excluded that would cause excess androgen activity.

Ovarian Dysfunction in PCOS

The ovulatory dysfunction in PCOS can be ascribed to disturbed follicular development with excessive early follicular growth and abnormal later stages of arrested follicle growth well before expected maturation [6]. This pattern of follicular growth with failure in the selection of a dominant follicle for ovulation results in one of the hallmarks of PCO morphology. Infertility affects 40% of women with PCOS, which is the most common cause of anovulatory infertility. Approximately 90-95% of anovulatory women presenting to infertility clinics have PCOS [7].

Antimullarian Hormone (AMH)

It is produced by the Sertoli cells of the fetal testis, induces the regression of the Müllerian ducts. However, after birth, this sex-dimorphic expression pattern is lost and AMH is also expressed in granulosa cells of growing follicles in the ovary. AMH is a glygoprotein hormone structurally related to inhibin and activin, and a member of the transforming growth factor-β (TGF-β) family [8]. In humans, the gene for AMH is on chromosome 19 [9].

In healthy females, AMH is either just detectable or undetectable in cord blood at birth and demonstrates 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 [10]. AMH continues to be expressed in the growing follicles in the ovary until they have reached the size and differentiation state at which, they are to be selected for dominance by the action of pituitary follicle stimulating hormone (FSH) [11]. AMH is not expressed in atretic follicles and theca cells [12].

AMH expression is strongest in preantral and small antral follicles (≤ 4 mm) [11]. AMH expression disappears in follicles of increasing size and is almost lost in follicles larger than 8 mm. This expression pattern suggests that, AMH may play a role in initial recruitment and in the selection of the dominant follicle [11]. So, there are local selectors for follicle recruitment and growth within the ovary that might contribute to the impaired follicle development in PCOS. AMH reflects the size and activity of the follicular pool [13,14]. There is also evidence of AMH involvement in the regulation of

recruitment of primordial follicles into the growing pool, presumably by decreasing the granulosa cell sensitivity to FSH [15]. In the small primordial and transitional follicles of anovulatory PCOS, AMH protein expression is reported to be reduced. This may contribute to the inappropriate recruitment of growing follicles. Additionally, in both circulation and antral follicular fluid of PCOS women, AMH levels are increased, and these are associated with poor reproductive responsiveness to treatment [16-18]. These high circulating levels may be a reflection of the increased pool of granulosa cells instead of an increased expression. Since high levels of AMH (normal value 7-70 pmol/l in young age female) are associated with lower levels of FSH, it has been suggested that the AMH excess is involved in the lack of FSH-induced aromatase activity that is characteristic of follicular arrest in PCOS [17]. In addition, testosterone exposure upregulates AMH expression in granulosa cells of small bovine follicles in culture and could possibly represent a mechanistic origin of PCOS [19].

The objectives of this study were to compare the serum level of AMH in women with PCOS with its level in normal ovulatory infertile women, and to assess if it could be used as diagnostic marker for PCOS.

Methods

This prospective study was conducted on 100 infertile women who were recruited from the outpatient clinic of the Department of Gynecology and Obstetrics at Um-Albaneen infertility Centre in Al-Imamein Al-Kadhimein Medical City during the period from march 2015 to January 2016. After verbally informed consents were obtained from the patients, they were divided into two groups,

The study group: includes 50 infertile women diagnosed to have polycystic ovary syndrome according to presence of any 2 out of 3 Rotterdam criteria (mentioned in introduction). Exclusion criteria include any woman with unexplained infertility (when no abnormality was found as a cause of her infertility) or endometriosis (laparoscopically diagnosed after confirmation by histopathological study), hypothalamic amenorrhea, thyroid diseases, hyperprolactinemia, hyperandrogenism from another cause e.g. adrenal or androgen secreting ovarian tumors were excluded. Furthermore, any patient with at least one follicle with a diameter >9 mm at a transvaginal ultrasound (U/S) done at a midcycle, or a serum estradiol (E2) level above 80 pg/ml and those with a history of tubal surgery, salpingectomy or ovarian cyst were excluded as well. All of the above conditions were excluded because they may bias the results of our study as they may have an effect on AMH level, as well to determine the pure correlation between infertile women with PCOS and the level of this hormone.

The control group includes 50 infertile women with other causes of infertility other than PCOS, such as male factors, tubal causes and with normal ovulatory cycle (25-35 days) and having no endocrine abnormalities (normal prolactin, basal FSH and E2, and no hyperandrogenism) and a normal ultrasonic ovarian morphology.

The control group was matched with study group for age (±2 years) and body mass index (BMI) (±10%). The control group did not receive any hormonal therapy. A complete history was taken from all the participants in both groups, as well clinical and physical exam was performed. The BMI was determined by measuring the weight and the height of the patient, BMI = weight kg / height m^2. Early-morning blood sample (5 ml) was obtained during the follicular phase for both control and study groups, at (Days 2-3 of the cycle) for the measurement of luteinizing hormone (LH), FSH, E2, Testosterone and AMH. Serum was separated from all blood sample and frozen at -2 °C until used for analysis. Serum AMH levels were determined using enzyme linked immunosorbent assay (ELISA). Serum FSH, LH and E2 levels were determined by using VIDAS method which is automated quantitative test, using ELFA technique (Enzyme Linked

Flourecent Assay). Transvaginal U/S was done at day 13 of the cycle to all participate to assess the number of small follicles (2-9 mm) and calculate the ovarian volume. Ovarian ultrasound scanning was performed using 4.5-7.2 MHz transvaginal probe, done by the same operator.

Statistical analysis

Statistical analyses were performed using the SPSS Statistics (Statistical Package for the Social Sciences) version 17. Descriptive analysis was used to show the mean and SD for age, BMI, Serum FSH, LH, E2, Testosterone and AMH. Comparisons of two independent groups were made using the Student t test. The correlation between AMH and the various parameters were evaluated, multiple regression analysis was used to evaluate the preferential effect of different studied variables on AMH level. A P-value ≤ 0.05 was considered significant and ≤ 0.001 highly significant.

Results

For both groups (the PCOS and the control groups), the age range was (18-35) years old and the BMI range was (18-39) kg/m^2. Comparison of the demographic characteristic, clinical, hormonal and ultrasound data for PCOS with that of the control group revealed the following results (Table 1). The mean FSH and E2 were not significantly different between the two groups. The mean LH, testosterone, androstenedione, AMH, number of antral follicular (2-9 mm) and ovarian volume were significantly higher in PCOS group.

Table 1. The demographic characteristics with clinical, hormonal and ultrasonographic data of study and control groups

Variables	PCOS n=50 Mean±SD	Control n=50 Mean±SD	P-value
Age (year)	27.5±4.1	28.6±4.6	0.295
BMI (kg/m^2)	26.1±4.9	25.9±3.7	0.848
AMH (pmol/L)	42.6±23.8	16.1±7.5	0.001*
FSH (IU/L)	5.6±1.7	6.1±1.8	0.236
LH (IU/L)	8.9±4.4	4.7±2.3	0.001*
Testosterone (nmol/L)	2.3±0.8	1.5±0.6	0.001*
E2 (pmol/L)	110.1±56.6	118.4±58.1	0.547
No. of antral follicles	21.3±7.3	7.5±3.4	0.001*
Ovarian volume (cm^3)	28.7±6.7	7.8±1.6	0.001*
Androstenedione (nmol/L)	9.2±4.3	6.6±1.8	0.002*

P value < 0.05 is significant, P value <0.001 is highly significant

Using the Pearson correlation (r) between AMH and other parameters in all group of patients, we found that there were negative statistical correlations between AMH and age, BMI, FSH and E2. There were positive correlations between AMH and LH, testosterone, androstenedione, number of antral follicle and ovarian volume.

From tables 2 and 3, there was positive correlation between AMH and LH, testosterone, androstendione, number of antral follicles and ovarian volume. Testosterone and androstendione strongly correlated with AMH exclusively in PCOS group (r=0.557; p=0.001), (r=0.451; p=0.007) respectively, also the number of small antral follicles. Multiple regression analysis was performered in the PCOS groupincuding AMH as dependent variable, and LH, FSH, testosterone, androstendione, E2 and ovarian

volume as independent variables. Testosterone was the only determinant for AMH level (r= 0.557; p<0.001), whereas other parameters were no longer Significantly related.

Table 2. Correlation between AMH and clinical, hormonal and ultrasounographic parameters (n = 100)

Variables	AMH	
	r	p
Age	- 0.205	0.089
BMI	-0.130	0.283
FSH	-0.358	0.002
LH	0.281	0.018
Testosterone	0.472	0.001
Androstenedione	0.371	0.002
E2	-0.095	0.434
AFC <10 mm	0.627	0.001
Ovarian volume	0.478	0.001

Table 3. Correlation between AMH and clinical, hormonal and ultrasonographic parameters in the study and control groups

Variables	PCOS		Control	
	r	p	r	p
age	-0.137	0.433	-0.098	0.575
BMI	-0.086	0.623	-0.195	0.262
FSH	-0.347	0.041	-0.356	0.036
LH	0.336	0.048	0.341	0.045
Testosterone	0.557	0.001	0.199	0.504
Androstendione	0.451	0.007	0.227	0.379
Estradiol	-0.085	0.627	-0.074	0.673
AFC <10	0.625	0.001	0.475	0.008
Ovarian volume	0.436	0.009	0.369	0.029

Discussion

The results of the present study revealed no significant correlations between AMH with age and BMI in both groups. As the mean age of the control group (28.6±4.6) and (27.5±4.1) for PCOS group, p-value 0.295, and BMI means (26.1±4.9) and (25.9±3.7) for PCOS and control groups respectively, p-value 0.848. This is in agreement with Pigny et al. [18]. However, Nardo et al. [20] indicated that AMH is generally decreased with chronological age and Chen et al. [21] found that AMH had a significant negative association with BMI and age. In the current study, there were negative statistical correlations between AMH with age and BMI, however, this does not reach the level of significance, probably because of the small sample size.

The results of the present study have shown higher serum AMH levels in the study group than that in the control group, as well the mean number of antral follicle count was significantly higher in the study group (21.3±7.3) compared to the control group (7.5±3.4) with a P- value of 0.001, and a significant positive correlation between AMH and number of follicles <10 mm in the whole group of patients (r=0.627) and in each group

separately (PCOS group r=0.625 and control group r=0.475) was found; these results are in line with the fact that serum AMH levels reflect the number of small antral follicles because the highest expression of AMH has been demonstrated in the stage of pre-antral and small antral follicle size (4-6 mm) and disappears in follicle size larger than 9 mm, this was demonstrated in several studies [18,20,22-26].

The current study findings regarding FSH are comparable with the results of previous studies [27,28]. However, Pigny et al. [18] found no relationship between AMH and FSH in PCOS and control groups. Current results revealed that there is negative correlation between AMH and FSH, the mean of FSH in PCOS group was (5.6±1.7) and in the control group was (6.1±1.8) with p-value 0.236, which is not significant. So with increasing age there will be an increase in the level of FSH and a decrease in AMH level, so AMH could be used as a marker of ovarian reserve [24]. Also it was found that there was positive correlation between AMH and LH as the mean of LH in PCOS was (8.9±4.4) and in the control group was (4.7±2.3) with p-value <0.001, which is significant, r=0.281 that's mean positive correlation.

In the present study, significant positive correlation was found between AMH and serum testosterone in the PCOS group exclusively. This finding is in accordance with the results of previous studies [18,21,27-29], and add to the existing evidence for the role of small ovarian follicles in the production of both AMH and androgens. However, Nardo et al. [20] indicated that AMH is similarly related to testosterone in women with and without PCOS. In the current study, the mean testosterone in PCOS group was (2.3±0.8) and in the control group (1.5±0.6), p-value <0.001, which is significant, r=0.472 indicates positive correlation between AMH and testosterone.

Pigny et al. [18] suggested that the increase in AMH serum levels in PCOS is a consequence of androgen-induced excess in small antral follicles and that each follicle produces normal amount of AMH.

However, Pellatt et al. [30] found that raised serum AMH in PCOS is a reflection of both an increase in production per cell and the increase in follicle number since they used cells from size-matched follicles in patients and controls plated at the same density.

It could be also speculated that since AMH inhibits FSH-induced aromatase activity in cultured mouse [31] and human granulose cells [21], it may also be responsible for the reduced aromatase activity in PCO granulosa cells [21] and contributes to the elevated androgen levels. Moreover, Crisosto et al. [32] proposed that AMH expression is modulated by androgens in bovine granulosa cells from small follicles; suggesting that androgens, by inhibiting AMH expression, may promote follicle recruitment, increasing the early growing follicular pool. Multiple regression analysis demonstrated that testosterone was the only determinant for AMH level in the PCOS group (r=0.557 ; P<0.001). This is in contrast with Pigny et al. [18] who found that only the number of 2-5 mm follicles, was significantly related to AMH. However, Eldar-Geva et al. [28] revealed that the number of small follicles and serum androgens were correlated to AMH.

This study concluded that there was strong correlation between AMH, testosterone and the number of small antral follicle, which were increased in PCOS patients so AMH can be considered as a good diagnostic marker for PCOS .

The authors of this study recommend that AMH can be used as diagnostic marker for PCOS and also may be used as prognostic marker for the extent of ovarian dysfunction in PCOS patients and whether it can predict response to ovulation induction and monitoring infertility treatment. Also, AMH can be used for the assessment of ovarian reserve and provide insight into the number of fertile years women has left .

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Author contributions:

Dr. Jumaa: cases collection, obtaining the results of the hormonal study and the findings of transvaginal ultrasound scan. Dr. Almoayad and Dr. Abdulrasul supervised the study and wrote the article and revised it.

Conflict of interest

The authors declared no conflict of interest for the present research outcome.

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