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Anti-mullerian hormone and antral follicle count in polycystic ovary syndrome and non-polycystic ovary syndrome women

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Jwan J. Namik* Shahla K. Alalaf** Namir G. Al Tawil***

Abstract

Background and objective: Although the ultimate pathogenesis of polycystic ovary syndrome remains obscure, the distinctive feature is the failure of follicular maturation resulting in an ovulation and accumulation of preantral and small antral follicles which contribute significantly to the production of the anti-mullerian hormone. This study aimed to compare anti-mullerian hormone concentration and antral follicle count in polycystic ovary syndrome and non-polycystic ovary syndrome women regarding clinical, hormonal and ultrasound parameter in both groups.

Methods: A cross-sectional study with comparison group study was conducted in the fertility and gynecology outpatient clinic in the Maternity Teaching Hospital, Erbil, Kurdistan region, Iraq from April 1st, 2015, to December 31st, 2015. The study involved a total of 100 infertile women aged 18 - 39 years; 50 polycystic ovary syndrome women based on the Rotterdam criteria and 50 infertile non-polycystic ovary syndrome selected as a comparison group. Anti-mullerian hormone and antral follicle count in both groups were compared.

Results: A strong, inverse and significant correlation was found between anti-mullerian hormone and age in each of the two study groups. A weak correlation was detected between anti-mullerian hormone with body mass index, luteinizing hormone, follicular stimulating hormone, and total testosterone, in each of the two study groups. A significant inverse correlation was detected between anti-mullerian hormone and luteinizing hormone/follicular stimulating hormone ratio in the non-polycystic ovary syndrome group (P <0.001). There was a statistically strong, significant and positive correlation between anti-mullerian hormone and antral follicle count in each of the study groups.

Conclusion: Anti-mullerian hormone and antral follicle count are higher in polycystic ovary syndrome group than in non-polycystic ovary syndrome group. Elevated levels of the anti-mullerian hormone were associated and related to increased number of follicles in women with polycystic ovary syndrome.

Keywords: Antimullerian hormone; Antral follicular count; Polycystic ovarian syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. It affects 5–7% of women in their reproductive ages.[1] PCOS is the most common form of anovulatory infertility. Anovulation in PCOS is due to arrested growth of antral follicles. Women with PCOS often seek care for menstrual disturbances, clinical manifestations of hyperandrogenism and infertility.[2] The diagnosis of PCOS based on the Rotterdam criteria includes oligomenorrhea /anovulation (O), clinical or biochemical hyperandrogenism (H), and the presence of polycystic ovaries morphology (P) on ultrasound. According to these criteria PCOS is diagnosed if at

* Maternity Teaching Hospital, Erbil, Iraq.
** Department of Obstetrics and Gynecology, College of Medicine, Hawler Medical University, Erbil, Iraq.
*** Department of Community Medicine, College of Medicine, Hawler Medical University, Erbil, Iraq.

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least two of the criteria were present.[3] Transvaginal ultrasound examination showed that polycystic ovaries are larger and contain more antral follicles and a biopsy study indicated a much-increased density of follicles at primary stages in polycystic ovaries when compared with normal ovaries, suggesting that PCOS women may actually have larger ovarian reserve at birth than non-PCOS.[4] Many studies have shown a positive correlation between AFC and serum androgen levels.[5] Anti-Mullerian hormone (AMH) is considered a useful marker of ovarian reserves.[6] It was proposed that serum AMH may be the marker of PCOS. AMH was shown to be two to three folds higher in PCOS than non-PCOS.[7] This study aimed to compare AMH level and AFC in two groups of women with polycystic ovary syndrome and non-polycystic ovary syndrome group regarding clinical, hormonal and ultrasonography parameters.

Methods

This cross-sectional study (with a comparison group) included a total of 100 infertile women aged 18 - 39 years, visiting the fertility clinic and gynecology outpatient clinic in the Maternity Teaching Hospital, Erbil city, Iraq from April 1st, 2015, to December 31st, 2015. The study protocol was approved by the Scientific Council of Obstetrics and Gynecology, Iraqi Board for Medical Specializations. Informed consent was obtained from all women who participated in the study. The PCOS group included 50 women of reproductive age group diagnosed to have PCOS. The diagnosis of PCOS in the participant was based on the Rotterdam-PCOS criteria. According to these criteria, PCOS was diagnosed if at least two of the following criteria were present; oligomenorrhoea/ anovulation (defined as delayed menses >35 days or <8 spontaneous hemorrhagic episodes/year), clinical hyperandrogenism (hirsutism using modified Ferriman–Gallwey score of ≥8) or biochemical hyperandrogenism (total testosterone >0.481 ng/ml) and ultrasonography morphology of the polycystic ovaries (12 or more follicles in each ovary measuring 2 –9 mm in diameter, and/or increased ovarian volume >10 ml^3.[3] The control group involved 50 infertile women aged 18–39 year who attended the hospital during the period of the study for investigation of infertility and who agreed to participate in the study. The women in the comparison group having no PCOS criteria (Non-PCOS group) had regular menstrual cycles (21-35 days), no evidence of hirsutism and no polycystic ovary morphology on ultrasonography, having male factor infertility, tubal factor, and unexplained infertility. Exclusion criteria for PCOS and non-PCOS groups included women with premature ovarian failure, women on regular medications for ≥3 months prior to the study such as oral contraceptives, glucocorticoids, ovulation induction agents, estrogenic or anti-androgenic medication which could alter clinical presentation or hormonal profile and women with other endocrinological abnormalities such as thyroid dysfunction, hyperprolactinemia, Cushing's syndrome and late-onset adrenal hyperplasia or androgen-producing tumor. Data regarding history and examination were collected in a specially designed questionnaire. Women were asked about their age, menstrual cycle regularity (regular, oligomenorrhea and amenorrhea), age at marriage, duration and type of infertility (primary or secondary). Women were examined for the presence of acne, alopecia, and hirsutism. Alopecia was described as male pattern balding, and it is the partial or complete loss of hair on the scalp. Hirsutism was defined as the amount of excess terminal hair growth assessed by using modified Ferriman- Gallwey method looking for terminal hair over nine body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and upper arm). Hair growth was rated from 0 (no growth of terminal hair) to 4 (Extensive hair growth) in each of the nine locations;

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a score of 8 or higher was regarded as androgen excess.[9] Weight and height were measured using a clinical balance scale. Height (cm) was measured using a vertical scale with a rigid adjustable arm piece with the women standing erect and without shoes. The body mass index (BMI) was defined according to WHO criteria by dividing the weight in kilograms by height in meters square, BMI was classified into Underweight <18.5 kg/m^2, normal weight 18.5-24.9 kg/m^2, overweight 25-29.9 kg/ m2 and obese as ≥30 kg/m^2.[10] Waist-to-Hip Ratio (WHR) was calculated after measuring the waist circumference at the top of the hip bones, while hip circumference was taken at the level of the greater trochanter. A WHR <0.85 was regarded normal, while a WHR ≥ 0.85 was regarded as abnormal. [11] A transvaginal ultrasound examination was performed using a 6.5 MHz frequency vaginal transducer, probe destination E8CS/E8C, USA. The ultrasound measurement was done by a specialist ultrasonographer at the early follicular phase for ovarian morphology, as well as the number of small follicles in each ovary. Polycystic ovaries (PCO) were diagnosed in the case of an increased follicular count (>12 follicles, 2 - 9 mm in one or both ovaries) and/or an increased ovarian volume (>10 ml^3) for at least one ovary. Women were asked to provide blood samples on day 2 or 3 of the menstrual cycle in the control group and after spontaneous bleeding in the PCOS group or randomly if they were in a state of amenorrhea. Serum luteinizing hormone (LH), Follicular stimulating hormone (FSH) and total testosterone were measured with electrochemiluminescence immunoassays machine using the E170 kit (Elecys 2010, cobase 601, Modular Analytics E170Roche Diagnostic, Germany). The normal range of FSH in the follicular phase was 3.5-12.5 mIU/mL. The normal range of LH in the follicular phase was 2.4-12.6 mIU/mL. The normal range of total testosterone for women is 0.084-0.481 (ng/mL). The conversion factor was ng/mL×3.47=nmol/L). A total testosterone level >0.481 ng/mL was regarded as biochemical Hyperandrogenemia. The anti -mullerian hormone was measured using an ultrasensitive enzyme-linked immunosorbent assay ELISA (AMH Gen II ELISA, Beckman Coulter, Inc250 S. Kraemer Blvd, Brea, CA 92821 U.S.A.). The unit of measurement used for AMH was ng/mL (1 ng/mL = 7.14 pmol/l). Serum hormonal levels of FSH, LH, total testosterone, AMH were performed at the laboratory of the Maternity Teaching Hospital. Data analysis was performed by using the statistical package for the social sciences (version 19). Categorical data were described as count and percentage while numerical data were described as means ± SD. Student's t-test was used to compare the means of two groups. A Chi-square test of association was used to compare between proportions. When the expected count of more than 20% of the cells of the table was less than 5, the Fisher's exact test was used. A *P* value of ≤0.05 was considered statistically significant.

Results

The mean age (± SD) of the sample was 27.61 ± 5.23 years, ranging from 19 to 38 years. The mean age of the non-PCOS group was 27.92 ± 5.5 years, and that of the PCOS group was 27.3 ± 4.98 (*P* = 0.556). No significant differences were detected between the two study groups regarding residency (*P* = 0.683), occupation (*P* = 0.424), age at marriage (*P* = 0.799), duration of infertility (*P* = 0.317), and type of infertility (*P* = 0.839) (Table 1). Table 2 shows that the menstruation was regular in 74% of the non-PCOS group compared with 14% in the PCOS group (*P* <0.001). The majority (78%) of the PCOS group had hirsutism compared with 38% in the non-PCOS group (*P* <0.001). Most (94%) of women in the PCOS group had WHR .0.85 compared with 80% in the non-PCOS group (p 0.037). No significant

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association was detected between PCOS with greasy skin (*P* = 0.107), scalp hair loss (*P* = 0.161), acne (*P* = 0.617), and BMI categories (*P* = 0.904).

Table 1: Distribution of samples by demographic variables, duration, and type of infertility.

		Non-PCOS		PCOS		Total		
		No.	%	No.	%	No.	%	*P* value
Residency	Outside Erbil	19	38.0	21	42.0	40	40	0.683
	Inside Erbil	31	62.0	29	58.0	60	60	
Occupation	Housewife	43	86.0	40	80.0	83	83	0.424
	Employed	7	14.0	10	20.0	17	17	
Age at marriage	≥ 30 years	10	20.0	9	18.0	19	19	0.799
	< 30 years	40	80.0	41	82.0	81	81	
Duration of infertility	≥ 2 years	38	76.0	42	84.0	80	80	0.317
	< 2 years	12	14.0	8	16.0	20	20	
Type of infertility	Secondary	21	42.0	20	40.0	41	41.0	0.839
	Primary	29	58.0	30	60.0	59	59.0	
Total		50	100	50	100	100	100	

Table 2: Association between study groups and clinical features.

		Non-PCOS		PCOS		Total		
		No.	%	No.	%	No.	%	*P* value
Menstruation	Amenorrhea	1	2.0	5	10.0	6	6	< 0.001*
	Oligomenorrhea	12	24.0	38	76.0	50	50	
	Regular	37	74.0	7	14.0	44	44	
Hirsutism	No	31	62.0	11	22.0	42	42	< 0.001
	Yes	19	38.0	39	78.0	58	58	
WHR	≤ 0.85	10	20.0	3	6.0	13	13.0	0.037
	> 0.85	40	80.0	47	94.0	87	87.0	
Greasy skin	No	26	52.0	18	36.0	44	44.0	0.107
	Yes	24	48.0	32	64.0	56	56.0	
Scalp hair loss	No	29	58.0	22	44.0	51	51.0	0.161
	Yes	21	42.0	28	56.0	49	49.0	
Acne	No	41	82.0	39	78.0	80	80.0	0.617
	Yes	9	18.0	11	22.0	20	20.0	
BMI (Kg/m^2)	< 25	27	54	25	50	52	52.0	0.904
	25-29	8	16	8	16	16	16.0	
	≥ 30	15	30	17	34	32	32.0	
Total		50	100	50	100	100	100	

*By Fisher's exact test
WHR = Waist-hip ratio
BMI= Body mass index

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The mean FSH in the non-PCOS group was significantly higher than the mean of the PCOS group (*P* <0.001). All the other means mentioned in Table 3 were significantly higher in the PCOS group compared with the non-PCOS group (*P* <0.001). Table 4 shows strong, inverse, significant correlation between AMH and age in each of the two study groups. A weak correlation was detected between AMH with BMI, LH, FSH, and total testosterone, in each of the two study groups. A significant inverse correlation was detected between AMH and LH/FSH ratio in the non-PCOS group.

Table 3: Hormonal and ultrasonographic findings of study groups expressed as mean ± SD.

	Non-PCOS		PCOS		
	Mean	**SD**	**Mean**	**SD**	***P* value**
FSH IU/L	5.74	1.04	4.73	.78	< 0.001
LH IU/L	4.39	1.53	8.02	1.49	< 0.001
LH/FSH ratio	.80	.41	1.71	.30	< 0.001
Total testosterone (ng/ml)	49.28	9.82	63.66	11.76	< 0.001
AMH ng/L	4.16	.85	9.22	1.21	< 0.001
AFC	19.78	2.39	32.60	4.42	< 0.001

FSH: Follicular stimulating hormone, LH: Luteinizing hormone, AMH: Antimullerian hormone, AFC: Antral follicular count

Table 4: Correlation between AMH and clinical, hormonal and ultrasonographic parameters in the PCOS and control groups.

		Non-PCOS	**PCOS**
Age	R	-0.98	-0.924
	p	< 0.001	< 0.001
BMI	R	.105	-0.279
	p	.470	.049
LH IU/L	R	-0.396	-.186
	p	.004	.197
FSH IU/L	R	.203	-.190
	p	.158	.187
LH/FSH ratio	R	-0.458	-.057
	p	.001	.695
Total testosterone	R	.274	-.174
	p	.054	.226
AFC	R	0.966	0.899
	p	< 0.001	< 0.001

BMI : Body mass index, FSH: Follicular stimulating hormone, LH: Luteinizing hormone, AFC: Antral follicular count

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Table 4 shows a strong, significant, positive correlation between AMH and AFC in each of the study groups. Figure 1 presents this correlation in the PCOS group.

Discussion

An overall significant variation in hormonal levels and ultrasound findings between PCOS group and the non-PCOS group has been detected in this study. AMH concentrations could be used as a marker in ovarian pathophysiology, like PCOS. Most women with PCOS present with polycystic ovaries, in which the number of pre-antral and small antral follicles is increased. This study also gives information on clinical, biochemical differences in both PCOS and those without PCOS. In the current study, there was a non-significant difference in mean age of both groups, a finding which is similar to that reported by Hollinrake et al. where a total of 103 women with PCOS and 103 control women were enrolled in their study.[12] The current study reported significant higher waist circumference WC and WHR in women with PCOS as compared to control women which is similar to studies done abroad.[13,14] Most investigators have found that 30% - 50% of women with PCOS are obese with a tendency to have an increased WHR or abdominal obesity.[14] Although there are no systematic studies to detect the exact prevalence of obesity in women with PCOS. There is evidence showing that normal weight PCOS patients have increased intra-abdominal fat.[15] There was no significant difference in body mass index categories between PCOS and non-PCOS in the current study. This finding may reflect the lifestyle of the female population in our region. Azziz et al. found that around 75% - 85% of women with PCOS had menstrual dysfunction,[16] this is in consistent with our study that reported a high frequency of oligomenorrhea (76%) among the PCOS group. Hirsutism was found in 78% of the study sample in women with PCOS. The prevalence and degree of hirsutism depend on the ethnicity of the patients. Hirsutism is less prevalent in women with PCOS of East Asian region or Pacific Islanders[17] but is more prevalent in women of Indian origin.[18] In this study, no significant difference was found regarding acne between PCOS and comparison group. Acne was more prevalent among women with PCOS than women without PCOS. Azziz *et al.* reported acne incidence of 12% - 14% among PCOS women.[16] The findings of this study regarding serum LH and LH/FSH ratio were consistent with

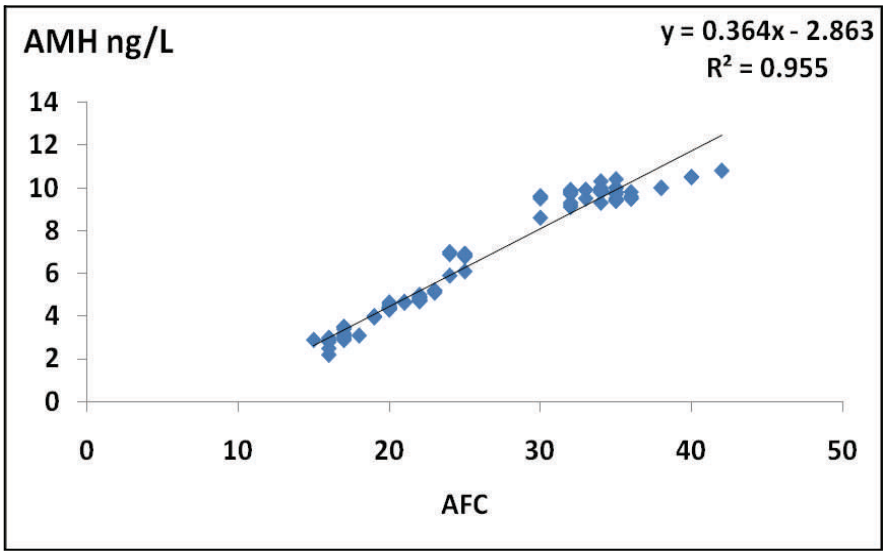

Figure 1: Correlation between AMH and AFC in PCOS.

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a study conducted by Dewailly et al., who showed that serum LH and LH/FSH ratios were higher in women with PCOS than controls.[19] In a study done by Sung et al., showed that women with PCOS exhibited a significantly higher total testosterone level, than women without PCOS,[20] which is similar to the current study. The present study clearly shows that AMH levels are increased in PCOS patients, and there is a highly significant difference with non-PCOS women which is consistent with the findings of Woo et al.[21] Laven et al. have demonstrated that serum AMH levels were significantly increased in PCOS than ovulatory women, this was consistent with AFC during ultrasonography examination which is similar to the result of the current study. [22] Serum AMH levels were positively correlated with PCOS clinical features like androgen level, ovarian volume, and cycle durations. Therefore, it was proposed that AMH may be a marker of ovarian dysfunction in these women with PCOS as represented by elevated testosterone or LH levels and ovarian volumes by ultrasound examination.[23] Fanchin *et al.* demonstrated that AMH and AFC were positively correlated in a study on infertile women and found that they were superior to other markers like inhibin B, FSH or estradiol [24] Other studies showed that AMH was 2- 4 folds increase as well as AFC in PCOS.[22] Many studies have shown that AFC has increased diagnostic threshold for PCOS.[25] In the current study, the mean AFC in PCOS was 32.60±4.42 versus 19.78±2.39 in the comparison group. Dewaily et al. concluded from their study a higher threshold of up to 19 follicles have showed increased sensitivity and specificity of 81% and 92%, respectively, for PCOS diagnosis[26] but this depends on the quality of the ultrasound rather than medical aspects. Consistent with this is a recent study by Lujan et al. who suggested increased threshold to 29.[27] The results of the present study have shown a significant strong positive correlation between AMH and number of follicles <10 mm in the whole group of patients which is in line with the findings of other studies. [7,26] Our findings regarding LH and LH/FSH are comparable with the results of previous studies.[22,28] However, Pigny et al. found no relationship between AMH and LH and LH/ FSH in PCOS and controls.[7] The results of the present study revealed a significant correlation between AMH and age, Nardo LG, et al. indicated that AMH is generally decreased with chronological age. In the present study, significant positive correlations were found between AMH and serum testosterone in PCOS group.[29] These findings are in accordance with the results of the previous studies[7,22,28] and add to the existing evidence for small ovarian follicles in the production of both AMH and androgens.

Conclusion

The means of serum AMH and AFC in PCOs group were higher than the means in the comparison group. Elevated levels of AMH were associated and related to the increased number of follicles in women with PCOS.

Competing interests

The authors declare that they have no competing interests.

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