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RESEARCH ARTICLE

Correlation between AMH and Polycystic Ovarian Syndrome Phenotypes among Iraqi Population

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Abstract

Background: Anti-Mullerian hormone is considered as a marker with has an important function in ovarian folliculogenesis besides the steroidogenesis. Anti-mullerian hormone with ovarian stimulation may guide the treatment plan in infertility. Objective: To evaluate the anti-Mullerian hormone role in identification and diagnosis of polycystic ovarian syndrome phenotypes in Iraqi population. Patients and Methods: This retrospective cohort study was carried at Al-Yarmuk Teaching Hospital in Baghdad from the 1st January 2016 to the 1st of December 2018. Ninety-nine women were enrolled in the study. Anti-Mullerian hormone was obtained from those women, those who had high AMH above 5 ng/ml were enrolled in the study, then they classified based on the level of AMH into three groups: First group, their AMH 5-10 ng/ml, the second group, the AMH level was 10-14 ng/ml, the third group their AMH was more than 14 ng /ml. Then the comparison between these groups was done according to their polycystic ovary syndrome phenotype, and their endocrine parameters. Results: The percentages of Hyperandrogenimia were not statistically significant except for that between group 3 and 2 (78.8% vs. 50% respectively; the P value was= 0.014). The polycystic ovaries by ultrasound was significantly higher in group 3 (as the P value was= 0.001). PCOS diagnosis was significantly more prevalent in group 2 (91.2%) and group 3 (100%) in comparison with group 1 (50%). The difference was statistically significant for women with polycystic ovary syndrome who had regular period and the percentages were (65.6% vs. 26.5% vs. 3% for group 1 vs. 2 and 3 respectively)while there was a significant higher percentages for oligomenorrrhea in group 2 (67.6%) ,and group 1 (31.3%), Whereas proportion of amenorrhea was significantly higher in group 2 (5.9%) , and group 3 (24.2%) in comparisons to group 1 (3.1%). Conclusion: Antimullerian hormone levels might be used for polycystic ovary syndrome diagnosis and determine its severity. The majority of women with Antimullerian hormone >10 ng/mL will have severe type of PCOS.

Keywords: (*PCOS), Antimullerian hormone, Polycystic phenotype.*

Introduction

Polycystic ovarian syndrome is one of the important endocrine disorders. In general population it affects around 4 to 12 percent [1]. Patients with PCOS frequently exhibit insulin resistance and hyperinsulinemia which participate in the ovarian steroidogenic dysfunction of PCOS [2] Ovarian follicular arrest, infertility, and metabolic features occur secondary to hormonal disturbances [3].

We need two of the following criteria which is 'Rotterdam Criteria for the diagnosis of PCOS and it includes: hyperandrogenism (clinical or biochemical), oligo-menorrhea or amenorrhea, polycystic ovaries by ultrasound, with the presence of > 12 follicles in the ovary ,measuring 2-9 mm in diameter, and ovarian volume (>10 cm^3). Among those PCOS women there is heterogeneity of signs and symptoms that may alter with time [4, 5]. In PCOS patient, the ovary has primary hyperandrogenism because there is overexpression of the CYP17 gene that leads to abnormality in the ovarian steroidogenesis, which effect synthesis of androgen and increased expression of the LH receptor, with increase the sensitivity of theca cells of ovary to LH [6]. Anti-Müllerian hormone (AMH) has important function in controlling the ovarian reserve by slowing the rate through inhibition of activation of primordial follicles [7].

AMH encourages follicular atresia, so it takes part in the ovarian follicle form in PCOS [8]. AMH is secreted mainly by the small-antral follicles (4-8 mm size), and its level is proportionate to the follicular fluid level of small preantral and antral follicular pool.

Its level gradually declines with the increase in the size of the follicles and a sharp decline in the serum/follicular AMH level takes place once the size of the follicle reaches 8 mm or dominant follicle is selected. The rate of decline occurs after the age of 25 years (peak) until 50 year old [9].AMH in females is reported at the 36th week of gestation. Then, the surge of AMH release which occurs gradually indicates a steady increase in the number of ovarian follicles in later life [10].

Serum AMH has a role in the PCOS diagnosis when the threshold at 4.7 ng/mL [11].In PCOS women the high serum AMH take part in chronic anovulation, and this play role in pathogenesis of PCOS [12].In assisted reproductive techniques, if the serum AMH is low, this means low quality and number of oocyte, and in PCOS patient the higher level of AMH, the less response to treatment will obtain [13].AMH used as an ovarian reserve marker.

The promoter gene expression in PCOS is responsible for the increase level of AMH, and the high level is usually related to sever form or phenotype of PCOS, which result from the androgen stimulation of follicular growing. [14, 15].It is higher than normal women by two to three folds, and it is related to the antral follicle count [16].Serum level is not altered by the use of oral contraceptives, or the menstrual cycle. AMH takes part in the severity of PCOS due to its ability to inhibit the activity of the aromatase enzyme [17].

Patients and Method

A retrospective cohort study conducted in the department of obstetrics and gynecology and infertility clinic at AL-Yarmouk Teaching Hospital, Baghdad, Iraq; in cooperation with laboratory department (Hormonal unit); for a period of 1 year from January 2017 to February 2018. It included 99 women who were attending the out patients infertility clinic of Al-Yarmouk Teaching Hospital and their random serum AMH level were more than 5 ng/ mL, and those with AMH less than 5 ng/mL were excluded from this study. After that the Women classified into 3 groups depending on level of serum AMH, 1st group AMH level was5 to 10 ng/mL (n=32), 2nd group >10 to14 ng/mL (n=34), and 3ed group >14 ng /mL (n=33).

Evaluation for PCOS was done for those women due to their high serum AMH level as one step for the investigation of infertility. The data collected from patients to take past obstetrical, gynecological, medical, and surgical history, then the following parameters obtained including: age, gravidity, parity, body mass index (kg/m2) and investigations was done; luteinizing hormone (LH), serum follicle-stimulating hormone (FSH), total testosterone, dehydroepiandrosterone sulfate (DHEAS), 17-OH-progesterone, Anti mullerian hormone (AMH), thyroid-stimulating hormone, prolactin and ultrasonography.

With full examination for all women .The diagnosis of women with PCOS depend on the Rotterdam criteria. Those Patients with highly elevated prolactin, or have thyroid problem congenital adrenal hyperplasia, or androgen-secreting tumors were excluded from the study. Random serum AMH levels were estimated by using enzyme linked immunosorbent assay for those woman and at any day during the menstrual cycle.

Statistical Analysis

Analysis of our data was done by using Statistical Package for Social Sciences (SPSS) version 25 . The categorical data were presented by frequencies and percentages and the associations were tested by Pearson's chi-square test. The continuous data were presented as mean and standard deviation. Independent t- test (two tailed) and Analysis of variances (ANOVA) test were used to compare the continuous parametric variables between study groups.

The correlations of Antimullerian hormone with other criteria of study groups was assessed by using Pearson's correlation. Weak correlation was obtained when the coefficient of correlation (r) (0 - 0.3), moderate if (r=0.3-0.7) and strong when (r>0.7), if the correlation proceeded by (+) sign then the correlation is direct or positive, while if it was preceded by (-) sign then the correlation is inverse or negative. Receiver Operator (ROC) curves used to assess the validity parameters of Antimullerian hormone.

Results

Our study involving examination of 450 women at reproductive age attending the infertility clinic for evaluation of fertility, testing of serum AMH level for those women was done in order to detect the proportion of the elevated serum AMH more than 10 ng/mo in women at reproductive age, our data collected during a period between 2016-2018, based on hormonal investigation and ultrasound.

We found that 99 patient in this study had their AMH more than 5 ng/ml, identification of women at high risk of poly cystic ovaries using AMH level >5 ng /ml, and depending on this level, those women classified into 3 groups: 1st group (32 women) with AMH 5 to 10 ng/mL, the 2nd group (34 women) AMH >10 to 14 ng/mL 3rd group (33 women) AMH >14 ng/mL. Tables 1 show the biochemical, clinical and hormonal features of the three groups and the comparison between them.

The comparison of body mass index among the study groups revealed that; group 2 significantly exceeded that in group 1 and 3 respectively (P<0.001), while there was no difference between group 1 and 3. The age was significantly greater in those group 1 than the other groups 2 and 3 respectively (P<0.001), The LH level, the LH/FSH, testosterone, and DHEAS were significantly higher in all three groups with the (P<0.001).

The percentages of patients with Hyperandrogenimia were not significant except for that between group 3 and 2, as the percentage was higher among group 3 in comparison with group 2 (78.8% vs. 50%; the P value was= 0.014). The polycystic ovaries by ultrasound was significantly higher in women of group 1 and 2 than the group 3 (P= 0.001).

While the diagnosis of PCOS was more significant in group 2 (91.2%) and group 3 (100%) groups compared with group 1 (50%). There was a significant rate of regular period among patients of 1st group (65.6%) and 2nd group (26.5%) than 3rd group (3%), while the oligomenorrrhea was significantly higher in 2nd group (67.6%), and 1st group (31.3%), Whereas proportion of amenorrhea was highly significant in 2nd group (5.9%), and 3rd group (24.2%) in comparisons to 1st group (3.1%) as shown with Table 1.

Table 1: Comparison of the main parameters among the study groups, n=99

Variables	Serum AMH (ng/ml)			P value		
	5 – 10 n= 32	>10-14 n= 34	>14 n= 33	5 - 10 vs. >10-14	5 - 10 vs. >14	>10-14 vs. >14
	Mean ± SD	Mean ± SD	Mean ± SD			
AMH (ng/mL)	6.8 ± 1.1	11.9 ± 1	21.7 ± 1.7			
BMI (kg/m2)	23.7 ± 1.1	27.4 ± 1.2	23.9 ± 1.4	<0.001**	0.504	<0.001**
Age (years)	32.1 ± 2.7	29.7 ± 3.3	27.2 ± 5.2	0.014*	<0.001**	0.009**
FSH (IU/L)	5.2 ± 0.9	5.6 ± 0.9	5.2 ± 0.8	0.107	0.973	0.097
LH (IU/L)	5.6 ± 0.8	7.9 ± 1.3	11.6 ± 2.3	<0.001**	<0.001**	<0.001**
LH/FSH RATIO	1.2 ± 0.4	1.7 ± 0.4	2.5 ± 0.5	<0.001**	<0.001**	<0.001**
Testosterone (ng/dL)	42.2 ± 1.9	51.9 ± 13.2	76.6 ± 3.7	<0.001**	<0.001**	<0.001**
DHEAS (mg/d)	201.6 ± 11.6	176.9 ± 11.3	258.7 ± 42.7	<0.001**	<0.001**	<0.001**
Androgenic features						
Hyperandrogenimia	20 (62.5%)	17 (50%)	26 (78.8%)	0.307	0.149	0.014*
Polycystic ovaries (US)	16 (50%)	31 (91.2%)	33 (100%)	<0.001**	<0.001**	0.239
PCOS Diagnosis	15 (46.9%)	26 (76.5%)	33 (100%)	0.013*	<0.001**	0.005**
Menstrual regularity						
Regular cycles	21 (65.6%)	9 (26.5%)	1 (3%)	0.001**	<0.001**	0.013*
Oligomenorrhea	10 (31.3%)	23 (67.6%)	24 (72.7%)	0.003**	0.001**	0.65
Amenorrhea	1 (3.1%)	2 (5.9%)	8 (24.2%)	0.591	0.027*	0.045*

SD: Standard deviation; *<0.05; **<0.01 significant by ANOVA test

Figure 1 demonstrates the receiver operator curve which measures the validity criteria of Antimullerian Hormone level in detecting PCOS.

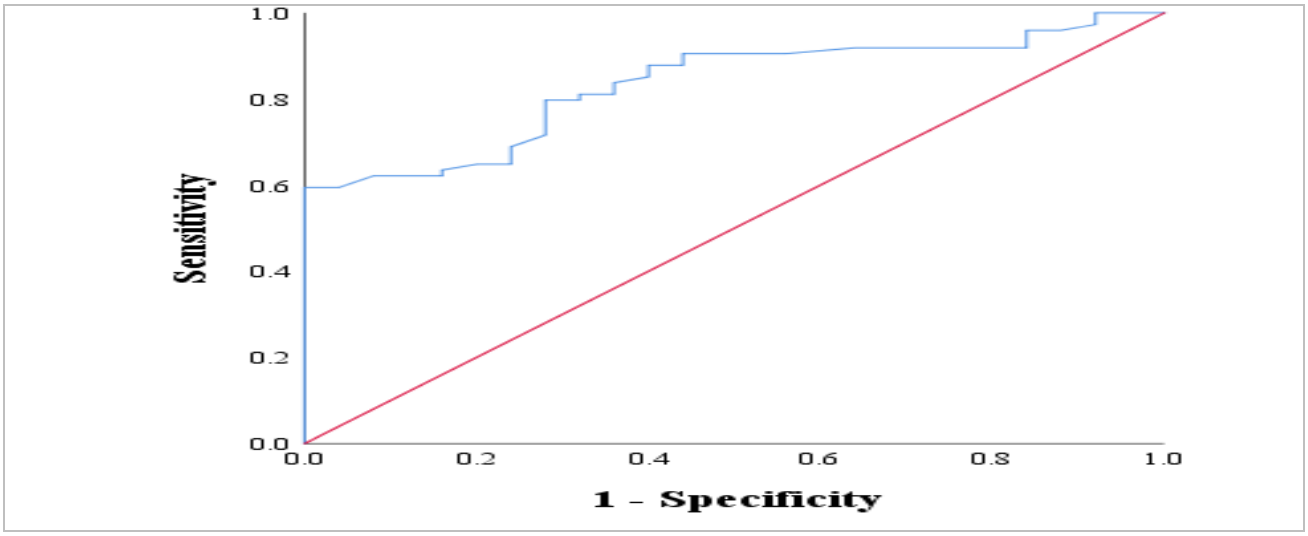

Fig.1 ROC curve, Antimullerian Hormone level ability to detect PCOS
Area under the curve, 0.87; 95% confidence interval, 0.80e0.92; P < .0001.

The largest Youden index and the specificity (72.0%) and sensitivity (79.7%) for the detection of polycystic ovarian syndrome was demonstrated when the threshold or cutoff point of AMH concentration was 10 ng/mL, with Positive predictive value(89.4%), Negative predictive value(54.5%), and the Accuracy (77.8%) (Table 2).

Table 2: Cutoff and Validity criteria of Antimullerian Hormone to detect PCOS

AMH (ng/mL) cutoff point	Area under curve	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
10	0.833	79.7%	72.0%	89.4%	54.5%	77.8%

The correlation analyses in (Table 3) showed that serum AMH levels correlated positively with LH (r Pearson Correlation 0.84, P-value <0.001**), LH/FSH RATIO(r 0.763, <0.001**), total testosterone (r 0.853, P <0.001**) and DHEAS (r 0.653, P <0.001**). In contrast, AMH levels did not correlate with BMI (r -0.118, P =0.243), age (r -0.441, P <0.001**) or FSH (r -0.041,P = 0.689)

Table 3: Correlation of Antimullerian Hormone with other parameters of the study participants

Variables	AMH (ng/mL)	
	Pearson Correlation	P-value
BMI (kg/m2)	-0.118	0.243
Age (years)	-0.441	<0.001**
FSH (IU/L)	-0.041	0.689
LH (IU/L)	0.84	<0.001**
LH/FSH RATIO	0.763	<0.001**
Testosterone (ng/dL)	0.853	<0.001**
DHEAS (mg/d)	0.653	<0.001**

Discussion

To date, PCOS represents a complex metabolic-endocrine disorder with profound effects on women fertility. AMH is a glycoprotein related to the growth of follicles [18].It has a strong correlation with PCOS phenotype as well as ovulatory dysfunction, whether morphological alterations in the ovary or biochemical-hormonal interactions play a major role in the hormone level elevation, is still controversial [18, 19]. Our study revealed the relationship between the very high level of AMH in a group of population women at reproductive age, that characterizes them into three groups depending on the level of AMH more than 10 ng/ml, those who had high AMH levels, their polycystic morphology prevalence was >76.5% ,and >67.% oligo/amenorrhea, >5.9% Amenorrhea ,>50% hyperandrogenemia, and polycystic ovaries by ultrasound 91.2% then >76.5 % of those patient diagnosed with PCOS. In Comparison between 1st and 2nd group, we found that 2nd group had higher proportion of polycystic morphology (PCOM), and PCOS Study by Matsuzaki T et al in 2017 showed there were a high AMH within PCOS patients and the cut value of serum AMH for PCOS diagnosis of 7.33 ng/mL had low efficacy as their specificity and sensitivity were (76.85, 44.7%) respectively. While there was a higher efficacy when the

cut-off value of 10 ng/mL, with specificity and sensitivity (92.6%, 24.6%) respectively [20].Other study by Kyeong et al. in 2017, is consistent with our study which reported that the serum AMH level is a good marker for the diagnosis of PCOS at any age and for the PCOS diagnosis, the cut off value was 10.0 ng/ml, with sensitivity and specificity (71% , 93%) respectively.

The women with polycystic morphology had higher level of serum AMH than without, ($p < 0.05$) and they found positive relation among Hyperandrogenism and AMH in PCOS; there was a ($\beta = 0.31, p < 0.01$), for AMH level as determinant of total testosterone [21].R. Tal et al in 2013 found that women with AMH>14ng/ml have a lower BMI and significantly higher level of androgen and amenorrhea than other groups of PCOS and they concluded that AMH correlate positively to LH level and androgen level ,and correlate negatively with BMI [22].Furthermore higher AMH level associated with increased risk of ovarian hyper stimulation syndrome in women using gonadotroghin [21].

Futher research to evaluate the level of AMH in follicular fluid could highlight the method to use it as indicator of "quality" as well as "quantity" of the ovarian follicles and open a new window to include it as a marker in evaluation of patients with PCOS and as a modality in the management of infertility.

Conclusion

AMH has high predictive and diagnostic accuracy in women with PCOS and it might be used to categorize those women depending on the AMH levels; Therefor assess the severity of PCOS and monitoring patients response and forecasting.

References

1. Cunningham Leveno, Bloom Spong Dashe et al (2016) Polycystic ovary syndrome and hyperandrogenisim. In: William gynecology; 3rd edition; ch. 17, McGraw-Hill companies, 413.
2. Jonathan SB et al (2015) Polycystic Ovary Syndrome. In: Jessie Dorais, Matthew Peterson. Berek & Novak's Gynecology 15th edition, 1876.
3. Keith Edmonds, et al (2016) Polycystic Ovary Syndrome and Secondary Amenorrhoea. In: Adam Balen. Dewhurst's Textbook of Obstetrics and Gynecology. 8th edition, 513.
4. David ML, Mark DK et al (2016) Polycystic ovary syndrome. In: Adam Balen. An Evidence-Based text book for MRCOG, 655.
5. Keith Edmonds, et al (2018) Polycystic Ovary Syndrome and Secondary Amenorrhoea. In: Adam Balen. Dewhurst's Textbook of Obstetrics and Gynecology. 9th edition, 637.
6. Jon Havelock et al (2018) Polycystic ovary syndrome. BCMJ, 60(4): 210-216.
7. Michael W P, et al (2017) A putative role for anti-Müllerian hormone (AMH) in optimizing ovarian reserve expenditure. Endocrinol. J., 233(1): 1-13.
8. Xinyu Qi, Yanli Pang, Jie Qiao et al (2016) The role of anti-Müllerian hormone in the pathogenesis and pathophysiological characteristics of polycystic ovary syndrome. Eur. J. of Obstetrics & Gynecology and Reproductive Biology, 82-87.
9. Awadhesh KS, Ritu Singh, et al (2015) Can anti-Mullerian hormone replace ultrasonographic evaluation in polycystic ovary syndrome. Indian J. Endocrinol and metabol., 19 (6): 731-743.
10. Zehra J, Syeda SF, Khalid A, Rabia M, et al (2016) Anti-Mulleria Hormone: Above and Beyond Conventional Ovarian Reserve Markers. J. Disease markers, 9.
11. Melissa P, Lisa K, Sarah M, Ying-HL, Bina S, et al (2012) Elevated Serum Anti-Müllerian Hormone in Adolescents with Polycystic Ovary Syndrom :Relationship to Ultrasound Features. J. Pediatr. Endocrinol. Metab., 25(0): 983-989.
12. Li J, Li R, Yu H, Zhao S, Yu Y, Qiao J et al (2016) The relationship between serum anti-Müllerian hormone and the follicular arrest for women with polycystic ovary syndrome. Eur. J. Obstet. Gynecol. Reprod. Biol., 199: 82-7.
13. Laura P, Suman R, Helen DM, et al (2010) Anti-Müllerian hormone and polycystic ovary syndrome: a mountain too high? In Reproduction, 139 (5): 825-833.

14. Budi W, Cynthia A. S, et al (2018) Anti Müllerian Hormone as a Predictor of Metabolic Syndrome in Polycystic Ovary Syndrome. Indones. J. Obestet. Gynecol., 83.

15. Nifise TO, Hakan N, Ayse TA, Gurkan U, et al (2017) The relation between serum anti-Mullerian hormone levels and follicle count in polycystic ovary syndrome. Eur. J. Research, 2149-3189.

16. Toshiya M, Munkhsaikhan M, Takeshi I, Altankhuu T, Kiyohito Y, Yiliyasi M, Rie Y (2017) Relationship between serum anti-Mullerian hormone and clinical parameters in polycystic ovary syndrome. J. Endocrine, 64(5): 234.

17. Budi W, Mila M, Nadia Sh, Darrell F, Kanadi S, Muharam N, Andon H, et al (2014) Anti-mullerian hormone as a diagnostic and prognostic tool for PCOS patients. J. Assist Reprod. Genet., 31(10): 1311-1316.

18. Parahuleva N, Pehlivanov B, Orbecova M, Uchikova E et al (2014) Anti-Mullerian hormone in the major phenotypes of polycystic ovary syndrome. Akush Ginekol (Sofiia), 53(5):22-7.

19. Hüseyin A , Sefa K, Ferhan E, Serpil A, Et al (2018) Can we use serum Anti-Mullerian hormone to differentiate the diagnosis between polycystic ovary syndrome patients and healthy women with polycystic ovarian morphology and regular menstrual cycles. Saudi. Med. J., 39(10): 1011-1016.

20. Matsuzaki T, Munkhzaya M, I T, Tu ngalagsuvd A, Yano K et al (2017) Relationship between serum anti-Mullerian hormone and clinical parameters in polycystic ovary syndrome. In Endocr J., 64(5):531-541.

21. Do Kyeong S, Jee-Y O, Hyejin L, Yeon-Ah S, et al (2017) Differentiation between polycystic ovary syndrome and polycystic ovarian morphology by means of an anti-Müllerian hormone cutoff value. In Korean J. Intern. Med., 32(4): 690-698.

22. R Tala, DB Seifera, M Khanimova, RV Grazia et al (2013) Characterization of women with ultra high serum anti-mullerian hormone (AMH) levels and its association with polycystic ovarian syndrome (PCOS) phenotype. Fertility and Sterility, 100(3):S127.

