Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.5, No.4, 2015

The Relation of Serum Anti-Mullerian Hormone with Polycystic Ovary Syndrome: Correlation with Clinical and Hormonal Parameters

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Abstract
Background: Polycystic ovary syndrome PCOS) is an endocrine disorder affects 5-10% of all women. The antimullerian hormone (AMH) secreted from granulose cells and is a marker of follicle pool size, in recent studies of PCOS the serum AMH levels were elevated two to threefold.**Objective:** to compare AMH between women with and without PCOS, and to investigate if any relationship of AMH to the clinical and hormonal parameters in both groups.**Design:** Prospective comparative and analytic study.**Setting:** In fertility center of Al-Sader medical city in Najaf.**Material and methods:** A total of 86 subfertile women divided into PCOS group (56) and control non-PCOS group (30). The PCOS group diagnosed according to Rotterdam consensus meeting definition (2004). For both groups during early follicular phase transvaginal sonography was performed. Blood samples were collected for: FSH, LH, testosterone, prolactin and AMH levels.**Results:** There was highly significant increase level of AMH in PCOS than in non-PCOS group. From 56 patients with PCOS, 28 patients took metformin treatment for at least 2 months and the other 28 patients on no treatment. There was no significant differences in all hormonal parameters between them. There were no significant correlations between the AMH and all the parameters in both PCOS and controls**Conclusion:** Increased AMH levels in PCOS possibly due to increased number of small antral follicles. However, there was no correlation between the AMH and other clinical or hormonal parameters. Large scale studies are needed to define the metformin effect on hormonal outcome.
Keywords:- PCOS, AMH

1. Introduction

PCOS is the most common female endocrine abnormality affects around 22% of female of reproductive age(1). It is characterized by: Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea, clinical and\or biochemical evidence of hyperandrogenism, presence of polycystic ovary by ultrasound as an ovary with 12 or more subcapsular follicles 2-9 mm in diameter and increased ovarian stroma and volume (> $10cm^3$) on trans-vaginal ultrasound (The Rotterdam consensus 2004)(2).

AMH is a homodimeric glycoprotein belongs to the Transforming Growth Factor-β superfamily, the AMH gene is located on short arm of chromosome 19(3). In females AMH is produced only by granulose cells from preantral and small antral follicles(4). AMH has an inhibitory effect on the primordial follicle recruitment as well as on the responsiveness of growing follicles to follicle-stimulating hormone (FSH), suppressing the FSH-depending aromatase and,also, diminish the LH receptors, thus helping the selection of the dominant follicle(5). AMH has been heralded as a marker of ovarian aging and reserve in humans(6). The cause of the increased AMH production in PCOS is unknown; however, the distinctive feature of PCOS is failure of follicular maturation, despite initial recruitment, resulting in anovulation and accumulation of preantral and small antral follicles, which contribute significantly to the production of AMH(7). Granulosa cells from anovulatory PCOs produced on average 18 times more AMH than granulosa cells from ovulatory PCOs (8), also increased concentrations may be a consequence of other factors altered in PCOS, the most obvious being androgen production. Evidence to support this comes from the studies showing that in serum, AMH has been positively correlated to androgen levels(9). Another candidate for the cause of the increase in AMH in PCOS is insulin. Insulin has been shown to enhance gonadotrophin-stimulated steroid production in granulosa cells and theca (10).

Although metformin is now one of the most common treatments for PCOS, to our knowledge, there are no studies in which the initial concentration of AMH has been correlated with response to treatment, but it is clear that AMH concentrations do fall during treatment, even if this does take some time(11), in some studies it was not until after 6 or 8 months of metformin treatment that AMH levels fell (12). The objectives of the present study were to compare serum AMH levels between women with and without polycystic ovary syndrome, and to investigate if any relationship of AMH to the clinical and hormonal parameters in both groups.

2. Patients and Methods

This study was done in the Fertility center of Al-Sader teaching hospital in Al –Najaf between March and

September 2013. The study was approved by the local ethical committee.

2.1 Patients:- A total of 86 patients at reproductive age were enrolled in our study, they were seeking consultation for either primary or secondary infertility, a complete history was recorded on specially prepared data sheet including; age, weight, height ,cycle history, hirsuitism. The inclusion criteria were: age 20-35 years, both ovaries present by trans-vaginal ultrasound, no previous ovarian operation, normal TSH levels, and no current hormone therapy.

Those 86 patients divided into PCOS group (56 women) and control group (30 women). The PCOS group diagnosed according to the Rotterdam consensus meeting definition of PCOS (ESHRE\ASRM, 2004), based on the association of at least two of the three following criteria: 1.Oligo- and\or anovulation(<6 menstrual period\year). 2.Hyperandrogenism, as defined either by hirsuitism (Ferriman-Gallwey score >8), or minor signs such as acne or seborrhea, and\or testosterone >3 nmol\l and\or androstenedione >12nmol\l. 3.Ultrasound PCO and\or increased ovarian volume.

Twenty-eight subjects from the 56 PCOS women were already on treatment with metformin at 1500-1700mg\day for at least 2 months.

The control group consisted of 30 healthy women with male, tubal or unexplained infertility. They had regular cycles, no endocrine abnormalities, and normal ultrasonic ovarian morphology.

2.2 Methods:- For both groups during the early follicular phase (cycle day 2 or 3) of a spontaneous or progestin induced cycle transvaginal sonography was performed for detection of the number of antral follicles (<10mm) using a 6.5 MHz endovaginal probe (HD7 Philips, Germany). Blood samples were collected for the following hormones: FSH, LH, TSH, testosterone, and prolactin levels. The blood on plain tube centrifuged after clotting, then serum samples were separated and stored at -70C until assayed. All these hormonal assays were measured by immunoassays RIA. Serum AMH levels were measured using Enzyme-Linked Immunosoebent Assay (ELISA), using kits supplied by (AMH Gen II ELISA, Beckman Coulter, Inc.250 S. Kraemer Blvd. Brea, CA 92821 U.S.A.). Results are expressed in nanogram per ml. ***Statistical analysis:*** was done by using SPSS version 20 in which we use independent sample T-test for measurement data and pearson correlation coefficient to compare between two continuous variables. We set *P* value <0.05 as significant.

3. Results

The result of our study consist of 86 women, fifty six of them had PCOS while the others healthy controls. Table-1 shows the clinical characteristics of the PCOS and the control groups.

Table 1. Comparison between control and PCO groups in different characteristics.

Characteristics		Control (n=30)	PCOS (n=56)	P value
		Mean ±SD	Mean ±SD	
Age		30.13±4.22	24.37±6.15	<0.001
BMI		24.64±2.65	26.6±3.58	0.004
Type of infertility	Primary	23(76.7%)	49(87.5%)	0.195
	Secondary	7(23.3%)	7(12.5%)	
Duration of infertility(years)		6.16±3.28	4.6±2.99	0.029

The main hormonal finding in each group are presented and compared in Table-2.

Table 2. Hormonal findings in controls and PCOS patients.

Characteristics	Control(n=30)	PCO(n=56)	*P* value
	Mean ±SD	Mean ±SD	
FSH	6.18±1.89	5.33±2.34	0.091
LH	5.08±4.25	7.52±4.83	0.03
LH/FSH ratio	0.84±0.7	1.56±1.21	0.005
Testosterone	0.39±0.26	0.65±0.49	0.01
Prolactin	16.24±8.53	24.41±17.54	0.019
AMH	3.27±1.37	6.51±2.03	<0.001

The mean FSH and TSH were not significantly different between the two groups, while the mean LH, LH\FSH ratio, testosterone, prolactin and AMH were significantly higher in the PCOS group compared with the control one. The mean serum AMH level was 2-fold higher in PCOS than controls.

Table 3/ Hormonal findings in metformin taking PCOS patients and not.

Characteristics	PCOS (n=28)	PCOS &Metformin (n=28)	P value
	Mean ±SD	Mean ±SD	
FSH	4.99±1.82	5.67±2.76	0.279
LH	7.59±5.88	7.48±4.23	0.942
LH/FSH Ratio	1.57±1.38	1.55±1.13	0.952
Testosterone	0.649±0.496	0.652±0.505	0.985
Prolactin	25.9±22.7	22.9±10.18	0.524
AMH	6.44±2.058	6.58±2.054	0.80

From 56 patients with PCOS, 28 patients took metformin treatment and the other 28 patients on no treatment. In table 3 shows the different hormonal levels between the metformin taking group and those PCOS without any treatment. There were no significant differences in all parameters between them.

Table 4. Correlation between AMH and different hormones in whole patients

Parameter	r	P value
FSH	- 0.153	0.162 NS
LH	0.123	0.303 NS
Testosterone	0.19	0.081 NS
Prolactin	0.177	0.106 NS
LH/FSH Ratio	0.229	0.053 NS

Table 4. present the correlation between AMH and hormonal parameter in the two groups together. No correlation was found between AMH and LH, LH\FSH, testosterone, and prolactin levels. A negative correlation was found between AMH and FSH although not-significant.

Table 5. Correlation between AMH and clinical, hormonal parameters in the PCOS and Control groups.

Parameters	PCO (n=56)			Control (n=30)		
	r	p	Sig.	r	p	Sig.
Age	0.008	0.956	NS	-0.29	0.127	NS
BMI	0.137	0.313	NS	0.283	0.136	NS
FSH	-0.115	0.397	NS	0.182	0.345	NS
LH	-0.117	0.450	NS	0.094	0.633	NS
Testosterone	0.024	0.860	NS	-0.029	0.882	NS
Prolactin	-0.003	0.980	NS	0.136	0.482	NS
LH/FSH	0.024	0.878	NS	0.015	0.939	NS

Table-5 presents the correlation between AMH with clinical and hormonal parameters in the PCOS and control groups separately. Also there were no significant correlations between the AMH and all the parameters in both PCOS and controls.

4. Discussion

This prospective study was conducted to evaluate the relevance of routine AMH measurement in infertile females with PCOS. The result of the present study have shown that the serum AMH level was significantly increase in PCOS. The present results confirm those of previous studies (Pigny et al. 2003, Begawy et al. 2010, Bushra et al. 2012, Woo et al. 2012, Homburg et al. 2013, Luisa Casadei et al. 2013) showing that AMH levels are 2- to 3-fold higher in women with PCOS compared with healthy women. Also there were significant increase in testosterone, prolactin, LH\FSH, and LH hormones in PCOS group, which are comparable with the results of previous studies Begawy et al. 2010 (7) and Nascimento et al. 2013(18). Table (3) in our study when we compared AMH levels among metformin treatment with PCOS and non-metformin treatment PCOS, we did not find a significant differences between the two subgroups. This in agreement with Aykut et al. 2007 (19), Romualdi et al. 2011 (8), and Nascimento et al. 2013 who showed that the AMH levels unchanged following a short course of metformin therapy (18). In contrast to our study Tomovac et al. 2011 (20) showed decreased AMH levels in women with maximal doses of metformin therapy and for 6months. Neagu et al. 2012 (21) also showed decrease AMH levels after 2 months of metformin treatment. This difference may be, the dose, duration and time of use of metformin are factors associated with reduction of AMH levels.

Table 4 & 5 in the current study we demonstrated the correlation between AMH with clinical and hormonal parameters in PCOS and control groups together and separately. The result of the present study

revealed no significant correlations between AMH and age, BMI. This is in agreement with Pigny et al. (13) and Begway et al. (7). Although this was in contrast to other studies like Chen et al. (22) and Nardo et al. (23) Differences in study populations and guidelines for treatment have to be borne in mind to explain discrepancies between the studies.

In the present study, we also found no correlations between AMH and serum LH, FSH, LH\FSH, testosterone, and prolactin levels in both groups. Pigny et al. (13) found no relationship between AMH and age, BMI, LH and LH\FSH in PCOS and controls, but found positive relation to the serum testosterone in PCOS only. While Begway et al. (7) found positive correlation between AMH and LH, LH\FSH in both groups and positive correlation with testosterone in PCOS group exclusively. Pigny et al. suggested that the increase in AMH levels in PCOS is a consequence of androgen-induced excess in small follicles and that each follicle produces normal amount of AMH. However, Pallet et al. (24) found that raised serum AMH in PCOS is a reflection of both an increase in production per cell and the increase in follicle number. Nascimento et al. (18) found a positive correlation between AMH and testosterone only prior to treatment with metformin. So the no correlation of AMH with androgen in our study may be because we used total PCOS patients that with metformin and without. However, Nardo et al. (23) indicated that AMH is similarly related to androgens in women with and without PCOS.

5. Conclusions

Increased AMH levels in PCOS patients possibly due to increased number of small antral follicles. AMH levels did not change after metformin treatment.

6. Recommendations

6.1 AMH assessment before and after metformin treatment for at least 6 months is recommended in the plan of management of PCOS.

6.2 Since serum AMH levels correlate well with antral follicle count the measurement of AMH could be used as a tool to diagnose PCOS and to evaluate treatment efficacy.

6.3 Studies are needed to determine the cutoff of AMH for diagnosis of PCOS.

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