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The Time for Thinking in Serum Anti-mullerian Hormone Levels and the Criteria of Polycystic Ovary Syndrome

Basil O. Saleh[1*], Wasan F. Ibraheem[2] and Nada S. Ameen[3]

[1]Clinical Biochemistry, College of Medicine, University of Baghdad, Iraq.
[2]Clinical Biochemistry, Ministry of Health, Iraq.
[3]Department of Obstetrics and Gynecology, Ministry of Education and Scientific Research, Baghdad, Iraq.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Studies indicated that anti-mullerian hormone (AMH) could be a potential biological marker for diagnosis of PCOS.
Aim: The aim of this study is to ensure the role of serum AMH levels in diagnosis of PCOS and is the time for thinking about the modification of the criteria of this syndrome.
Subjects and Methods: This study was carried out at Clinical Biochemistry Unit, Biochemistry Department, College of Medicine, Baghdad University, Iraq, during the period from November 2009 to July 2010. It included 33 infertile women with PCOS who were subdivided into; Group I (GI) involved 20 women who were studied on day 2-4 of their menstrual cycle and Group II (GII) which consisted of 13 women who were studied on 11-13 cycle day. Eighteen healthy fertile women were served as controls. Investigation included serum measurements of AMH, inhibin B, FSH, LH, E2, prolactin and free testosterone in PCOS and control women by using ELISA technique.

**Corresponding author: E-mail: basil_omsal@yahoo.com;*

Results: The present study showed significantly increased serum AMH in PCOS women (both GI and GII) compared with control women (P=0.027, P=0.002, respectively). There was no significant difference between the PCOS women. There was a significant positive correlation between serum AMH levels and the values of ovarian volume in PCOS women of GI (r=0.476, P=0.035).
Conclusion: Measurement of serum AMH level could be considered as a useful tool in diagnosis of PCOS and it is appropriate for considering changes in the criteria for distinguishing this syndrome.

Keywords: PCOS; AMH; ultrasonic study.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility in women, affecting approximately 8% of women of reproductive age [1]. The Androgen Excess Society evidence-based definition considers PCOS as a mainly hyperandrogenic disorder, and therefore sustains a diagnosis of PCOS only in the presence of clinical and/or biochemical hyperandrogenism, which should be accompanied by either oligo-ovulation and/or polycystic ovarian morphology [2]. Anti-mullerian hormone (AMH), also known as Müllerian-inhibiting substance, is a member of the transforming growth factor-β (TGFβ) superfamily, which includes more than 35 structurally related peptides including activins, inhibins, bone morphogenetic proteins (BMPs) and growth differentiation factors. Many of these are involved in the reproductive function of both sexes [3]. AMH is a homodimeric, disulfide-linked glycoprotein with a molecular weight of 140 kDa. Its gene is located on the short arm of chromosome 19, band 19p 13.3 in humans [4]. It is strongly expressed in the Sertoli cells from testicular differentiation up to puberty and, but to a much lesser degree in the granulosa cells (GCs). It is responsible for the ipsilateral regression of the Müllerian duct by eight weeks. After the involution of the Müllerian system, AMH continues to be secreted, but it has no known function. Although it may have no role in the female development, its production later in life by the GCs raises the possibility of autocrine and paracrine actions in oocyte maturation and follicle development [5].

AMH is expressed in the growing pre-antral or small antral follicles in the ovary and reflects the recruited ovarian follicular pool [6]. During reproductive age of a woman, AMH is secreted from granulosa layer cells of primary follicles which are developed from primordial follicles. It is secreted from small antral and preantral follicles which are less than 4 mm in diameter. Secretion of AMH is reduced during follicle maturation, and in follicles which are more than 8 mm AMH is not secreted anymore; therefore AMH serum level is constant during the menstruation cycle [7]. The aim of the present study is to ascertain the role of serum AMH measurement in the diagnosis of PCOS and to consider the modification of the criteria used to identify this syndrome.

2. SUBJECTS AND METHODS

This study was carried out at Clinical Biochemistry Unit, Biochemistry Department, College of Medicine, Baghdad University and at Kamal AL-Samaraee Hospital- Baghdad, Iraq, during the period from November 2009 to July 2010. It included 33 infertile women with PCOS; their age range was (18-38 years). These women were subdivided into 2 groups; Group I (GI) which involved 20 women who were diagnosed to have PCOS and were studied on days 2-4 of their menstrual cycle and Group II (GII) which consisted of 13 women with PCOS and were studied on cycle days 11-13. Eighteen healthy women who have had regular and ovulatory menstrual cycle were included to serve as controls; their age range was (19-40 years). In this study, the diagnosis of PCOS was based on the Rotterdam Consensus Group criteria for the definition of PCOS (Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004 a, b) [8,9]. The diagnosis included the presence of at least two of the following three criteria; 1) oligo-ovulation and/or anovulation, 2) clinical and/or biochemical features of hyperandrogenism (clinical hyperandrogenism includes hirsutism or acne and/ or biochemical hyperandrogenism and 3) the presence of polycystic ovaries on ultrasound (defined as 12 or more follicles in either ovary measuring 2–9 mm in diameter, and/or increased ovarian volume greater than 10 ml). Women were queried for the following information; age, marital status, number of children, history of high blood pressure or diabetes mellitus and gynecological diseases, regular or irregular menstrual cycle,

amenorrhea or oligomenorrhea and acne or hirsutism.

Formal consent was taken from each woman. We received ethical approval from the Scientific Committee of the Biochemistry Department, College of Medicine, University of Baghdad, Iraq.

Women with other causes for hyperandrogenism that mimic PCOS (e.g. congenital adrenal hyperplasia, Cushing syndrome or androgen secreting tumors) as well as pregnant women and diabetic PCOS patients have were excluded.

The ultrasound study was performed in Kamal AL-Samaraee Hospital/ Ultrasound Departments under supervision of a Specialist Gynecologist. Ovarian morphology was objectively assessed by pelvic ultrasound. The majority of ultrasound examinations were performed transvaginally to optimize image quality. Ultrasound examinations were performed in real-time on the same machine (AG50149 with a transvaginal 3.5 MHz probe, Siemens, Germany) and interpreted under the highest possible magnification. Assessment of polycystic morphology was based on a standardized protocol of the Rotterdam Consensus Group criteria for the definition of PCOS [8,9] and before blood sampling. Each ovary was scanned in both longitudinal and transverse cross-section from the inner to the outer margins to enumerate the total number of follicles. All follicles between 2 and 9 mm in diameter were counted. The follicle number per ovary (FNPO) was defined as the average for the total number of follicles counted from both ovaries.

Five milliliter of blood sample was collected by venipuncture of the peripheral vein from each PCOS and healthy control women, transferred into plain tube, allowed to clot and the serum was separated immediately by centrifugation at 2500–3000 rpm for a period of 10 min. Investigation included serum measurements of the following hormones in groups of PCOS and control women: AMH, inhibin B, follicle stimulating hormone (FSH), lutenizing hormone (LH), estradiol 17-β (E2), prolactin, and free testosterone (FT). The ACTIVE MIS/AMH enzyme linked immunosorbent assay (ELISA) Kit (AMH/ MIS Kit obtained from Diagnostic Systems Laboratory, Inc., USA) provides materials for the quantitative measurement of MIS/AMH in serum according to reported methods [10]. The remainder protein and hormones (inhibin B, FSH, LH, prolactin, E2, and FT) were measured using the Enzyme Linked Immunosorbent Assay (ELISA) technique according to reported methods, [11] the kits were provided from Diagnostic Systems Laboratory, Inc., USA. ELISA study was performed using Biotek instrument-USA. The Statistical Package for Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL., USA), and Minitab analysis programs were used for all statistical studies. ANOVA and Student's t-tests were used to test for statistical significance. Linear regression was utilized to test for correlation between different studied parameters, and the significance of the r-value was assessed by related t-test. P-values of less than 0.05 were considered significant.

3. RESULTS

Table 1 shows the clinical characteristics of PCOS and control women groups. The mean (±SEM) values of age of GI (27.5 ± 1.3 year), GII (28.2 ± 1.5 year) and controls (29.0 ± 1.3 year) did not differ significantly among and between groups. With respect to BMI, the mean of GI and GII PCOS [(30.9 ± 0.95 Kg/m^2), (31.2 ± 1.3 Kg/m^2), respectively] were significantly higher than that of control women (25.6 ± 1.01 Kg/m^2, P=0.002, P=0.003, respectively), but with no significant difference between PCOS women themselves (GI and GII). The same table reveals that the mean (±SEM) value of the number of ovarian follicles of GII was significantly lower than that of GI [(9.1 ± 0.5), (10.8 ± 0.5), P=0.037, respectively]. However, there was no significant difference in the mean value of ovarian volume between GI (8.5 ± 0.8 ml) and GII (9.2 ± 0.7 ml). Table 2 illustrates the mean (±SEM) values of the measured hormones in PCOS and control women. The mean (±SEM) values of serum AMH levels were (4. ± 0.5 ng/ml), (6.1 ± 1.5 ng/ml), and (1.99 ± 0.7 ng/ml) in GI, GII and control women, respectively. The least significant difference in mean AMH levels revealed that the mean of serum AMH levels was significantly increased in each of GI and GII compared to controls (P<0.027, P<0.002; respectively), while there was no significant difference between GI and GII PCOS women. Also, there was significant positive correlation between serum levels of AMH and ovarian volume in PCOS women of GI (r=0.476, P=0.035). The mean (±SEM) values of serum inhibin B levels were (88.6 ± 17.9 pg/ml) in GI, (116.5 ± 28.6 pg/ml) in GII, and (112.9 ± 20.2 pg/ml) in control group, with no significant differences among and between these groups.

Table 3 shows the mean (±SEM) values of serum levels of FT, LH, FSH, E2, and prolactin in GI, GII, and controls. The mean value of serum FT levels in groups of PCOS women (GI; 25.4 ± 3.8 pg/ml), and (GII; 17.5 ± 4.7 pg/ml) did not differ significantly from that of control women (14.2 ± 3.1 pg/ml). The mean (±SEM) value of serum LH levels of GI (19.95 ± 2.1 mIU/ml) and GII (22.6 ± 5.3 mIU/ml) were increased compared to that of control women (13.8 ± 2.1 mIU/ml), but such difference failed to reach significance. The mean (±SEM) values of serum FSH levels in GI (10.8 ± 0.6 mIU/ml) and GII (10.8 ± 0.9 mIU/ml) were decreased in comparison to control women (13.8 ± 1.5 mIU/ml), but did not reach statistical significance. In addition, there were no significant differences in the mean (±SEM) values of serum levels of E_2 among the studied groups (GI; 23.5 ± 1.4 pg/ml, GII; 21.5 ± 1.01 pg/ml, and control women 24.4 ± 1.5 pg/ml, respectively). Furthermore, there was no significant increase in mean LH/FSH ratio in each of PCOS groups [GI (2.03 ± 0.3) and GII (2.2 ± 0.5)] compared to that of control women (1.2 ± 0.2). The mean (±SEM) value of serum levels of prolactin did not differ significantly among PCOS and control women; (9.7 ± 1.1 ng/ml) in G I (7.9 ± 1.7 ng/ml) in G II and (11.1 ± 1.6 ng/ml) in control women.

4. DISCUSSION

Serum AMH level is thought to be increased in PCOS women because their ovaries exhibit an increased number of AMH-producing preantral and small antral follicles and also because of increased granulosa cell production of AMH [12]. AMH had higher area under curve (AUC) estimates than androgens, ovarian volume, LH and LH/FSH ratio for detecting mild PCOS. It has been suggested that in cases where transvaginal ultrasonography is not feasible or in women without hyperandrogenemia (HA) AMH may be used as a surrogate parameter in PCOS

Table 1. Mean (±SEM) values of clinical and ultrasonic characteristics of PCOS women and controls

Parameter	GI (n=20)	GII (n=13)	Controls (n=18)
Age (year)^{NS}	27.5±1.3	28.2±1.5	29.0±1.3
BMI$^{\bullet}$ (Kg/m^2)	30.9±0.95	31.2±1.3	25.6±1.01
No. of$^{\blacktriangle}$ ovarian follicles	10.8±0.5	9.1±0.5	
Ovaries^{NS} Volume (ml.)	(8.5±0.8)	(9.2±0.7)	

ANOVA and t-tests revealed ● significant difference between each of GI and GII PCOS with control women (P=0.002, P=0.003, respectively), ▲ significant difference between GI and GII PCOS (P=0.037). NS no significant differences among and between the studies groups

Table 2. Mean (±SEM) values of serum levels of AMH and inhibin B of PCOS women and controls

Parameter	GI (n=20)	GII (n=13)	Controls (n=18)
AMH (ng/ml)$^{\bullet}$	(4.5±0.5)	(6.1 ± 1.5)	(1.99 ± 0.7)
Inhibin B^{NS} (pg/ml)	(88.6±17.9)	(116.5 ± 28.6)	(112.9 ± 20.2)

ANOVA and t-tests showed ● significant difference between each of GI and GII PCOS with control women (P=0.027, P=0.002, respectively). NS no significant difference among and between studied groups

Table 3. Mean (±SEM) values of serum levels of free testosterone, LH, FSH, LH/FSH, E2, and prolactin of PCOS women and controls

Parameter	GI (n=20)	GII (n=13)	Control (n=18)
Free^{NS} Testosterone (pg/ml)	(25.4±3.75)	(17.5 ± 4.7)	(14.16±3.1)
LH (mIU/ml)^{NS}	(19.95 ± 2.1	(22.6 ± 5.3)	(13.8 ± 2.1)
FSH (mIU/ml)^{NS}	(10.8±0.6)	(10.8±0.9	(13.8 ± 1.5)
LH/FSH^{NS}	(2.03±0.3)	(2.2±0.5)	(1. 2 ± 0.2)
E2 (pg/ml)^{NS}	(23.5±1.4)	(21.5 ± 1.01)	(24.4 ± 1.5)
Prolactin^{NS} (ng/ml)	(9.6 ± 1.1	(7.9 ± 1.7)	(11.1 ± 1.6)

NS no significant differences among and between studied groups

diagnosis that is, superior to androgens and gonadotropins [13]. The recent availability of AMH Gen II assay, which appears to produce reliable and reproducible results, should make AMH an emerging biochemical marker of PCOS and could be an exciting alternative to the transvaginal ultrasound (TVUS) examination. Moreover, some authors found [12] that AMH concentration correlates significantly with the oligomenorrhea and HA and proposed that AMH could be a suitable substitute for diagnosis of PCOS that could replace TVUS in the future [12]. More recently, Dewailly [14] suggested that serum AMH assay seems to be an excellent substitute for follicular count and is likely to emerge as the official PCOM marker. A new consensus conference is needed.

Serum AMH measurement is very valuable in the diagnosis of PCOS women. The serum AMH level in women with hyperandrogenism or oligo-anovulation could indicate the diagnosis of PCOS when reliable ultrasonography is not available or when typical clinical and laboratory findings are not available. The serum AMH level is a new and useful diagnostic tool in PCOS diagnosis [15]. It has been demonstrated that there was positive correlation between AMH level and PCOS diagnosis using 3.2 ng/ml as cut off level (sensitivity and specificity of 70.4% and 77.4% respectively) for PCOS diagnosis ($p=0.001$) [16]. Moreover, it has been shown that AMH levels can be used as diagnostic and prognostic modalities in PCOS patients [17]. AMH value rise when hyperandrogenism is present therefore serum AMH levels also reflect the phenotype of PCOS [17]. In the present study, the increased BMI in PCOS women compared to healthy women confirmed that obesity may play a role in the pathogenesis of PCOS. Women suffering from PCOS have been shown to have higher amount of body fat compared to healthy women even when they are of normal weight [18]. 40-60% of women with PCOS are overweight or obese, although it was not included in the diagnostic criteria, the role of obesity as a contributing factor in the development of PCOS has been widely accepted [19]. BMI levels correlate with body fat and the obesity contributes to the manifestations of PCOS by increasing the magnitude of hyperandrogenism and the rates of anovulatory cycles. The pathophysiologic mechanism is related to hyperinsulinemia which is induced by insulin resistance [20].

The mean values of serum AMH levels were significantly increased in PCOS women of the present study (both GI and GII) than in control women (Table 2). Several studies found significant increase of serum AMH levels being 2- to 4-fold higher in women with PCOS compared with healthy women [21]. AMH is secreted by the granulosa cells of small antral and pre-antral follicles in the ovary. It diminishes aromatase induction by FSH in antral follicles and inhibits recruitment of primordial follicles [22]. An increased production of AMH induces a decrease in the sensitivity of follicles to FSH at the receptor level, which is necessary for their growth. It leads to an increase of the number of antral follicles at the expense of folliculr size: the number of small antral follicles (2-5 mm in size) increases, thereby restraining the selection of a dominant follicle. Such a situation is clinically characterized by anovulation cycles, manifesting as oligo- or amenorrhea [4]. The present study found the significant and positive relation of ovarian volume on AMH levels in G I ($r=0.476$, $p=0.035$) and the importance of obesity as one of the factors correlated well with AMH regulation in agreement with Chen et al. [23] since both GI and GII PCOS women were considered obese.

The results of the present study confirmed the non-significant fluctuation of serum AMH throughout the menstrual cycle in PCOS women as there was no significant difference in its level between GI and GII PCOS women. This finding that the day of cycle has no effect on AMH levels is in agreement with previous studies in which serum AMH levels have been measured at three different times during the menstrual cycle (follicular, ovulatory and luteal phases) and suggest minimal fluctuation. The peak value (not significant) appears to be reached in the late follicular phase [24]. Minimal fluctuations in serum AMH levels may be consistent with continuous non-cyclic growth of small follicles. Hence, AMH measurement seems relatively independent of cycle day, especially since it exhibits a relatively stable expression during the menstrual cycle [24]. Serum AMH correlates with the severity of PCOS and with the severity of both hyperandrogenism [25] and oligo-anovulation [26]. By principal component analysis, it has been shown that a high serum AMH level can be considered a marker of hyperandrogenism and also may be considered for inclusion in the Rotterdam classification [27].

5. CONCLUSION

In conclusion significantly increased serum AMH levels could indicate that the diagnosis of PCOS is possible when reliable ultrasonography is not available or when typical clinical and laboratory results are not available. Serum AMH level could be considered as a useful diagnostic tool in diagnosis of PCOS. Limitation of the present study is the very small number of PCOS women studied.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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