Int J Biol Med Res. 2013; 4(3) : 3290 - 3293

BioMedSciDirect Publications

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original Article

PCOS: correlation amongst Serum Levels of Testosterone, Anti-Mullerian Hormone and Other Sex Hormones

Bushra Fiza[a,b] , Rati Mathur[b] and Pushpendra Saraswat[a]

[a]*Mahatma Gandhi Medical College & Hospital, RIICO Institutional Area, Sitapura, Jaipur, India-302 022*
[b]*S.M.S. Medical College, JLN Marg, Jaipur, India-302 004*

ARTICLE INFO

Keywords:
Polycystic ovarian syndrome
PCOS
Anti-mullerian hormone
AMH
PCOD

ABSTRACT

Polycystic ovarian syndrome is a complex heterogeneous disorder of unknown etiology and shows mild to severe degree of signs and symptoms affecting the reproductive, endocrine and metabolic functions. Anti-mullerian hormone, a dimeric glycoprotein belonging to the transforming growth factor–beta superfamily, is produced by the pre and small antral follicles. In polycystic ovarian disease, the hormonal imbalances occur, mainly in anti-mullerian hormone, androgens, and other sex hormones. AIM: The aim of the present study is to estimate and correlate serum levels of testosterone, anti-mullerian hormone and other sex hormones in polycystic ovarian disease patients. METHOD: After initial screening, baseline hormonal study and gynecological ultrasound, the patients were diagnosed for polycystic ovarian syndrome on the basis of Rotterdam consensus and grouped according to the level of serum testosterone. Moreover, the control group has also been included. The results thus obtained were compared amongst the three groups and applied the student's t-test. RESULT: Women with polycystic ovarian syndrome have higher serum anti-mullerian hormone levels and luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio. Increased serum testosterone is associated with additional increase in anti-mullerian hormone, luteinizing hormone, estradiol, dihydroepiandrostenidione and LH/FSH ratio, whiles serum FSH shows a decreasing pattern that further justifies the increase of LH/FSH ratio. CONCLUSION: Serum anti-mullerian hormone shows a significant increase in polycystic ovarian syndrome as compared to women of similar age with normal ovarian morphology, hence its inclusion in the diagnostic criteria for polycystic ovarian syndrome is therefore recommended. The correlation of anti-mullerian hormone with hyperandrogenism requires additional studies for females undergoing in vitro fertilization treatment, because anti-mullerian hormone could be a predictor of ovarian stimulation outcome in polycystic ovarian syndrome.

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and is thought to be one of the leading causes of female subfertility. Strong evidences shows that it may be classified as a genetic disease. The main symptoms of polycystic ovaries are anovulation; resulting in irregular menstruation, amenorrhea and infertility, excessive release of androgenic hormones; resulting in acne and hirsutism, insulin resistance; often associated with obesity, diabetes type-2, and hypercholesteremia [1-7]. Moreover, it is the most common cause of anovulation in women with normal serum Follicle Stimulating Hormone (FSH) and Estradiol (E_2) levels [8].

The diagnostic criteria for PCOS has been defined time and again; in 1990, a consensus workshop sponsored by NIH/NICHD suggested that a patient is suffering from PCOS if she has oligo-ovulation, signs of androgen excess (by measuring serum testosterone levels) and other entities that would cause polycystic ovaries are excluded [9,10].Recently in 2003, a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated that a patient is suffering from PCOS if she has any two of the following three criteria; oligo and/ or anovulation, excess androgenic activity and polycystic ovaries (by gynecologic ultrasound) while, other entities are excluded that would cause the same [11]. The Rotterdam definition is wider, including more

* Corresponding Author : **Bushra Fiza**
Mahatma Gandhi Medical College & Hospital,
RIICO Institutional Area, Sitapura,
Jaipur, India-302 022
E-mails:bushrafiza786@gmail.com

patients with or without androgen excess. Moreover, the findings obtained from the study of patients with androgen excess can not necessarily be extrapolated to patients without androgen excess [12, 13].

Besides androgenic excess during PCOS, studies suggest that imbalance of some other hormones also occur. PCOD patients have higher serum Anti-mullerian hormone (AMH) levels than normal ones [14-16]. AMH, also known as Mullerian inhibiting substance, is a dimeric glycoprotein and a member of the transforming growth factor-β superfamily. In male, AMH is produced during fetal sex differentiation by sertoli cells and where it induces Mullerian duct inhibition, while in female, it produces only post-natally by granulosa cells from pre-antral and small-antral follicles [17-19]. Women with PCOS have both increased serum androgens and higher number of small-antral follicles. Although serum AMH levels have been positively correlated with the numbers of small-antral follicles but controversies exist with its correlation to serum androgens [19, 20].

There is no correlation study in patients of PCOD amongst serum levels of AMH, testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), FSH/LH ratio, estradiol (E2) and dihydroepiandrosteinidione (DHEAS) hitherto.

The aim of the present study is to estimate and correlate serum levels of testosterone, AMH and other sex hormones (FSH, LH, LH/FSH ratio, E_2 and DHEAS) in PCOD patients.

2. Materials and Methods

Three hundred and eleven female patients aged 25-45 years, visited the infertility clinic (Jaipur Fertility Centre, Jaipur, India) of Mahatma Gandhi Medical College & Hospital (MGMC&H), Jaipur, India and were investigated for the infertility due to PCOD. These patients were subjected to initial screening that included complete history, physical examination, routine clinical investigations, hormonal and other immunoassays. After initial screening, patients were further subjected to baseline study on day third (day 3rd) of the menstrual cycle that included estimation of serum LH, FSH, E2 and testosterone by enzyme linked fluorescent assays (ELFA) technique using VIDAS instrument and kits (Biomerieux, France). Serum DHEAS and AMH were estimated by enzyme linked immunosorbent assay (ELISA) technique using Monobind and Beckman Coulter gen II kits respectively.

A total of forty eight patients were diagnosed for PCOS, on the basis of Rotterdam consensus, from initial screening and baseline hormonal study. These patients were grouped into group-A and group-B on the basis of the level of serum testosterone; group-A included twenty five patients (n=25) suffering from PCOS with normal S. testosterone levels, while group-B included remaining twenty three patients (n=23) with elevated S. testosterone levels (>0.9 ng/ml). Moreover, LH/FSH ratio was also calculated in each case.

Another twenty five women of similar age with no evidence of tubal blockage, normal ovulation and having normal morphology were selected as the control group, called group-C (n=25).

The results were compared amongst these three groups; A versus C, B versus C, A versus B and applied student's t-test. A p value of <0.05 was considered statistically significant.

3. Results

The endocrine data obtained from the patients in three groups has been tabulated in Table 1; a perusal of the data reveals that the patients of group-B were significantly different from the remaining two groups in their hormonal profile.

Serum AMH levels were significantly different amongst three groups; highest in group-B and lowest in group-C.

Serum DHEAS levels show statistically significant change on comparison of group-B and group-A, and also with the control group-C, while the serum androgens (S. testosterone & S. DHEAS) are similar in group-A versus group-C comparison.

A significant rise is also occurring in serum LH and E2 levels in group-B as compare to group-A and group-C, while serum FSH shows a decreasing pattern amongst the groups. Serum FSH levels are highest in the control group (group-C) and the lowest in the group-B, but the changes are not significant.

The rise in LH and fall in FSH with increasing levels of AMH is clearly reflected by the significant rise in the LH/FSH ratio. This ratio is lowest in the control group, slightly higher in the group-A, and highest in group-B.

Table 1: Comparison of hormone levels in normal and PCOS patients

	Group-A (n=25)	Group-B (n=23)	Group-C (n=25)	A vs. C	B vs. C (p Values)	A vs. B
Age (years)	30.8 + 5.69	27.96 + 4.26	31.48 + 5.36	NS	NS	NS
Testosterone (ng/ml)	0.56 + 0.21	1.65 + 0.59	0.55 + 0.19	NS	<0.0005	<0.0005
AMH (ng/ml)	4.88 + 0.88	12.50 + 3.57	1.62 + 0.58	<0.0005	<0.0005	<0.0005
LH (mIU/ml)	4.57 + 1.74	6.29 + 1.37	3.89 + 1.45	NS	<0.0005	<0.0005
FSH (mIU/ml)	5.79 + 1.20	5.22 + 0.83	6.72 + 2.33	NS	<0.005	NS
LH/FSH	0.81 + 0.33	1.24 + 0.37	0.62 + 0.28	<0.05	<0.0005	<0.0005
E2 (pg/ml)	45.04+10.02	65.57 + 9.58	39.36+ 10.81	NS	<0.0005	<0.0005
DHEAS (mcg/dl)	283.4+35.65	348.7+51.86	279.44+35.65	NS	<0.0005	<0.0005

a) Values are presented as mean + SD.
b) Group A= PCOD patients with normal Testosterone; Group B= PCOD patients with raised testosterone; Group C= Normal controls;
c) NS = Non-Significant

4. Discussion

PCOS exhibit a broad spectrum of clinical and biochemical characteristics and the most distinctive feature is the failure of follicular maturation despite initial recruitment.

The role of intra-ovarian androgens is still debated; AMH is synthesized in the small antral follicles and it inhibits FSH sensitivity. It is an important parameter that can play a pivotal role in the diagnosis of PCOD. The result of the present study shows that the patients with PCOD have significantly higher serum AMH levels; similar as the other studies support the same. Moreover, it reveals that the elevated serum testosterone leads to an additional rise in serum AMH levels; similar as the previous finding that showed the hyper-androgenism was associated with an additional increase in serum AMH, furthermore, also showed that serum testosterone was independently related to levels of serum AMH. Significant correlations amongst serum AMH and androgens in PCOS have been reported, while on the contrary, no such correlations found in either PCOS or in normal women [15-23].

The present study shows a positive relationship between serum AMH and serum E2 levels; these are significantly higher in PCOD patients with increased serum testosterone level. Serum E2 levels of PCOD patients with normal testosterone level are also higher than the control group, though the rise is non-significant. These findings are similar as previous study that shows an increase in E2 level in the PCOD patients. Contrary to our finding; an inverse relationship has also been reported between AMH and E2 in PCOD patients and non PCOD patients respectively. Since AMH is an earlier product from the follicular cohort than estradiol, the discrepancies mentioned above might reflect difference in the day of sampling [18, 20, 23-25].

The present study reveals; a negative relationship between the levels of AMH and FSH. Thus, the higher levels of AMH are associated with lower levels of FSH similar as the previous study, though; the changes are significant only in patients of group-B versus control group (group-C). The above finding is in support of the speculation that excess of AMH is involved in diminishing FSH-induced aromatase activity that characterizes the follicular arrest of PCOS [26].

Moreover, the LH/FSH ratio is increasing, though it is above 1.00 only in group-B. It is lowest in control group, slightly raised in PCOD patients with normal testosterone and highest in PCOD patients with raised testosterone. The previous studies have also showed similar rise in the LH/FSH ratio, but the pattern was nonspecific and present in less than 50% cases in their study [27, 28].

5. Conclusion

It is obvious from the results of present study that serum AMH shows significant increase in PCOS as compared to women of similar age group with normal ovarian morphology, hence it can be strongly recommended to include in the diagnostic criteria for PCOS. Moreover, correlation amongst serum levels of AMH,

testosterone, and other sex hormones (FSH/LH/E2/DHEAS) could also be significant to diagnose PCOS clearly.

As the study reveals; the estimation and correlation between the serum testosterone and AMH levels could be useful to PCOD patients especially in assisted reproductive techniques (ART).Thus, the correlation of AMH with hyperandrogenism requires additional studies for females undergoing in vitro fertilization (IVF) treatment, because AMH could be a predictor of ovarian stimulation outcome in PCOS.

5.References

[1] Legro RS, Strauss JF. Molecular progress in infertility: polycystic ovary syndrome. FertilSteril. 2002; 78(3): 569 – 576.

[2] Kandarkis ED, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. Endocrine. 2006; 30 (1): 19 – 26.

[3] Fauser BCJM, Diedrich K, Bouchard P, Dominiguez F, Matzuk M, Frank S, Hamamah S, Simon C, Devroey P, Ezcurra D, Howles CM. Contemporary genetic technologies and female reproduction. Human Reproduction Update 2011; 17 (6): 829 – 847.

[4] Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impact on health across the lifespan. BMC Medicine. 2010; 8: 41.

[5] Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of polycystic ovary syndrome in an unselected population. J. Clin. Endocrinol. Metab. 2004; 89(6): 2745 – 2749.

[6] Boomsma CM, Fauser BC, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. SeminReprod Med.2008; 26(1): 72 – 84.

[7] Goldenberg N, Glueck C. Medical therapy in women with polycystic ovary syndrome before and during pregnancy and lactation. Minerva Ginecol. 2008; 60(1): 63 – 75.

[8] Farid NR, Kandarkis ED. Diagnosis and Management of Polycystic Ovary Syndrome. Springer, 2009; p 243.

[9] Goodarzi MO and Azziz R. Diagnosis, epidemiology and genetics of the polycystic ovary syndrome. Best Practice and Research. 2006; 20: 193-205.

[10] Hsu MI, Liou TH, Chou SY, Chang CY, Hsu CS. Diagnostic criteria for polycystic ovary syndrome in Taiwanese Chinese women: comparison between Rotterdam 2003 and NIH 1990.FertilSteril. 2007; 88: 727-729.

[11] Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group Revised 2003 consensus on the diagnostic criteria and long term health risks related to polycystic ovary syndrome. Hum Reprod. 2004; 19: 41-47.

[12] Carmina E. Diagnosis of polycystic ovary syndrome: from NIH criteria to ESHRE-ASRM guidelines. Minerva ginecologica. 2004; 56 (1): 1–6.

[13] Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. Best Practice & Research Clinical Obstetrics & Gynecology. 2004; 18 (5): 671–683.

[14] Fallat ME, Siow Y, Marra M, Cook C, Carillo A. Mullerian inhibiting substance in follicular fluid and serum: a comparison of patients with tubal factor infertility, polycystic ovary syndrome and endometriosis.FertilSteril. 1997; 67: 962-965.

[15] Cook CL, Siow Y, Brenner AG, Fallat ME. Relationship between serum mullerian- inhibiting substance and other reproductive hormones in untreated women with polycystic ovary syndrome and normal women. Fertil Steril. 2002; 77: 141-146.

[16] Laven JS, Mulders AG, Visser JA, Themmen AP, De Jong FH, Fauser BC. Anti-Mullerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age. J. Clin. Endocrinol. Metab. 2004; 89: 318-323.

[17] Cate RL, Mattaliano R J, Hession C, Tizard R, Farber NM, Chenng A, Ninfa EG, Frey AZ, Gash DJ, Chow EP. Isolation of the bovine and human genes for Mullerian inhibiting substance and expression of the human gene in animal cells. Cell. 1986; 4: 685-698.

[18] Durlinger AL, Gruijters MJ, Kramer P, Karels B, Ingraham HA, Nachtigal MW, Uilenbroek JT, Grootegoed JA, Themmen AP. Anti-Mullerian hormone inhibits initiation of primordial follicle growth in the mouse ovary. Endocrinology 2002; 143: 1076-1084.

[19] Weenen C, Laven JS, Von Bergh AR, Cranfield M, Groome NP, Visser JA, Kramer P, Fauser BC and Themmen AP . Anti-Mullerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod. 2004; 10: 77-83.

[20] Pigny P, Merlen E, Robert Y, Cortet-Rudelli C, Decanter C, Jonard S, Dewailly D. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. J ClinEndocrinolMetab. 2003; 88: 5957-5962.

[21] Alexandra L, Durlinger AL, Gruijters MJ, Kramer P, Karels B, Kumar TR, Matzuk MM, Rose UM, de Jong FH, Uilenbroek JT, Grootegoed JA, Themmen AP. Anti-Mullerian hormone attenuates the effects of FSH on follicle development in the mouse ovary. Endocrinology. 2001; 142: 4891-4899.

[22] La Marca A, Orvieto R, Giulini S, Jassoni VM, Volpe A, De Leo V. Mullerian-inhibiting substance in women with polycystic ovary syndrome: relationship with hormonal and metabolic characteristics. Fertil Steril. 2004; 82(4): 970-972.

[23] Eldar-Geva T, Ben Chetrit A, Spitz IM, Rabinowitz R, Markowitz E, Mimoni T, Gal M, Zylber-Haran E, Margalioth EJ. Dynamic assays of inhibin B, anti-Mullerian hormone and estradiol following FSH stimulation and ovarian ultrasonography as predictors of IVF outcome. Hum Reprod. 2005; 20: 3178-3183.

[24] Siefer DB, MacLaughlin DT, Christian BP, Feng B, Shelden RMF. Early follicular serum Mullerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles. Fertil Steril 2002; 77: 468-471.

[25] Fanchin R, Schonauer LM, Righini C, Frydman N, Frydman R, Taieb J. Serum anti-Mullerian hormone dynamics during controlled ovarian hyperstimulation. Human Reprod. 2003; 18: 328-332.

[26] Coffler MS, Patel K, Dahan MH, Malcom PJ, Kawashima T, Deutsch R, Chang RJ. Evidence for abnormal granulosa cell responsiveness to FSH in women polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 2003; 88: 1742-1747.

[27] Robinson S, Rodin DA, Deacon A, Wheeler MJ, Clayton RN. Which hormone tests for the diagnosis of polycystic ovary syndrome? Br J Obstet Gynaecol. 1992; 99(3): 232-238.

[28] Banaszewska B, Spaczyński RZ, Pelesz M, Pawelczyk L. Incidence of elevated LH/FSH ratio in polycystic ovary syndrome women with normo- and hyperinsulinemia. Rocz Akad Med Bialymst . 2003;48: 131–134.