Original Research Article

Correlation of serum androgen and gonadotropin with anti-mullerian hormone in polycystic ovarian syndrome in Eastern Indian population

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ABSTRACT

Background: Ovarian steroidogenesis requires gonadotropin stimulation, Luteinizing Hormone (LH) is a key factor in the hyperandrogenemia of the polycystic ovary syndrome. Progesterone is the primary regulator of Gonadotropin-Releasing Hormone (GnRH) pulse frequency; however, in the polycystic ovary syndrome, the GnRH pulse generator is relatively resistant to the negative feedback effects of progesterone. Study aims to evaluate the association of Anti-mullerian hormone with serum androgen and gonadotropin level in adolescents and young women of Polycystic Ovary Syndrome (PCOS).

Methods: This was a single centre observational Cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from March 2017 to January 2019. Total number of study subjects were 207 out of which 138 were cases.

Results: The AMH had strong positive correlation with serum testosterone in both case and control groups (r 0.542, p<0.001 and r 0.57, p<0.001) respectively. After the adjustment of age and BMI, the AMH moderately positive but extremely significant correlation with serum testosterone as compare to control.

Conclusions: Hyperandrogenemia and higher ratio of LH and FSH associated with higher serum AMH level is associated with the higher serum AMH in polycystic ovarian syndrome.

Keywords: Androstenedione, Anti-mullerian hormone, Dehydroepiandrosterone, Follicle stimulating hormone, Luteinising hormone

INTRODUCTION

Ovarian steroidogenesis requires gonadotropin stimulation, Luteinizing Hormone (LH) is a key factor in the hyperandrogenemia of the polycystic ovary syndrome. Progesterone is the primary regulator of Gonadotropin-Releasing Hormone (GnRH) pulse frequency; however, in the polycystic ovary syndrome, the GnRH pulse generator is relatively resistant to the negative feedback effects of progesterone.1 This resistance to progesterone negative feedback appears to be mediated by androgen excess (since it is reversed by the androgen- receptor blocker flutamide).2 Resulting high GnRH pulse frequencies favor production of LH and limit production of Follicle-Stimulating Hormone (FSH), which promote androgen production and interfere with normal follicular development. The polycystic ovary syndrome is associated with inherent abnormalities of ovarian and adrenal steroidogenesis. Study aims to evaluate the association of Anti-mullerian hormone with serum androgen and gonadotropin level in adolescents and young women of Polycystic Ovary Syndrome (PCOS).

METHODS

This was a single centre observational Cross-sectional study carried out in the department of Endocrinology and
metabolism, Medical College, Kolkata from March 2017 to January 2019.

Total number of study subjects were 207 out of which 138 were cases. Adolescents and young woman of reproductive age group between 16-40 yrs. attended the in-patient and outpatient clinic of the Department of Endocrinology and metabolism in whom PCOS was diagnosed according to the Rotterdam criteria and participated by signing the consent form. Subject should have least two of the following elements,

- Hyperandrogenism (H): Modified Ferriman-Gallwey score ≥8 or serum total testosterone (TT) ≥80 ng/dL (≥2.77 nmol/L). 3
- Ovulatory dysfunction (O): Oligomenorrhea (cycles longer than 35 days OR less than 6 cycle in a year) or amenorrhea (no menses in the last 6 months) after a negative screening pregnancy test. In patients with regular menses, progesterone level <4 ng/mL (12.72 nmol/L) in the luteal phase of two consecutive cycle.
- Polycystic ovaries (P): 12 or more follicles of 2 to 9 mm diameter and/or increased ovarian volume (>10 mL) in at least one ovary by ultrasonography.

**Inclusion criteria**

Female between 16-40 age group with features of PCOS, as defined by Rotterdam criteria 2003, characterized by at least two of the following three features;

- Oligo or anovulation
- Clinical and/or biochemical hyperandrogenism, and
- Ultrasound appearance of polycystic ovaries.

**Exclusion criteria**

- Other causes of hyperandrogenism like Cushing’s syndrome, late-onset congenital adrenal hyperplasia and androgen-secreting tumors were excluded with appropriate diagnostic tests. Thyroid dysfunction, except euthyroid on stable dose of medication for 3 months. Hyperprolactinemia, Pregnancy, OCP or any other hormonal contraception.

Descriptive statistical analysis was carried out with SAS (Statistical Analysis System) Version 21.0 for windows, SPSS, Inc., Chicago, IL, US. Results on continuous measurements were presented as Mean±SD. Results on categorical measurements are presented in Number (%). The level of Significance was assessed at 5%. Unpaired t-test was used to find the significant changes between the quantitative parameters between two groups i.e. PCOS and Controls. Chi-square test use for qualitative data to compare the test of significance difference between proportions. Spearman correlation test was done to find out whether any significant correlation exists between the two variables.

**RESULTS**

The total number of subjects in the study were 207, out of which 138 were cases (PCOS) and 69 control (NON-PCOS). The mean age were 22.5 year and 23.25 year in the case and control respectively and the difference was nonsignificant. The mean height were 154.33 cm and 155.14 cm among the case and control group and the difference in the mean height were not significant. The mean BMI were 24.73 and 22.25 kg/m² in the case and control respectively and there is significant difference in the BMI. There was nonsignificant difference among the neck circumference, waist circumference and hip circumference among the case and control groups. The was significant difference in the Waist hip ratio among the case and the control. The mean systolic and mean diastolic blood pressure were significantly higher among the cases as compare to control. There was significant difference among the mean serum total testosterone with a mean value of 87.68±36.622 ng/dl and 33.93±11.36 ng/dl among the case and control group respectively.

There was significant difference among the mean 17OHP (17 hydroxy progesterone) with a value of 0.75±0.67 ng/ml and 0.36±0.48 ng/ml among the case and control group respectively. There were nonsignificant differences in the Androstenedione and DHEAS among the case and control groups. There were significant differences among the mean LH with a value of 6.95±5.18 MIU/ml and 4.51 MIU/ml in the case and control group respectively. There were nonsignificant differences in the mean value of FSH among the case and control group.

**Table 1: Biochemical parameters in the case and control group.**

| Group Statistics       | Group      | Mean±SD     | p    |
|------------------------|------------|-------------|------|
| Total Testosterone     | PCOS       | 87.6±36.622 | <0.001|
|                        | Non-PCOS   | 33.93±11.361|      |
| Androstenedione        | PCOS       | 2.65±0.949  | 0.560|
|                        | Non-PCOS   | 2.80±2.593  |      |
| DHEAS (ug/dl)          | PCOS       | 168.21±121.782 | 0.649|
|                        | Non-PCOS   | 149.80±61.418 |      |
| 17OHP (ng/ml)          | PCOS       | 0.75±0.671  | <0.001|
|                        | Non-PCOS   | 0.36 ± 0.484 |      |
| LH (mIU/ml)            | PCOS       | 6.95±5.189  | <0.001|
|                        | Non-PCOS   | 4.51±1.677  |      |
| FSH (mIU/ml)           | PCOS       | 6.29±2.678  | 0.143|
|                        | Non-PCOS   | 11.01±37.664 |      |
| TSH (mIU/ml)           | PCOS       | 2.27±1.064  | 0.025|
|                        | Non-PCOS   | 1.91±1.067  |      |
| PRL (ng/ml)            | PCOS       | 11.32±5.024 | <0.001|
|                        | Non-PCOS   | 8.22±3.217  |      |
| SHBG (nmol/l)          | PCOS       | 24.00±15.160 | <0.001|
|                        | Non-PCOS   | 55.99±17.429 |      |
| AMH (ng/ml)            | PCOS       | 11.15±4.604 | <0.001|
|                        | Non-PCOS   | 3.68±2.090  |      |
The mean Prolactin were significantly higher with the value of 11.32±5.02 ng/ml and 8.22±3.21 ng/ml among case and control group respectively (Table 1). The Mean TSH were not significantly different among the case and the control groups. The mean SHBG were significantly lower in the cases as compare to control with a value of 24±15.16 nmol/l and 55.99±17.42 nmol/l respectively. The mean AMH were significantly higher in the case as compare to control group with a value of 11.15±4.6 ng/ml and 3.68±2.09 ng/ml respectively (Table 1).

The AMH had strong positive correlation with serum testosterone in both case and control groups (r 0.542, p<0.001 and r 0.57, p<0.001) respectively. After the adjustment of age and BMI, the AMH moderately positive but extremely significant correlation with serum testosterone as compare to control (Table 2).

| Group | AMH (ng/ml) | Variable | r    | p    |
|-------|-------------|----------|------|------|
| PCOS  | Testosterone (ng/dl) | 0.392 | <0.001 |
|       | Androstenedione (ng/ml) | 0.111 | 0.199 |
|       | DHEAS (mcg/dl) | 0.083 | 0.33  |
|       | 17 OHP (ng/ml) | 0.061 | 0.48  |
| Control | AMH (ng/ml) | Testosterone (ng/dl) | 0.346 | 0.004 |
|       | Androstenedione (ng/ml) | - | 0.736 |
|       | DHEAS (mcg/dl) | 0.006 | 0.961 |
|       | 17 OHP (ng/ml) | 0.190 | 0.124 |

The AMH had weak positive correlation with LH (r=0.21, p<0.01) in the case group. There is weak negative correlation of AMH with the serum FSH level in the case group. There is no significant correlation of AMH with LH and FSH in the control group (Table 3).

| Group | AMH (ng/ml) | Variable | r    | p    |
|-------|-------------|----------|------|------|
| PCOS  | LH (miu/ml) | 0.218 | 0.01  |
|       | FSH (miu/ml) | 0.242 | 0.004 |
| Control | AMH (ng/ml) | LH (miu/ml) | 0.134 | 0.271 |
|       | FSH (miu/ml) | 0.000 | 0.998 |

DISCUSSION

In the present study mean serum total Testosterone level was 87.6±36.622 ng/dl vs. 33.93±11.361 ng/dl p<0.001) among the PCOS and control group respectively. The Testosterone level was significantly higher in the PCOS patients.

The AMH had strong positive correlation with serum testosterone in both case and control groups (r 0.542, p<0.001 and r 0.57, p<0.001) respectively. Even after the adjustment with age and BMI, the AMH had significant positive correlation with serum testosterone as compare to control. Finding was consistent with Piltonen et al, where serum AMH correlated positively with serum concentrations of testosterone (T) and negatively with age.5

The association between androgens and AMH remains uncertain and its exact function in follicular recruitment and long-term effects is not well understood.5 Hyperandrogenemia associated with an additional increase in AMH level in women with polycystic ovaries. Hyperandrogenemia may affect AMH secretion.

- It has been hypothesized that intra-ovarian Hyperandrogenemia (HA) promotes early follicular growth in a mechanism involving the androgen receptor.6 Increased serum AMH level in women with PCOS could be due to increased androgen levels in the presence of an excess of small antral follicles.7

There was no correlation between the AMH and Androstenedione and DHEAS. The serum Androstenedione had weak positive correlation with ovarian volume and follicular number (r=0.27, p 0.001 and r=0.286, p 0.001) but there was no correlation in the control group.

The serum testosterone had strongly positive correlation with the ovarian volume and follicular number in the cases (r=0.47, p<0.001) and (r=0.58, p<0.001). Serum testosterone had strongly negative correlation with the follicular size in PCOS (r=0.532, p<0.006). In the control group serum testosterone had a weak negative and nonsignificant correlation with follicular size. According to Song DK, et al. the serum AMH level was positively correlated with total testosterone (r=0.33), ovarian volume (r=0.57), and follicle number (r=0.39) after adjustment for age in women with PCOS.7 AMH was positively associated with HA only in women with PCOS, not in regular cycling women regardless of the presence of PCOM.8

The AMH had a weak positive correlation with LH (r=0.21, p=0.01) in the PCOS and the weak negative correlation with the serum FSH level. There was no significant correlation of AMH with LH and FSH in the control group. The finding was similar to Laven et al. AMH levels were positively correlated with individual features of PCOS, including LH concentrations, testosterone, mean ovarian volume and the number of ovarian follicles.9 Finding was similar to Neoklis A. Georgopoulos et al, where the AMH levels were correlated with LH levels in women with PCOS (r=0.414, p<0.001).10

A F Begawy et al, found significant positive correlations between AMH, and LH, LH/FSH, and significant negative correlation between AMH and FSH.
According to Piouka A et al, AMH concentration was positively influenced by LH levels. After all, LH levels were markedly high in women with “severe” PCOS, who also had the highest AMH concentrations.\(^{10}\)

In conditions of increased LH and normal to low FSH levels (such as in PCOS), the AMH serum levels are increased and tend to be associated with serum LH levels; whereas in conditions of increased FSH levels (such as in premature ovarian failure), AMH serum levels are decreased and tend to be associated with serum FSH levels.\(^{11}\)

Limitation of the study were study population had the potential for bias since participants were recruited based on self-reported concerns over PCOS not from population survey. It would be expected that those with the most concerns over PCOS would be selected for evaluation (i.e. Frank PCOS).

Most of the population were unmarried so the prevalence of infertility could not be assessed. The metabolic and clinical manifestation may be less common due to the younger population in the study.

In this study the ratio of the case and control was not as per the standards. So, the findings of this study may not be applicable to the general population.

So, in the future the longitudinal and prospective study may address the causal relationship.

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