

Autoimmune markers and Polycystic Ovary Syndrome

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Abstract: Background: The aetiology of PCOS remains uncertain but there is increasing evidence for auto immune disease so screening for auto antibodies in PCOS women may help in diagnosis of PCOS. **Aim of the work** to determine the association between autoimmunologic processes and PCOS. **Patients and methods:** Fifty patients with PCOS were selected from the infertility clinic of Al azhar University Hospital compared with fifty aged-matched health fertile controls as regard to clinical characteristics, hormonal profile and autoimmune markers (ANA, Anti-dsDNA). **Results:** There was significant increase of body weight, BMI, LH, LH/FSH ratio, TSH levels and autoimmune markers (Anti-dsDNA and ANA) in PCOS patients compared with healthy control. These results suggest the role of auto immunologic processes in the pathogenesis of PCOS. **Conclusion:** The study showed that the serologic parameters of auto-immunity (i.e. ANA and Anti-dsDNA) are elevated in women with PCOS. And suspect the role of autoimmunologic process.

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1. Introduction

In their reproductive age, polycystic ovarian syndrome is the commonest endocrine disorder in women, occurring in approximately one in seven women. Approximately two-thirds of these women will not ovulate on a regular basis¹.

There was a controversy in definition of the polycystic ovary syndrome for a long time. Rotterdam consensus established precise criteria since two among three set the definition as follow: oligo- or anovulation, hyperandrogenism (clinical or biochemical) and polycystic ovaries in ultrasound examination².

Polycystic ovary syndrome is characterized by an excessive number of small antral follicles in the ovaries that fail to produce a dominant follicle on a regular basis and by dissociation in LH and FSH release³. Ovarian diseases such as premature ovarian failure (POF) have been shown to be associated with autoimmunologic processes⁴.

Recently few studies addressed the association between PCOS and autoimmunity with controversial results. One study evaluated 109 sera from PCOS patients and performed anti-nuclear antibodies (ANA) screen, anti-histone, anti-nucleosome, and the anti-ds-DNA utilizing ELISA tests. The study showed that: Women with PCOS had significantly elevated serum levels of antihistone and anti-dsDNA antibodies, whereas serum levels of ANAs and antinucleosome antibodies were similar between the two groups. When serum levels of ANAs, antihistone, antinucleosomes, and anti-dsDNA antibodies were correlated with clinical and

biochemical parameters, a significant correlation between serum levels of ANAs and serum TSH was established⁵.

Aim of the Work

The aim of the present study is to evaluate whether women with the polycystic ovary syndrome (PCOS) have an increased rate of elevated serum levels of common autoimmunologic parameters (ANA, Anti double-stranded DNA) or not.

2. Patients and Methods

This Study was held in Obstetrics and Gynecology Department of Al Azhar university hospitals, between the periods of March 2013 To October 2013. The study included 100 women divided into two groups: **Group (1)** included 50 women diagnosed as PCOS according to Rotterdam Criteria (2003)⁶ and picked up from the infertility clinic; and **group(2)** included 50 control fertile patients seeking contraception in the outpatient clinic.

Inclusion criteria:

Women were included in this study if they had no medical or hormonal treatment for at least 3 months, had normal thyroid function tests and normal prolactin levels; and had history of primary infertility.

Exclusion criteria:

Women were excluded from this study if they had any medical or hormonal treatment in the last 3 months; had hyperthyroidism, hyper-prolactinemia, chronic hypertension, autoimmune disorders (e.g., SLE) and history of drug intake.

After taking a written informed consent,

complete history taking was obtained, general, abdominal and pelvic examinations were done. Pelvic ultrasound was conducted for PCOS criteria at ovaries (12 or more follicles measuring 2-9mm and/or an increased ovarian volume of $>10\text{cm}^3$). Finally, hormonal assays were conducted and included FSH, LH levels at day 3 of menstruation, TSH.

Statistical methods:

The collected data were coded, tabulated, and statistically analyzed using Med Calc software for windows. Descriptive statistics were done for numerical parametric data as mean, standard deviation, minimum & maximum of the range, while relative frequency and per cent distribution were done for categorical data. Inferential analyses were done for quantitative variables using independent t-test. Inferential analyses were done for qualitative data using Chi square test. Correlations were done using Pearson correlation coefficient. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

3.Results

In the present study, comparison between the

study and control groups as regards to clinical characteristics revealed that, there was significant increase of body weight and BMI in study group when compared to control group (Table 1). In addition, there was highly significant increase of LH, LH/FSH ratio and TSH in the study group when compared to control group. Similarly, there was significant increase of ANA and Anti-dsDNA in study group in comparison to control group (Table 2).

Regarding correlation, there was only positive (proportional), powerful correlation of ANA and TSH levels in study and control groups (Table 3). Regarding serum level of ANA in PCOS group the best cut-off value was >9.8 , with sensitivity and specificity of (77.8%, 100.0% respectively); the positive predictive value was 100.0, the negative predictive value was 88.9% and the accuracy was 0.944%. In addition, for serum level of Anti-ds DNA of the PCOS group the best cut-off value was >74 , with sensitivity and specificity of (78.5%, 100.0% respectively); the positive predictive value was 100.0%, the negative predictive value was 92.3% and the accuracy was 0.878% (Figures 1 and 2).

Table (1): Comparison between study and control groups as regards to clinical characteristics

| | STUDY | CONTROL | T VALUE | P VALUE |
|--------------------------|-------------|-------------|---------|---------|
| Age (year) | 25.5 ± 5.7 | 26.8 ± 3.7 | -8.886 | 0.058 |
| Weight (Kg) | 79.4 ± 3.6 | 69.8 ± 4.5 | 4.739 | <0.01* |
| Height (Cm) | 167.5 ± 4.9 | 169.0 ± 4.5 | -1.649 | 0.102 |
| BMI (Kg/m ²) | 28.2 ± 1.3 | 24.2 ± 0.9 | 9.87 | <0.01* |

Table (2): Comparison between study and control groups as regards endocrinal function and autoantibodies

| | STUDY | CONTROL | T VALUE | P VALUE |
|--------------------|-------------|-------------|---------|---------|
| FSH (mIU/mL) | 6.9 ± 1.4 | 7.3 ± 1.2 | -1.651 | 0.113 |
| LH (mIU/mL) | 10.2 ± 2.1 | 5.2 ± 1.4 | 14.322 | <0.001* |
| LH/FSH ratio | 1.5 ± 0.3 | 0.70 ± 0.12 | 15.865 | <0.001* |
| TSH (μU/mL) | 1.5 ± 0.6 | 1.1 ± 0.4 | 3.922 | <0.001* |
| ANA (U/mL) | 9.0 ± 6.1 | 5.4 ± 2.3 | 4.586 | <0.001* |
| Anti-dsDNA (IU/mL) | 56.3 ± 25.7 | 26.0 ± 10.8 | 7.728 | <0.001* |

Table (3): Correlation between the serum level of ANA and clinical characteristics

| | ANA | | | | dsDNA | | | |
|--------|--------|---------|---------|---------|--------|-------|---------|-------|
| | Study | | Control | | Study | | Control | |
| | r | p | r | p | r | p | r | p |
| Age | 0.068 | 0.437 | 0.208 | 0.159 | 0.067 | 0.754 | -0.220 | 0.143 |
| Parity | | | 0.024 | 0.897 | | | 0.051 | 0.743 |
| Weight | -0.183 | 0.215 | 0.149 | 0.400 | 0.043 | 0.768 | 0.063 | 0.676 |
| Height | -0.185 | 0.198 | 0.083 | 0.567 | 0.079 | 0.584 | 0.166 | 0.345 |
| BMI | -0.002 | 0.897 | 0.091 | 0.543 | -0.049 | 0.839 | -0.070 | 0.746 |
| FSH | -0.278 | 0.063 | -0.148 | 0.413 | -0.047 | 0.846 | 0.000 | 0.989 |
| LH | -0.201 | 0.174 | -0.144 | 0.418 | 0.041 | 0.768 | 0.015 | 0.819 |
| LH/FSH | 0.072 | 0.619 | -0.090 | 0.537 | 0.078 | 0.694 | 0.002 | 0.886 |
| TSH | 0.955 | <0.001* | 0.906 | <0.001* | 0.190 | 0.198 | -0.035 | 0.788 |

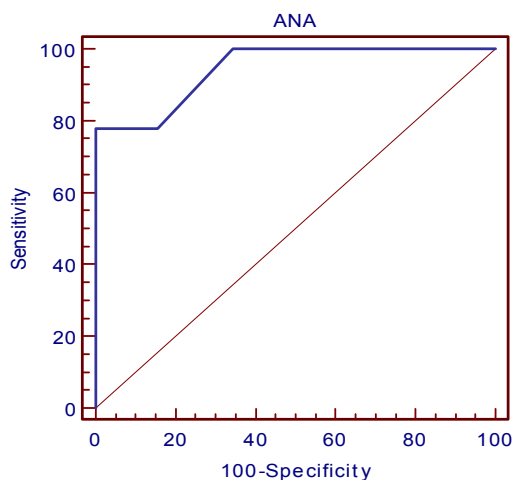


Figure (1): ROC curve of ANA (PCOS group)

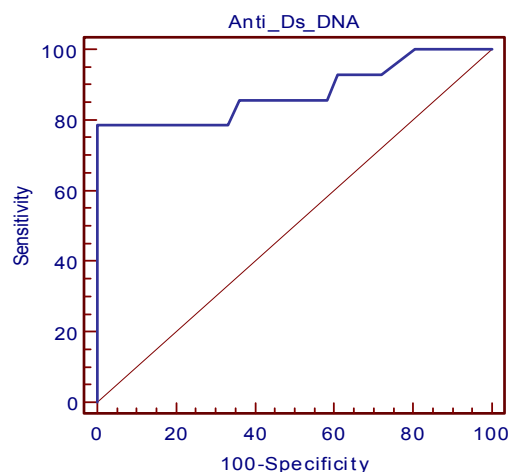


Figure (2): ROC curve of Antids-DNA (PCOS group)

4. Discussion

The current study was conducted to evaluate the role of autoimmune processes in fifty women with PCOS compared with fifty age matched healthy fertile women as controls. We selected a panel of well-established markers of autoimmunity, which are used in clinical practice in the diagnosis of autoimmune diseases (Anti-dsDNA and ANA).

In the present study, it was shown that the mean age of the study group was 25.5 ± 5.7 years and the mean age of the control group was 26.8 ± 3.7 years. The mean weight of PCOS patients was 79.4 ± 3.6 kg and the mean weight of the control group was 69.8 ± 4.5 kg. The mean height of the study group was 167.5 ± 4.9 cm and the mean height of the control group was 169.0 ± 4.5 cm. The mean BMI of PCOS patients were 28.2 ± 1.3 kg/m² and the mean BMI of the control group was 24.2 ± 0.9 kg/m²; and there was significant increase of weight and BMI in PCOS patients when compared to control group. These are in agreement with study at Gulf medical college (GMC) hospital & research centre⁷. They reported that 54% of the women with PCOS were overweight or obese according to BMI. In addition, this agrees with **Moran** study⁸ on young women with PCOS aged 18-25 years with ($n = 24$) or without ($n = 22$) PCOS (with the mean age: 22.41 ± 0.39 years versus 21.95 ± 0.47 years), ($p = 0.46$); BMI: 29.17 ± 1.54 kg/m² versus 22.05 ± 0.83 kg/m², ($p = 0.0003$) who reported that women with PCOS were significantly more likely to be overweight or obese ($p = 0.012$) than women without PCOS.

Unfortunately, there were no available studies to show the correlation between the serum level of ANA or the serum level of Anti-ds DNA with BMI in patients with PCOS.

The mean serum level of FSH of the study group

was 6.9 ± 1.4 mIU/mL and 7.3 ± 1.2 mIU/mL of control group, with no significant difference between the study and the control group. The mean serum level of LH in the study group was 10.2 ± 2.1 mIU/mL and 5.2 ± 1.4 mIU/mL of the control group. The mean LH/FSH ratio of the study group was 1.5 ± 0.3 and 0.70 ± 0.12 of the control group. The mean serum level of TSH of the study group was 1.5 ± 0.6 μ U/mL and 1.1 ± 0.4 μ U/mL of the control group, and there were significantly higher levels in study group than the control group. These findings are in agreement with the results obtained by **Rosenfield**⁹ who revealed that full expression of PCOS depends on the maturation of the hypothalamic-pituitary-ovarian axis that occur during puberty. The increases in circulating level of LH that are characteristic of normal puberty are exaggerated in girls with a predisposition to PCOS. In addition, this is in agreement with the finding reported by **Niken and Kanadi**¹⁰ study on 105 women with PCOS. They revealed that 34.3% are with hyperandrogenism and 66.7% are with increasing LH / FSH ratio. This agrees also with **Yanira et al.**¹¹ study on twenty-four women with PCOS who reported that Patients with polycystic ovarian syndrome (PCOS) had increased LH relative to FSH. Percent inhibition of LH was decreased in PCOS patients compared with normal women (53.9 ± 1.5 vs. 63.1 ± 4.1 , respectively; $P < 0.01$).

The mean serum level of ANA of the study group was 9.0 ± 6.1 U/mL with a range of 3.0-25.0 U/mL. It showed that 32 PCOS patients from 50 women with PCOS (about 64%) had negative serum level of ANA, and 18 PCOS patients from 50 women with PCOS (about 36%) had positive serum level of ANA. In addition, the mean serum level of ANA of the control group was 5.4 ± 2.3 U/mL with a range of 4.0-13.0 U/mL. It showed that only 3 women had positive

serum level of ANA from 50 women (about 6%), and 47 women had negative serum level of ANA from 50 women (about 94%) of the control group. From these results our study revealed that the serum level of ANA was significantly higher in the study than the control group. This is in agreement with the finding reported by **Reimand et al.**¹² in their study, 36 PCOS patients were evaluated for ANA using indirect immunofluorescence method. The results of this study showed that there was a significant difference in detection of ANA. The detection of ANA was found in 7 PCOS patients (19,4 %) versus (3,6 %) incidence in detection of ANA in the control group of 392 women ($p < 0,005$). In addition, this is also in agreement with **Reimand et al.**¹² who showed that 40.7% of the patients' sera and 14.8% of the controls' sera contained one or more common autoantibodies; ANA and (smooth muscle antibodies) SMA were most frequently detected (difference between two groups $P < 0.005$).

In present study the mean serum level of anti-dsDNA of the study group was 56.3 ± 25.7 IU/mL with a range of 10.0- 95.0 IU/mL. It showed that, 7 PCOS patients had negative serum level of anti-ds DNA from 50 women (about 14%) , 29 PCOS patients had equivocal serum level of anti-ds DNA from 50 PCOS women (about 58%), and 14 PCOS patients from 50 women had positive serum level of anti-ds DNA (about 28%) of the study group. The mean serum level of anti-dsDNA of the control group was 26.0 ± 10.8 IU/mL with a range of 10.0 - 67.0 IU/mL. While in the control group only one woman had positive serum level of anti-ds DNA from 50 women (about 2%), 32 women had negative serum level of anti-ds DNA from 50 women (about 64%), and 17 women were equivocal according to the serum level of anti-ds DNA from 50 women of the control group (about 34%). Our results showed that the serum level of anti-ds DNA was significantly higher in the study group than the control group. These results are in agreement with **Hefler et al.**⁵ who revealed that women with polycystic ovary syndrome (PCOS) had significantly elevated serum levels of anti-double-stranded DNA (anti-dsDNA) antibodies than the control group.

In the present study, there was no significant relationship between the serum level of ANA with the serum level of FSH, LH and LH/FSH ratio while there was a significant relationship between the serum levels of ANA with the serum level of TSH. The results are in agreement with the study done by **Hefler et al.**⁵ who reported a significant correlation between the serum levels of ANAs and the serum level of TSH ($p = 0.03$).

In short, This study shows that the serologic parameters of autoimmunity (i.e. ANA and Anti-dsDNA) are elevated in women with PCOS. so A role of autoimmunologic process can be suspected.

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