Serum levels of androgens and prostate-specific antigen in endometriosis

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Summary

Objective: The aim of the present study was to evaluate the levels of serum androgens and prostate-specific antigen (PSA) levels in patients with endometriosis. *Materials and Methods:* Patients with Stage III/IV(advanced stage) endometriosis were compared to controls with respect to basal serum levels of total testosterone (T), free testosterone (fT), androstenedion (A), dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and PSA in the early follicular phase of menstrual cycle for this prospective case control study. *Results:* Level of T, fT, A, DHEA, and DHEA-S were higher in patients with endometriosis when compared to control subjects, but the difference was not statistically significant. The mean PSA level was 0.0074 ± 0.0120 ng/ml in patients with endometriosis and 0.0059 ± 0.0056 ng/ml in control group and there was no statistically significant difference between groups ($p = 0.58$). *Conclusion:* Serum basal androgens and PSA levels are higher in endometriosis group with respect to control but the differences are not statistically significant.

Key words: Endometriosis; Androgens; Prostate-specific antigen.

Introduction

Endometriosis is a gynecological condition where endometrial gland and stromal structures are situated outside of the uterine cavity. This hormone-dependent disease in which estrogen plays the most prominent role affects five to ten percent of the women in their reproductive age. The patients frequently complain of chronic pelvic pain, dyspareunia, and infertility [1-3]. Danazole is a testosterone derivative which is used in the clinical treatment of endometriosis and induces regression of endometrial foci [4].

In women, sources of hormones are ovaries, adrenal glands, and peripherally transformed forms of precursor hormones released from these organs. With their systemic effects androgens play a role in physiological events such as sexual hair growth, calcium storage in bones, and libido [5,6]. In the ovary; androgens, primarily testosterone (T) and androstenedione (A), in addition to their roles in acting as metabolic precursors for steroid production, have paracrine effects so as to enhance follicular recruitment and maturation [7,8]. In physiological and pathological conditions of endometrium; androgens have been reported to counteract against estrogen effects during cellular proliferation [9].

Prostate-specific antigen (PSA) is a molecule produced in the prostatic tissue and secreted in seminal fluid. It is quite specific for the diagnosis and monitorization of prostatic adenocarcinoma [10]. Production of this marker which represents androgenic load, was recently revealed in women and its presence has been demonstrated in ovary, breast tissue, amniotic fluid, and breast milk. Increase in PSA levels in female patients with PCOS, hyperandrogenemia, and hirsutism relative to the control group has been demonstrated and decrease in PSA levels with anti-androgen treatment has been reported [11-15].

Keeping in mind the fact that endometriosis is an estrogen-dependent disease and androgen derivatives cause clinical symptomatic relief in endometriosis [3,4]. Theoretically intrinsic androgen insufficiency can be implicated in endometriosis. Adequate numbers of studies investigating androgens levels have not been conducted so far, and PSA levels which represent androgenic load in endometriosis patients have not been investigated previously. To the best of the authors' knowledge, this is the first study to investigate the effect of PSA in the pathophysiology of endometriosis. In this study, evaluation of androgens and PSA levels in patients with endometriosis was intended.

Materials and Methods

The present prospective case control study was performed between January to June 2012 in the Obstetrics and Gynecology Clinic at the Dicle University Medical Faculty. Sixty-seven patients who had undergone laparoscopy and/or laparotomy for infertility evaluation and/or for benign gynecologic disorders, such as dermoid cyst (23 women), tubal ligation (11 women), and endometriosis (33 patients) were recruited in the study. Endometriosis was diagnosed by laparoscopy and/or laparotomy with histological

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confirmation of the disease. Stage I/II endometriosis (three patients) were not included in the study because of small sample size. Women with endometriosis which were Stage III/IV (advanced stage) according to the revised American Fertility Society classification for Endometriosis [16] were enrolled as the study group.

Patient and control groups were in reproductive age period and their ages ranged from 19-38 years. All women had regular menstrual cycle (intervals of 21 and 35 days) and had no acute or chronic inflammatory diseases or history of hormonal treatment for the last three months.

Women who had history of a diagnosis of polycystic ovary syndrome, endocrinopathy, and complaint/sign of hirsutism were not included in the study. Also exclusion criteria for control group included: complaint of secondary dysmenorrhea, chronic pelvic pain, and dyspareunia.

Six patients in endometriosis group and nine patients in control group were not included in the study because their PSA level was not available. Following application of inclusion and exclusion criteria, women in study group consisted of 24 patients whereas controls were 25 patients.

Groups were compared with respect to demographic, hematologic parameters, CA-125, and basal hormones including androgens total T, free testosterone (fT), A, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulphate (DHEA-S), and PSA levels. The study protocol was approved by the Medical Ethics Committee of Dicle University and the informed consent was obtained from all subjects involved in the study.

Serum sampling

Blood samples were drawn from women (day 2-4) in the follicular phase during menses between 8.00-10.00 a.m. on the day after an overnight fasting period before the surgery. The phases of menstrual cycle were determined by the last menstrual period. Each collected blood sample was immediately centrifuged at 4,000 rpms + four C for ten min and then transferred into an Eppendorf tube. Samples were transferred on ice and kept in -70°C deep freeze until the end of the study. Only the serum samples of the patients in both groups were studied after the histological confirmation of endometriosis and after exclusion of the noneligible patients for the study.

Hormone assays

Serum PSA, FSH, E2, LH, and DHEA-S levels were measured by the method of electrochemiluminescence immunoassay (ECLIA) assay. The intra-assay and inter-assay coefficients of variation for all of these assays were < 4.3% and < 6.1%, respectively.

Radioimmunoassay was used for the determination of Serum T, fT, A, and DHEA levels. The intra-assay and inter-assay coefficients of variation for these assays were < 6.2% and < 9.7%, respectively.

Statistical analysis

Statistical analysis of the obtained data was conducted by using Statistical Package for Social Sciences (SPSS) version 15.0. Data were presented as mean ± standard deviation. Normality of variance was tested with Kolmogorov-Smirnov test. Comparisons of continuous variables between two groups were applied using Student's t test. Variables showing non-parametric distribution were compared between groups by using Mann-Whitney U test. A p value less than 0.05 was accepted as statistically significant.

Results

The mean age and body mass index (BMI) were: 31.4 ± 3.8 years, 23.3 ± 2.67 kg/m², respectively, for endometriosis subjects and 31.5 ± 3.6 years, 23.7 ± 2.25 kg/m², respectively, for control group. Demographic, hematologic, and some selected parameters compared between groups are presented in Table 1.

Table 1. — *Comparison of demographics, hematological, and hormonal parameters between groups.*

Characteristics	Endometriosis (n = 24, mean ± SD)	Control (n= 25, mean ± SD)	p
Age, years	31.4 ± 3.8	31.5 ± 3.6	0.95
BMI, kg/m²	23.3 ± 2.67	23.7 ± 2.25	0.62
Htc,%	37.28 ± 3.01	37.31±2.49	0.97
WBC, K/ul	8.444 ± 1.630	6.261±1.870	<0.001
Plt, K/ul	298 ± 76	292 ± 68	0.777
CA125, u/ml	105.7 ± 164	20.96 ± 8.16	<0.001
E2, pg/ml	52.4 ± 34.5	39.5 ± 29.2	0.11
FSH, mIU/ml	8.46 ± 2.21	7.68 ± 2.07	0.21
LH, mIU/ml	6.88 ± 2.68	5.41 ± 2.7	0.06
PRL, ng/ml	22.1 ± 30.8	13.7 ± 4.8	0.42

SD = standard deviation, BMI = body mass index, Htc = Hematocrit, WBC = white blood cell, Plt = platelet, E = estradiol, FSH = follicle stimulant hormone, LH = luteinizing hormone, PRL = prolactin.

Table 2. — *Serum androgens and prostate-specific antigen levels between groups.*

Characteristics	Endometriosis (n = 24, mean ± SD)	Control (n = 25, mean ± SD)	p
T, ng/mL	0.240 ± 0.124	0.215 ± 0.057	0.38
fT, ng/mL	1.674 ± 1.0139	1.237 ± 0.432	0.06
A, ng/mL	1.599 ± 1.279	1.068 ± 0.946	0.12
DHEA, ng/ml	9.439 ± 6.441	7.348 ± 2.119	0.38
DHEA-S, µmol/mL	173.6 ± 74.01	169.5 ± 59.9	0.93
PSA, ng/mL	0.0074 ± 0.0120	0.0059 ± 0.0056	0.58

T = total testosterone, fT = free testosterone, A = androstenedion, DHEA = dehydroepiandrosterone, DHEA-S = dehydroepiandrosterone-sulphate, PSA = Prostate-specific antigen

Levels of T, fT, A, DHEA,and DHEA-S were higher in patients with endometriosis when compared to control subjects, but the difference was not statistically significant. The mean PSA level was 0.0074 ± 0.0120 ng/ml in patients with endometriosis and 0.0059 ± 0.0056 ng/ml in control group and there was no statistically significant difference between groups (p = 0.58). Comparison of serum androgens and PSA levels are shown in Table 2.

Discussion

In this prospective well-designed controlled study, the authors investigated the role of androgens and PSA in the pathophysiology of endometriosis by measuring serum levels of androgens and PSA which has been known as a good marker of androgen load in human body. They found that androgens and PSA has a tendency to increase in endometriosis patients without reaching the statistical significant value.

The role of androgens in the pathogenesis of endometriosis is involved in intricate interactions because of the intermingling factors as hormone levels, variations in the hormone receptor levels, and conversion of androgens via aromatization to estrogens.

In the literature, limited number of studies have compared androgen levels between endometriosis and control group. Studies performed in various compartments in the body as serum, peritoneal, and follicular fluids are not sufficient for precise evaluation [17]. Furthermore, androgen levels in these cavities may not correlate with each other. Studies performed during various stages of the menstrual cycle have confronted with difficulties in comparisons between androgenic hormone levels which potentially show variations in different phases of the cycle.

Mahmood *et al*. [18] compared sex steroids between patients with mild endometriosis and controls at preovulatory period and reported similar A levels in the peritoneal fluid. Pellicer *et al*. [19] assessed steroid levels in follicular milieu in patient with endometriosis with in vitro fertilization (IVF) cycle and reported decreased T accumulation with the severity of the disease. The role of androgens in the pathophysiology of endometriosis is highly suspected by means of danazol study results. The most recent study reported the effect of danazol in patients having endometriosis associated pelvic pain. Based on Cochrane analysis report, the authors concluded that danazol was an effective therapy in relieving endometriosis associated pelvic pain symptoms [20]. This study may support the hypothesis that androgenic therapy may decrease the estrogenic micro environment volume in patients with endometriosis. However in this study, the authors could not find significant changes in serum levels of androgens in women with endometriosis, compared with controls.

Higher basal testosterone levels have been associated with improved IVF outcomes in diminished ovarian reserve, and higher serum testosterone has been correlated with higher oocyte numbers retrieved at IVF in this group [21]. DHEA is a precursor hormone for estradiol and testosterone and adrenal secretion of it, is potentiated by ovarian hyperstimulation with gonadotropins. Recent clinical reports with encouraging results have demonstrated that co-treatment with androgens, such as DHEA and transdermal testosterone, could increase both quantity and quality of oocytes and embryos, and improve pregnancy outcomes in women with diminished ovarian function [22]. In this study, DHEA levels in patients with endometriosis were higher than those of controls but the difference could not reach statistical significance.

Higher levels of T, fT, A, DHEA, DHEA-S, and PSA were observed in the endometriosis group when compared with the control group without any statistically significant difference. This study has some limitations. Small sample size of the study prohibits generalizability of the results. Serum levels of hormones may not correlate to follicular micro environment. Further studies are welcomed to clarify this issue.

Conclusion

Serum basal androgens and PSA levels are higher in endometriosis group with respect to control but the differences are not statistically significant. Increased production of androgens may have protective effect such as increasing quality of oocytes.

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