Evaluation of Cancer Antigens (CA125&CA15- 3) in some Iraqi women with polycystic ovarian syndrome

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Abstract:

Background:
Polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenism anovulatory infertility; it affects 5- 10% of females in the reproductive age. PCOS is a risk disease; it has an association with gynecological malignancy.

Objectivs:
To determine whether Cancer Antigen 125 (CA125) and Cancer Antigen 15- 3 (CA15- 3) levels are increased in PCOS and possibility of CA125 and CA15 -3 to be used as a diagnostic marker of PCOS

Methods:
Seventy females with PCOS diagnosed depending on three criteria: Menstrual history of oligomenorrhea, ultrasound examinations revealed polycystic ovaries and biochemical hyperandrogenism. Twenty normal fertile females serve as control group. Blood samples were obtained from all individuals from 2nd-4th day of menstrual cycle to measure levels of FSH, LH and testosterone. Second blood samples were collected from the same patients during late follicular phase to measure CA15 -3 and CA125 (by ELISA).

Results:
Females with PCOS and controls differed significantly ($p< 0.05$) in total serum testosterone (p). Females with PCOS and controls have highly significant difference ($p< 0.001$) in LH mean level (7.88+ 1.83 vs 3.9+ 0.73) respectivelyand, highly significant difference ($p< 0.001$) in LH/FSH ratio and BMI parameters. No significant differences ($p> 0.05$) were found in FSH, CA125 and CA15- 3 between PCOS patients and the controls. There were positive correlation between testosterone and CA125. Negative correlation between testosterone and CA15 -3 serum values.

Conclusion:
There were no changes in the serum levels of CA125 and CA15- 3 in PCOS patient at the age of reproduction and those cancer antigens could not be used as diagnostic markers for polycystic ovarian syndrome.

Keywords: PCOS, CA125, CA15- 3, Testosterone, LH, and FSH

Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrine problem in women of reproductive age(1). PCOS affects 5–10 percent of all women of reproductive age and is associated with anovulation/ oligoovulation, hyperandrogenism, and PCO (1,2). PCOS is associated with metabolic disturbances including obesity and insulin resistance with a high risk of developing type 2 diabetes, and cardiovascular disease1. In addition, women with PCOS display reduced health related quality of life as well as symptoms of anxiety and depression (3,4). It has been known for many years that severe oligomenorrhea and amenorrhoea in the presence of premenopausal levels of estrogen can lead to endometrial hyperplasia and carcinoma(6). In women with PCOS intervals between menstruations of more than 3 months may be associated with endometrial hyperplasia(7). A small number of studies have addressed the possibility of an association between PCOS and epithelial ovarian cancer risk; the results are conflicting but generally reassuring(8). Risk for breast cancer and benign disease of the breast have not been confirmed(9). However, no good data are available to support the increased risk for breast cancer in women with PCOS. Most studies have failed to demonstrate a particular risk for breast cancer in these women with a hyperoestrogenic state(10). Tumor markers are soluble glycoproteins that are found in the blood, urine, or tissues of patients with certain types of cancer. They are typically produced by tumor cells, but in some cases they may be produced by the body in response to malignancy or to certain benign conditions(11). Elevated CA125 values most often are associated with epithelial ovarian cancer, although levels also can be increased in other malignancies. So, the primary tumor associated with elevated CA125 tumor marker is ovarian cancer, but this marker also elevated in additional associated malignancy: (endometrial, fallopian tube, breast, lung, esophageal, gastric, hepatic, pancreatic cancers) and in some benign conditions (pregnancy, menstruation, fibroids, ovarian cysts, pelvic inflammation, cirrhosis, ascites, pleural and pericardial effusions and endometrios).(12) Cancer antigen 15 -3 is an antigen expressed in benign and malignant breast ductal epithelium. It may also be elevated in individuals with other cancers, such as, lung cancer, pancreatic,ovarian,liver,and colorectal, and cancers(13). The CA 15- 3 may also be elevated in healthy people and in individuals with cirrhosis, hepatitis, and benign breast disease(14). The most clinical utility of CA15- 3 is in the setting of monitoring therapy in patients with advanced breast cancer through serial determinations of CA15 -3 in conjunction with diagnostic imaging, history, and physical exams(15). This study was conducted to determine whether serum Cancer Antigen 125 (CA125) and Cancer Antigen 15- 3 (CA15- 3) levels are increased in PCOS and possibility of CA125 and CA15 -3 to be used as a diagnostic marker of PCOS.

Materials and Method

Seventy females in their reproductive age (20-40 years old), who had been diagnosed as PCOS, were recruited from Infertility Clinic at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University,from the period between July 2011 and October 2011. The diagnosis of PCOS was based on the presence of polycystic ovaries on ultrasonography (10 or more follicles of 2–9 mm in diameter in each ovary). One polycystic ovary is sufficient for the diagnosis with one or more of the following criteria5:

1. Oligo-/anovulation; clinically diagnosed as oligo-/amenorrhoea, i. e. menstrual cycles longer than 35 days, or fewer than 10 menstruations per year.
2. Hyperandrogenism; clinical or biochemical. Clinical manifestations of hyperandrogenism such as a hirsutism, acne and/or an elevated serum testosterone level.

Twenty apparently healthy age matched fertile women were served as control. They have regular menstrual cycle and normal ovaries by ultrasound.

Five ml of blood samples were aspirated at 8:00-12:00 am during the 2nd – 4th day of menstrual cycle (early follicular phase) for normal and patients. The serum was aspirated, and stored at -20°C until time of assay. Serum FSH and LH level along with LH/FSH ratio and testosterone were performed for those samples. Second blood samples were aspirated from the same patients during the late follicular phase of the same cycle and processed as similarly for determination of serum levels.

Statistical analysis

Data were analyzed using SPSS version 16 and Microsoft Office Excel 2007. Numeric variables were expressed as mean± standard deviation. Student t-test was used to compare between two independent variabes. Pearson>s correlation coefficient was used to study correlation between two numeric variables. The differences between values were consid-

ered statistically significant at the level of (P<0.05) and highly significant at the level of (P<0.001).

Results:

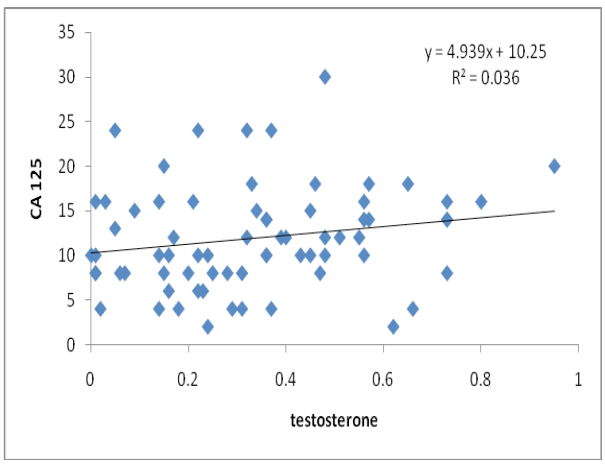
Table(1) Comparison between control and PCOS patients

Parameter	Group 1 (control= 20) Mean+SD	Group2 (PCOS =70) Mean+SD	P value
Number	20	70	
Age(years)	29.58± 3.32	28.05± 2.68	0.162 NS
CA125(IU/ml)	11.91+ 5.79	12.30 +6.48	0.799 NS
CA15 -3(IU/ml)	16.00 +2.91	17.21+ 2.69	0.084 NS
FSH (mIU/ml)	5.34+ 0.65	5.65+ 1.47	0.372 NS
LH(mIU/ml)	3.90+ 0.73	7.88+ 1.83	<0.001 **
LH/FSH	0.73+ 0.12	1.43+ 0.36	<0.001 **
TESTO(ng/dl)	0.22+ 0.09	0.33+ 0.22	0.036 *
BMI kg/m2	24.33 +1.35	27.62 +1.96	<0.001 **

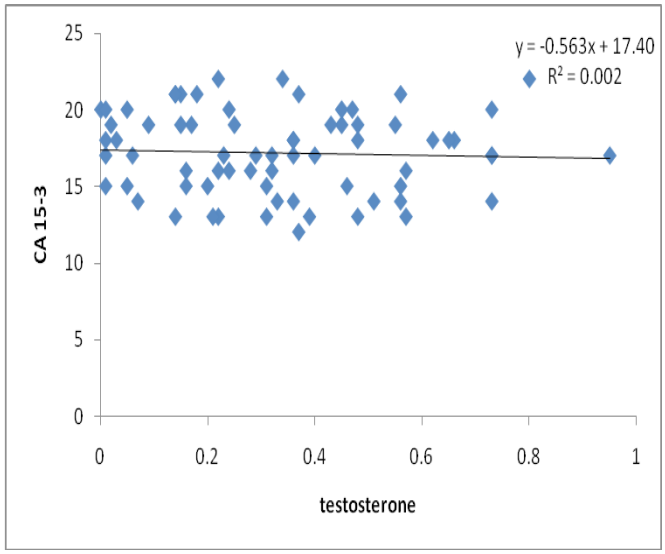
NS: no significant difference (P> 0.05) as compared to the control group.
*: significant difference (P<0.05) as compared to the control group.
**: highly significant difference (p<0.001) as compared to the corresponding group.

In table1 the mean serum levels of total testosterone in patients with PCOS was equal to (0.33± 0.22) ng/dl which was significantly (P=0.036). elevated when compared with normal controls group (0.22 ±0.09) ng/dl. The mean serum levels of CA125 in patients with PCOS was equal to (12.30± 6.48) IU/ml is within the normal range with no significant difference (P=0.799) when compared with the normal control group (11.91 ±5.79) IU/ml The mean serum levels of CA15- 3 in patients with PCOS was equal to (17.21± 2.69) IU/ml is not significantly different (P =0.084) when compared with the normal control group (16.00± 2.91 IU/ml;).

Figure(1) –revealed a non significant positiv correlation (r=0.192, p =0.112) between serum testosterone and CA 125 level in PCOS patients. Whereas a negative correlation (r=-0.047, p =0.600) was observed between the testosterone and CA 15 -3 level in PCOS patients (figure2).



Figure(1): Persons correlation between testosterone and CA 125 in PCOS patients (r=0.192, p =0.112).



Figure(2): Persons correlation between testosterone and CA 15 -3 in PCOS patients (r=-0.047, p =0.600).

Discussion:

Polycystic ovary syndrome is a heterogeneous disorder, characterized by hirsutism, abdominal obesity, hyperandrogenism, polycystic ovaries and insulin resistance. The syndrome is often accompanied by infertility because of anovulation(16).

Women with PCOS may be at increased risk of breast and ovarian cancer, although these risks are not well-documented. Also women with PCOS are at increased risk of endometrial abnormalities, including carcinomas, and should be followed carefully for these disorders(17). The gonadotropin theory suggests that increased gonadotropin (LH and/or FSH) exposure increases estrogenic stimulation of the ovarian surface epithelium (OSE) either directly or indirectly(18). Frequently women who are infertile undergoing infertility treatments are exposed to increased levels of gonadotropins to induce ovulation. These women have 2.8 times the risk of invasive ovarian cancer and 4.0 times the risk of low malignant potential ovarian cancer compared to a control group of women who were infertile and not undergoing therapy(19). Risch *et al* suggest that androgens may play a role in ovarian carcinogenesis, since the ovary is known to contain androgen receptors, and androgens have been shown to stimulate growth in ovarian cancer cell lines(20). Epidemiologically the theory is supported by the increased risk seen with PCOS when levels of androgens are increased(21). Women with PCOS have long term risk of endometrial hyperplasia and endometrial carcinoma due to chronic anovulation and unopposed oestrogen action; similarly, there may be an increased risk of breast carcinoma(22). The risk of developing endometrial cancer has been shown to be adversely influenced by a number of factors including obesity, long term exposure to unopposed oestrogen, nulliparity

and infertility(23). The result of this study showed that there was no significant difference in the mean value of CA125 between the control group and the PCOS group. This might be due to the fact that although there is hormonal disturbances in PCOS patient but these changes don't cause stimulation of the serosal surfaces which represent a basic step in CA125 elevation.

Cancer antigen 15 -3 is an antigen expressed in benign and malignant breast ductal epithelium. Antibodies against CA15- 3 have been used as possible serum markers of occult and recurrent breast carcinoma (24,25). Obesity, hyper androgenism and infertility occur frequently in PCOS patients and are features known to be associated with the development of breast cancer(22). The result of this study showed that there is no significant difference in the mean value of CA15 -3 between the control group and the PCOS group. Coulam *et al*(26) found a relative risk of 1.5 of breast cancer in patient with chronic anovulation, but this was not statistically significant. Gammon and Thompson(27) reported a reduced risk of breast cancer in PCOS patient.

In support of the present finding, the Cancer and Steroid Hormone (CASH) study, a large case-control study of women aged 20–54, found significant protective effect of a history of PCOS on breast cancer risk in these mostly premenopausal women(28). Anderson *et al*(29) found that women with PCOS do not have any significant increase in risk of developing breast cancer compared with those without (RR 1.2; 95% CI 0.7–2.0). A small number of studies have addressed the possibility of an association between PCOS and epithelial ovarian cancer risk, the results are conflicting but generally reassuring30. As there was no association with breast or ovarian cancer, no additional surveillance is required beyond routine screening. Therefore, from the results of the present study it was concluded that cancer antigens CA125 and CA15 -3 could not be used as diagnostic markers for polycystic ovarian syndrome. In the light of finding of the current study, we recommend to estimate CA125 and C15- 3 levels in postmenopausal PCOS patients to assess the risk of ovarian and brest cancer.

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