Evaluation of Cancer Antigens (CA125&CA153-) 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 510- % 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 153-(CA153-) levels are increased in PCOS and possibility of CA125 and CA153- 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 CA153- 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 (7.881.83+ vs 3.900.73+) 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 CA153- between PCOS patients and the controls.There were positive correlation between testosterone and CA125.Negative correlation between testosterone and CA153- serum values.

Conclusion:
There were no changes in the serum levels of CA125andCA153- 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, CA153-, Testosterone, LH, and FSH

Introduction:

Polycystic ovary syndrome(PCOS) is the most common endocrine problem in women of reproductive age1. PCOS affects 5–10 percent of all women of reproductive age and is associated with anovulation/oligoovulation, hyperandrogenism, and polycystic ovaries (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 depression3, 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 carcinoma6. In women with PCOS intervals between menstruations of more than 3 months may be associated with endometrial hyperplasia7. 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 reassuring8. Risk for breast cancer and benign disease of the breast have not been confirmed9. 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 state10. 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 conditions11.Elevated CA 125 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 153- 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 cancers13. The CA 153- may also be elevated in healthy people and in individuals with cirrhosis, hepatitis, and benign breast disease14. The most clinical utility of CA 153-is in the setting of monitoring therapy in patients with advanced breast cancer through serial determinations of CA 153-in conjunction with diagnostic imaging, history, and physical exams15. This study was conducted to determine whether serum Cancer Antigen 125 (CA125) and Cancer Antigen 153-(CA153-) levels are increased in PCOS and possibility of CA125 and CA153- to be used as a diagnostic marker of PCOS.

Materials and Method

Seventy females in their reproductive age (2040- 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 8:0012:00- 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 considered 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
CA153-(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 the mean serum levels of total testosterone in patients with PCOS was equal to (0.330.22+) ng/dl which was significantly (P=0.036). elevated when compared with normal controls group (0.220.09+) ng/dl. The mean serum levels of CA125 in patients with PCOS was equal to (12.306.48+) IU/ml is within the normal range with no significant difference (P=0.799) when compared with the normal control group (11.915.79+) IU/ml The mean serum levels of CA153- in patients with PCOS was equal to (17.212.69+) IU/ml is not significantly different (P =0.084) when compared with the normal control group (16.002.91+ IU/ml;).

Figure(1)revealed a non significant positive 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 153- level in PCOS patients(figure2).

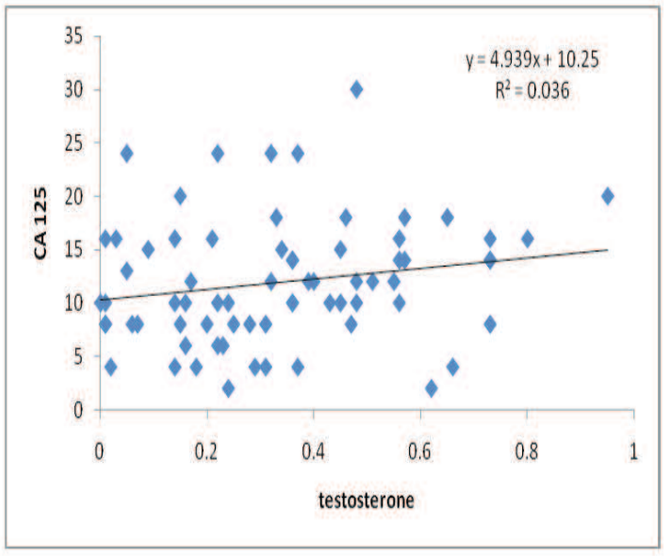

Figure (1): Persons correlation between testosterone and CA 125 in PCOS patients (r=0.192, p =0.112).

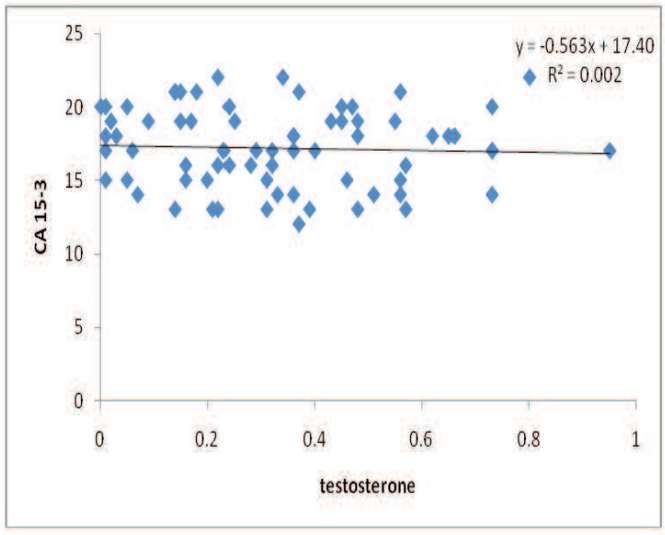

Figure (2): Persons correlation between testosterone and CA 153- in PCOS patients (r=-0.047, p =0.600).

Discussion:

Polycystic ovary syndrome (PCOS) 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 disorders17. 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 therapy19. 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 infertility23.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 153- is an antigen expressed in benign and malignant breast ductal epithelium. Antibodies against CA 153- 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 cancer22.The result of this study showed that there is no significant difference in the mean value of Ca153- between the control group and the PCOS group .Coulam et al26 found a relative risk of 1.5 of breast cancer in patient with chronic anovulation, but this was not statistically significant. Gammon and Thompson27 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 women28.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 CA153- 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 C153- levels in postmenopausal PCOS patients to assess the risk of ovarian and brest cancer.

References:

1. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007; 370: 685697-.
2. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod .2004; 19:41–47.
3. Jedel E,. Waern M, Gustafson.D, Landen M, Eriksson.E,. Holm G , L.et al. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. Hum Reprod. 2010; 25:450–456.
4. Li Y, Yu Ng EH, Stener-Victorin E,Hou L, Wu T, Han F, et al. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta analysis. Fertil Steril. 2011; 96:452–458.
5.ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long–term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81: 19–25.
6. Chamlian DL, Taylor HB. Endometrial hyperplasia in young women. Obstet Gynecol. 1970;36:659–66.
7. Cheung AP. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. Obstet Gynecol. 2001;98:325–31.
8. Gadducci A, Gargini A, Palla E, Fanucchi A, Genazzani AR. Polycystic ovary syndrome and gynecological cancers: is there a link? Gynecol Endocrinol. 2005;20: 200–8.
9. Soran A, Ibott EO, Zborowski JV, Wilson JW. The prevalence of benign breast disease in women with polycystic ovary syndrome: a review of a 12 year follow-up. Int J Clin Pract. 2005; 59: 795- 797.
10. Norman R, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab. 2002; 13: 251 -257.
11. Tchagang AB, Tewfik AH, DeRycke MS, Skubitz KM, Skubitz AP.Early detection of ovarian cancer using group biomarkers. Mol Cancer Ther. Jan 2008;7:2737-.
12. Gallup DG& Talledo E. Management of the adnexal mass in the1990s. South Med J 1997;90:97281-.
13. Tietz Wu A Clinical Guide to Laboratory Tests, 4th Edition: Saunders Elsevier, St. Louis, MO. 2006. pp 206- 207.
14. Clarke W. and Dufour D R. Contemporary Practice in Clinical Chemistry: AACC Press, Washington, DC. 2006. P p 247.
15. Chan DW, Beveridge RA, Muss H, Fritsche HA, Hortobagyi G, Theriault R, et al. Use of Truquant BR radioimmunoassay for early detection of breast cancer recurrence in patients with stage II and stage III disease. J Clin Oncol. 1997; 15:2322 -2328.
16. Xita N& Tsatsoutis A. Fertile programming of PCOS by androgen excess; Evidence from experimental, Clinical and genetic association studies. J Clin Endocrinol Metab . 2006;7.
17. Chittenden B G, Fullerton G, Maheshwari A ,Bhattacharya S.Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod. Biomed. Online. 2009; 19: 398–405.
18. Fleming J, Beaugie C, Haviv I, Chenevix-Trench G, Tan OL.Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: Revisiting old hypotheses. Molecular and Cellular Endocrinology. 2006;247:4- 21.
19. Ahonen, MH, Zhuang, YH, Aine, R, Ylikomi, T, Tuohimaa, P.Androgen receptor and vitamin D receptor in human ovarian cancer: growth stimulation and inhibition by ligands. Int J Cancer. 2000; 86:40 -6.
21.Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst .1998; 90:1774 -86.
22. Schildkraut JM, Schwingl PJ, Bastos E,Evanoff A, Hughes C. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. Obstet Gynecol. 1996; 88:554- 9.
23. Murphy AA, Cropp CS, Smith BS, Burkman RT, Zacur HA. Effect of low-dose oral contraceptive on gonadotropins, androgens, and sex hormone binding globulin in nonhirsute women. Fertil Steril. 1990; 53:35 -9.
24. Adam Balen .PCOS and cancer, Human reproduction. 2001; 7:522-525.
25. Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A. The epidemiology of endometrial cancer in a young women. Br.J.cancer. 1983;47:749- 756.
26. Eloowd JM, Cole P, Rothman KJ,Kaplan S.D. Epidmiology of endometrial cancer.J.Natl cancer Inst. 1977;59:1055- 1060.
27. Nicolini A, Anselmi L, Michelassi C, Carpi A.Prolonged survival by 'early' salvage treatment of breast cancer patients: A retrospective 6-year study. Eur J Cancer. 1997; 76: 1106- 1111.
28. Ohuchi N, Sato S, Akimoto M Taira Y, Matoba N, Takahashi K, et al. Correlation between the immunohistochemical expression of DF3 antigen and serum CA 153- in breast cancer patients. Jpn J Surg. 1991; 21: 129-137.
29. Coulam, CB, Annegers JF and KranzJS . Chronic anovulation syndrome and associated neoplasia.Obestet.Gynecol. 1983;61,403 -407.
30.Gammon MD and ThompsonWD.() polycystic ovaries and the risk of breast cancer. Am.J.Epidmiol. 1991;134: 818 -824.
31. Gammon MD, Thompson WD. Polycystic ovaries and the risk ofbreast cancer. Am J Epidemiol. 1991;134:818–24.
32.Anderson KE, Sellers TA, Chen PL,Rich SS, Hong CP, Folsom AR.Association of Stein–Leventhal syndrome with the incidence of postmenopausal breast carcinoma in a large prospective study of women in Iowa. Cancer 1997;79:494–9.
33. Gadducci A, Gargini A, Palla E,Fanucchi A, Genazzani AR.Polycystic ovary syndrome and gynecological cancers: is there alink? Gynecol Endocrinol .2005;20:200–8.