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Original Research Article

Polycystic Ovary Syndrome: does it Increase the Level of Cancer Antigen125?

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Abstract

PolyCystic Ovary Syndrome(PCOS) is an important cause of androgen excess, menstrual irregularity, and cardiometabolic dysfunction in women. iLong term manifestations such as gynaecological malignancies, like endometrial carcinoma increased to more than three folds due to endometrial hyperplasia resulting from chronic anovulation and obesity. Cancer antigen 125(CA125)glycoprotein mucin in nature tumour marker is valuable in screening for ovarian and endometrial malignancies, monitoring therapy, early detection of recurrence and, prognosis of these cancers. This study is arranged as PCOS women are considered risky group and CA125 early screening may make a change in the type of treatment..This study was done in Iraq in 2019 between July and October Forty women aged 18-42 year were included they were distributed into two groups, PCOS group, and non PCOS group. BMI was within normal for both groups. Blood samples were taken in early follicular phase for assessing luteinizing hormone (LH), follicular stimulating hormone (FSH) and free testosterone (FT) hormone. Other blood samples were taken at late follicular phase to calculate CA125levels using enzyme linked immunosorbent assay (ELISA). This study revealed no significant difference in CA125 between normal group and PCOS group .In spite of the hormonal disturbance in PCOS and increasing risk of malignancy, CA 125 was not increased in non-cancerous patients

Keywords: Body Mass Index (BMI), Cancer antigen CA125, Polycystic ovarian Syndrome (PCOS)

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the commonest problem affecting women in period of reproduction. It is characterized by hyperandrogenism, infrequent ovulation, and multiple follicular cysts in an increased size of ovaries (Park Chun., 2016). Around 5-10% of women are affected. This condition was known since 1935 (Kabel, 2016). The metabolic and reproductive abnormalities causing infertility due to failure of ovulation (Selman *et al.*, 2019). The syndrome may also be associated with hyperinsulinemia, insulin resistance (IR), type 2 diabetes mellitus (T2DM), obesity, hyperlipidaemia and cardiovascular diseases (Sachdeva *et al.,* 2019).

Moreover, metabolic abnormality in this syndrome may also result in long term morbidity such as endometrial carcinoma (EC) (C.J.M.Fauser, 2004).

Rotterdam criteria for diagnosis of PCOS had been innocent since 2003. Presence of two of three findings ensure the diagnosis these include Chronic anovulation, hyperandrogenism (clinical or biologic), and polycystic appearance of ovaries (PCOM) on ultrasound. Exclusion of other causes of androgen excess and anovulatory infertility is a must. In addition to the history and clinical findings, an assessment of free testosterone (T) level is recommended as it is more sensitive than total

testosterone level for determining androgen excess (Rojas *et al*., 2014).

It has been found that anti-Müllerian hormone (AMH) reflects an elevated number of pre-antral and small antral follicles (Filippou and Homburg, 2017)

Androgens play an essential role in the pathogenesis of ovarian cancer through their effect on stimulating the epithelial cells. Ovarian cancer is the most lethal gynaecologic malignancy This malignancy has a poor prognosis and that is mainly due to: late presentation and consequently late diagnosis, in addition to the lack of targeted therapies for advanced disease, and manifesting chemo-resistance (Zhu *et al.,* 2017).

The risk of ovarian cancer is increased in polycystic ovarian syndrome (PCOS) which is a hyper-androgenic state (Barry *et al.,* 2014).

Androgenic drugs are associated with a high risk of ovarian cancer. This provides an additional supportive piece of evidence to the androgen theory. A 3.2 fold increase in risk of cancer when danazol is used for treatment of endometriosis (Zhu et al., 2017). Furthermore, the same association had been found between ovulation-induction drugs used in treating infertility in PCOS patients (Balen, 2001). Overweight risk in PCOS can be explained as adipose tissue contains aromatase activity which converts androstenedione to oestrone and testosterone to oestradiol a situation where these women have excessive androgens and oestrogens which increase the risk for breast cancer (Gardener *et al.,* 2018).

Women with PCOS have 2.7 times higher risk of developing endometrial cancer (Mujawar *et al.,* 2018).
Risks may include LH hypersecretion, chronic hyperinsulinemia, obesity, hyperandrogenism and increased serum insulin-like growth factor [IGF]-I levels Allahbadia, Merchant, 2011). Increased levels of oestrogens unopposed by progesterone leading to endometrial hyperplasia hence increased risk for endometrial cancer over a period of years (Gadducci *et al.,* 2005). In addition, there was a Concerns about assisted reproductive technology (ART) ovulation induction agents and the association with endometrial cancer (Mujawar *et al.,* 2018). As a result of these factors, screening by using CA125 tumour marker need to be recommended.

Cancer antigen 125 (CA-125)

Cancer antigen 125(CA-125) is a soluble protein that belongs to mucins family.CA125 is expressed by endometrial, ovarian, corneal, normal bronchial epithelial cells and digestive tract and implicated in antiviral and antibacterial activity and against injuries and toxins) (Felder *et al.,* 2014). It is produced by the secretory epithelial cells lining ducts and lumens within the human body. Secretion is stimulated by epidermal growth factor (EGF) or tyrosine phosphatase. Epithelial shedding is decreased by glucocorticoids .The key role of mucins is to keep epithelial surfaces moist and hydrated, which is needed for the proper functioning of ducts and passage ways (Wagner et al., 2018).

Plasma concentration of CA-125is increased in normal physiological conditions such as a mild increase at ovulation, notably during menstruation and obviously during pregnancy (Aithal., 2018). In some benign conditions elevation of CA125can be shown in ovarian hyperstimulation syndrome (OHSS), functional ovarian cyst, ectopic pregnancy, fibroid, tubo-ovarian abscess, and moderate and sever endometriosis. Other non-gynaecological diseases such as heart failure and liver diseases. CA125 is valuable in dealing with ovarian, endometrial, fallopian tubes cancers, as well as those cancers of lung, breast and gastrointestinal tract (Sharma, 2009).

CA125 is not a specific tumour marker because it is associated with various diseases. Thus, to improve sensitivity and specificity, combination patterns of multiple markers such as Human Epididymis Protein 4(HE4) and CA125 might be used together in the detection of ovarian malignancies (Chen *et al*., 2013)

Other investigating procedures can be combined with tumour markers e.g., combination of ultrasonography with CA125 for early detection of ovarian malignancy (Aithal*.,* 2018). Detecting recurrence of the cancer by tumour marker serial assessment are needed. Elevation in concentration of tumour marker before any clinical or radiological evidence of the disease is apparent this is regarded as biochemical recurrence. Scheduling for sampling should be typically arranged after 5-6 half-lives of the marker but this is still debated (or choosing the marker with the longest half-life if multiple markers are being used); but when tumour marker elevated, the next sampling should be after 2-4 weeks, with additional radiological examination may be arranged to confirm the recurrence (Chen *et al*., 2013).

Aim of study

To study the correlation between PCOS and CA 125 level in non-cancerous women of reproductive age

PATIENTS AND METHODS

This is a cohort prospective study was performed at the infertility clinic of High Institute of Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University- Baghdad / Iraq in the period from July 2019 to October 2019. Ethical approval was issued. All participants were informed about the study and written informed consent was obtained from each participant. The present study was done on forty women who were

grouped into two groups. Each group included twenty women: Group1 (G1) was on PCOS women and Group 2 (G2) was PCOS patients.

The assessment was done in the infertility clinic of High Institute of Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University while the biochemical investigations for measuring the hormones and CA 125 marker were done in the biochemical lab of the institute and in a private lab. Weight and height were measured for every female to calculate their body mass index (BMI) according to the equation:

BMI= Weight (Kg)/ (height)m^2 (WHO)

Women selected for this study, age were (18-42) year, BMI>18.5kg/m^2<25kg/m^2 not pregnant at time of assessment.

PCOS patient were diagnosed according to Rotterdam criteria, (Lujan *et al*., 2010) no history of endocrine disease, no history of endometriosis or ovarian cyst or chronic disease. Women who were out of range of age <18- 42> year. BMI <18.5kg/m^2 (underweight), overweight, obese and pelvic mass by U/S as cyst or fibroid, chronic diseases, hormonal disturbances such as thyroid dysfunction, Cushing's syndrome, hyperpro-lactinemia hypogonadotropic hypogonadism and congenital adrenal hypertrophy were excluded. Physical and gynaecological examination in addition to pelvic U/S was performed for confirmation of PCOS diagnosis and no history of chronic disease was recorded. For all females chemical investigation was done for detection of CA125 level and hormonal examination including LH, FSH, Free T done by, ELISA. The body weight, height, and body mass index (BMI)were calculated. Blood samples were collected from all females included in the study attended in the 2nd-4th day of their menstrual cycle. Women who had amenorrhea were treated by progesteone to induce bleeding. Disposable syringes and plain plastic tubes were prepared and labelled. Special forma with their written name, date, serial number, cycle day, and history. Venous blood samples of 5 ml were taken by venous puncture.

Serum was used for hormonal tests of FSH,LH, and free Testosterone (FT). 5ml blood samples were collected again from all women enrolled in this research at late follicular phase of the same cycle (at cycle day CD 8-12) of menstrual cycle. Hormones and CA 125marker antigen was measured by Enzyme Linked Immune Sorbent Assay (ELISA). Kits used were CA125Ag (ELISA) HUMAN Germany number of kit REF 52050 LOT 19001.

Free Testosterone (ELISA) De medi tec Germany number of kit REF DE2924 LOT5050A.

FSH HUMAN Germany number of kit REF 53020 LOT 17007.

LH (ELISA) Monobind USA kit number LOT 6D1B8.

Data were analysed using SPSS version 22 and Microsoft Office Excel 2010. Numeric variables were expressed as mean(±)standard deviation, range, numbers, and percentage (%). Student t-test was used to compare independent two samples. Person's correlation coefficient (r) was used to study correlation between two variables. The differences between values were considered statistically insignificant at the level of (P>0.05) and significant at the level of (P<0.05) and highly significant at the level of (P<0.01).

RESULTS

The demographic data was demonstrated in (Table 1). There was no significant difference in mean age, between G1 and G2 (P = 0.144). Regarding BMI there was no significant difference (P>0.05) between the two groups, normal non PCOS G1 and PCOS G2(22.66 ±1.91) and (22.53 ±2.010) respectively, as reported in Table 1. There was highly significant difference in hirsutism (P< 0.001) between normal group and PCOS group. According to ultrasound findings was highly significant difference between control women and PCOS women (p< 0.001), see (Table 1).

There was highly significant difference in mean serum luteinizing hormone (LH) between study groups (P<0.001) being elevated in PCOS group above the normal group, being (9.10 ±3.42) and (5.49 ±1.60) respectively, as reported in (Table 2)

There was no significant difference in mean serum follicle stimulating hormone(FSH) between study groups (P = 0.467), (Table 2). On the other hand, there was highly significant difference in mean serum testosterone between the two groups (P< 0.001). The level was higher in G2 than G1 as (1.22 ±0.59) (0.81 ±0.21) respectively as shown in Table 2. There was highly significant difference in mean LH/FSH ratio between G1 and G2 study (P = 0.001). The ratio was higher in PCOS group than control group (1.39 ±0.72) (0.85 ±0.39) respectively.

There was no significant difference between control group and PCOS group in level of CA125(P >0.05) (15.40 ±2.53 U/ml) (15.38 ±4.16 U/ml) respectively, as shown in Figure1. The figure shows CA125 concentration in G1 (control normal weight) and G2 PCOS.P>0.05.

DISCUSSION

As far as to our knowledge there are small number of published studies about CA125 in non-cancerous women, and even less published studies about A12andPCOS.

Age of control group of women and PCOS women were< 35 versus ≥ 35of age, and there was no significant difference between the groups. for BMI regarded as within normal BMI according to WHO classification of BMI normal weight (18.5-24.9) kg/m^2were included for this study (WHO 2020). There was no significant difference in BMI between groups. The mean of appearance of

Table 1. Demographic characteristics of women enrolled in the present study

Characteristic	Control G1 normal weight *n* = 20	PCOS G2 normal weight *n* = 20	P
Age (Years)			
Mean ±SD	28.05 ±6.07	25.30 ±6.88	0.144 †
Range	19 -38	18 -39	NS
< 35, *n* (%)	16 (80.0 %)	18 (90.0 %)	0.667
≥ 35, *n* (%)	4 (20.0 %)	2 (10.0 %)	NS
BMI (kg/m^2)			
Mean ±SD	22.66 ±1.91	22.53 ±2.01	> 0.05 †
Range	18.5 -24.71	19.28 -24.9	NS
Normal, *n* (%)	20 (100.0 %)	20 (100.0 %)	>0.05 †
Overweight, *n* (%)	0 (0.0 %)	0 (0.0 %)	NS
Obese, *n* (%)	0 (0.0 %)	0 (0.0 %)	
Hirsutism			
Positive	0 (0.0 %)	15 (75.0 %)	< 0.001
Negative	20 (100.0 %)	5 (25.0 %)	HS
Ultrasound			
Positive	0 (0.00 %)	20 (100.0 %)	< 0.001
Negative	20 (100.0 %)	0 (0.0 %)	HS

n: number of cases; SD: Standard deviation; BMI: Body mass index; †: One-way ANOVA test; NS: Not significant at P> 0.05; HS: Highly significant at *P* ≤ 0.01

Table 2. Serum hormonal levels of women with PCOS and control women

Characteristic	Control G1 normal weight *n* = 20	PCOS G2 normal weight *n* = 20	P
Luteinizing hormone (LH)			
Mean ±SD	5.49 ±1.60	9.10 ±3.42	< 0.001 †
Range	3.14 -8.46	2.5 -15.7	HS
Follicle stimulating hormone (FSH)			
Mean ±SD	6.77 ±1.48	7.11±1.88	0.467 †
Range	3.25 -9.26	3.71 -9.27	NS
Testosterone			
Mean ±SD	0.81 ±0.21	1.22 ±0.59	< 0.001 †
Range	0.62 -1.30	0.61 -2.41	HS
LH/FSH ratio			
Mean ±SD	0.85 ±0.39	1.39 ±0.72	<0.001 †
Range	0.53 -2.45	0.27 -3.18	HS
Serum Ca-125 (U/ml)			
Mean ±SD	15.40 ±2.53	15.38 ±4.16	>0.05 †
Range	7.08 -18.07	7.48 -22.68	NS

n: number of cases; SD: Standard deviation; †: One way ANOVA test; NS: Not significant at P> 0.05; HS: Highly significant at P ≤ 0.01.

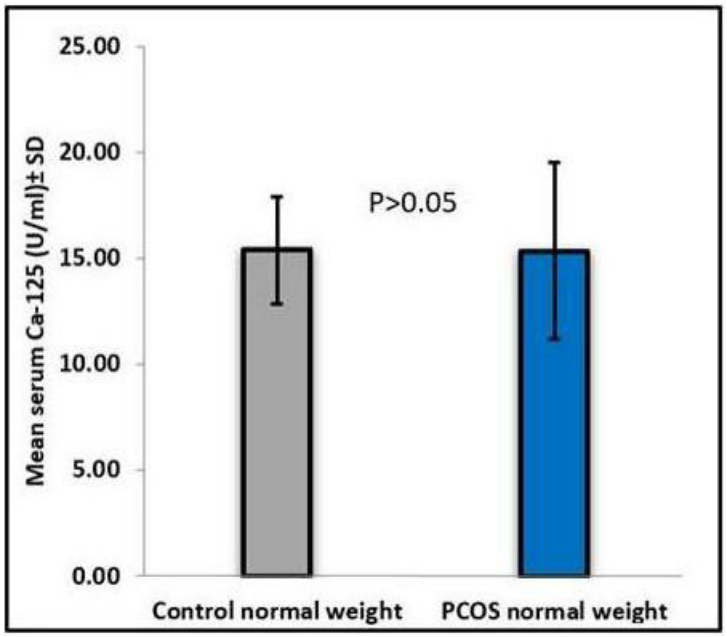

Figure 1. Serum CA-125 values

hirsutism between the two groups was highly significant. Hirsutism is one of an important clinical manifestation of PCOS caused by hyperandorgenism, hair growth in certain anatomic areas is determined by androgen (Kabel, 2016).

There was highly significant difference in mean of ultrasound finding between the two groups. Ultrasound U/S finding in the diagnosis of PCOM are including follicular number per ovary (FNPO) is ≥12 of 2-9ml in diameter and the ovarian volume (OV) threshold of ≥10 ml, Rotterdam criteria for the diagnosis of PCOM in all women within control group, were negative for the difference in the frequency was highly significant (Dewailly *et al*., 2007). History may be enough for diagnosis of PCOS. Investigation needed for confirmation of diagnosis and to assess the severity of disease also hormonal assessment suggestive not diagnostic, LH, FSH LH/FSH they were not included in the Rotterdam criteria.

Regarding the result of the current study the LH was elevated or normal so it match with many previous studies for example the study done by De Leo *et al*. in 2016 (De Leo *et al*., 2016) and also match Shaaban *et al* in 2018 (Shaaban *et al.,* 2018). Another study done by Park and Chun on Korean women with PCOS in 2016 that identify increased LH secretion.

There was no significant difference in mean serum follicle stimulating hormone (FSH) between study groups (P = 0.425), (Table 2). FSH was within normal range(2.9-10.88). Park and Chun, in 2016 and many studies shows that FSH were normal or low in PCOS (Park Chun., 2016).

Furthermore, there was highly significant difference in mean LH/FSH ratio between study groups (P = 0.001). The ratio was higher in PCOS women as it was more than one. Hsu suggested that an LH/FSH ratio of >1 offered the best combination of sensitivity and specificity for the diagnosis of PCOS (Hsu, 2015), which was similar to the ratio in current study (more than one). Testosterone also was measured and found that there was highly significant difference between PCOS and control group (1.22 ± 0.59) (0.81 ± 0.21) respectively. High androgen level in PCOS patient were seen in 40% of PCOS caused by the testosterone secreted by the ovary mainly (Kabel, 2016).

There was no significant difference between control group and PCOS group in level of CA 125 (15.40 ± 2.53 U/ml) (15.38 ± 4.16 U/ml) respectively. As far as to our knowledge gynaecological cancer risk increase with PCOS more than non PCOS women (Balen, 2001) never the less the level of CA125 not differ from that of normal non PCOS women. CA125 regarded as normal when it value<35(U/ml)CA15 not elevated in PCOS.

This result was agreed with result of study done in 2012 in Iraq on Iraqi women in reproductive age where there was no significant difference between PCOS and control in mean concentration of CA125thisresult might be explained as that even there were hormonal disturbance in PCOS women ,still there were no stimulation to serosal surface of the ovaries in CA125 (Rzaij and AL-Ani, 2013).

In contrast to the current research, Mujawar and *et al.* in their study done in Governmental Hospitals in Mumbai, India he found that there was significantly

higher (p<0.001) serum CA-125 levels in PCOS patients than control group (Mujawar *et al,* 2018).

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CONCLUSION

No significant difference in CA 125 level between normal women and women who complain of polycystic ovarian syndrome so no additional screening isneeded in PCOS women during reproductive age.

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