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Original Article

Diagnostic Value of Serum Prolactin in Ovarian Cancer

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Ovarian cancer ranks fifth in cancer deaths among women, and causes more deaths than any other cancer of the female reproductive system. Since diagnosis at an early stage is associated with improved survival rate, an effective screening strategy that detects early stage ovarian cancer could have a significant impact on mortality from this disease. Cancer antigen 125 (CA125) is an established biomarker for ovarian cancer detection. As CA125 effectiveness in the identification of the malignancy is threatened by its low diagnostic specificity, measurement of prolactin (PRL) in serum have been proposed for improving the sensitivity and specificity of disease identification. The aim of the present study was to assess the level of serum PRL among healthy and ovarian cancer women at Khartoum state, Sudan. 90 Sudanese ladies with age range (16-80) years old who attended the gynecological oncology clinic in Omdurman Military hospital were enrolled in this study. Blood samples were collected, and quantitative determination of serum prolactin (PRL) levels was performed by immunoassay. Epithelial ovarian cancer was the most common ovarian cancer type followed by germ cell tumors. PRL serum levels were within the reference range in both control and study groups. No significant difference in PRL levels was observed when considering the parity or the stage of cancer ($P > 0.05$). Investigating different isoforms of PRL may help to better understand the mechanism of action of this hormone in ovarian cancer induction.

Keywords: Ovarian cancer, serum biomarker, prolactin

Ovarian cancer has been called the "silent killer" because symptoms often become apparent only when the cancer has spread and is harder to treat. It's the fifth leading cause of cancer-related death in women in the United States and is the leading cause of gynecologic cancer deaths. Despite being one-tenth as common as breast cancer, it is three times more lethal, and carries a 1:70 lifetime risk. It was estimated that in 2018, approximately 22,240 women would be diagnosed with ovarian cancer, and 14,070 would die from the disease in USA (1). The high mortality rate of ovarian cancer is due to the lack of a screening strategy to detect early-stage disease. Ovarian cancer presents with very few, if any, specific symptoms. Twenty percent of patients are diagnosed at stage I and II when the disease is still confined to the ovary. In patients diagnosed with advanced disease, the 5-year survival rate ranges from 20% to 25%, depending on the stage and grade of tumor differentiation (2). Of these patients, 80% to 90% will initially respond to chemotherapy, but less than 10-15% will remain in permanent remission (2).

Approximately 90% of ovarian cancers are carcinomas, and based on histopathology, immunohistochemistry, and molecular genetic

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analysis, at least five main types are currently distinguished: high-grade serous carcinoma (70%); endometrioid carcinoma (10%); clear-cell carcinoma (10%); mucinous carcinoma (3%); and low-grade serous carcinoma (<5%) (3, 4). These tumor types which account for 98% of ovarian carcinomas can be reproducibly diagnosed by light microscopy, and are inherently different diseases (3, 4). Much less common are malignant germ cell tumors and potentially malignant sex cord-stromal tumors. Several studies have suggested that the ovarian cancer risk is associated with parity and oral contraceptive. Parity women have a lower risk of ovarian cancer development in comparison with nulliparity women. The risk goes down with each full-term pregnancy, and women who have their first full-term pregnancy after age 35 have a higher risk of ovarian cancer (5).

Also, it appears that breastfeeding protects against ovarian cancer. Correspondingly, it was shown that the risk of ovarian cancer development is reduced by 37% in women who have breastfed for a year or more (6) Women who have used oral or an injectable contraceptive have a lower risk of ovarian cancer, and the risk is lower the longer the contraceptives are used (7). Tubal ligation may reduce the chance of developing ovarian cancer by up to two-thirds, and hysterectomy also seems to reduce the risk of getting ovarian cancer by about one-third (5).

About 5 to 10% of ovarian cancers are a part of family cancer syndromes resulting from inherited mutations. Symptoms in early-stage disease are either absent or vague, and may resemble menopausal symptoms and intestinal illnesses. Individuals in later stages may report indigestion, gas, nausea, vomiting, loss of appetite, a feeling of fullness after small meals, pelvic or abdominal pain, swelling, increased frequency or urgency of urination, unexplained change in bowel habits, unexplained weight gain or loss, pain during intercourse, ongoing fatigue, lower back pain, shortness of breath, and, postmenopausal vaginal bleeding in rare cases,. These symptoms usually do not become apparent until the later stages of the disease when the cancer mass is large enough to interfere with pelvic organs such as the bladder or rectum, or after the cancer has metastasized to the abdominal cavity. Obtaining a personal obstetric and gynecologic history and a family history of gynecologic disease may be important in diagnosis (8). A number of case–control studies investigating symptoms in women with ovarian cancer and comparing them to symptoms in women without ovarian cancer demonstrated that patients with ovarian cancer are symptomatic for a variable period before diagnosis and challenge the perception of ovarian cancer as the "silent killer" (Network SIG, 2013) (9).

The polypeptide hormone prolactin (PRL) has numerous functions in addition to its important role in lactation, including a role in reproduction by maintaining normal ovarian function, modulating the effects of gonadotropins, and modulating immune function. Though PRL is primarily produced in the pituitary gland it is also produced in other tissues, including the ovaries. The PRL receptor is expressed in normal ovarian and fallopian tube tissues, the primary sites of origin for ovarian tumors. There are several ways that PRL could influence ovarian cancer development. Animal and *in vitro* studies have shown that PRL promotes the growth of ovarian surface epithelial cells, inhibits apoptosis, and increases ovarian cancer cells survival. Furthermore, PRL levels increase in response to psychosocial and physical stresses, which was associated with greater tumor burden and tumor invasiveness in a mouse model of ovarian cancer (10, 11).

In a cross-sectional study, nulliparity and endometriosis which are known risk factors for ovarian cancer were associated with higher PRL levels, which suggests that PRL may be part of the underlying mechanism through which these factors influence the disease (12). PRL receptor expression and circulating PRL levels have been shown to be

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higher among women with ovarian cancer versus benign-condition or healthy controls (10, 13). However, a major limitation of these retrospective studies is that PRL levels may have been affected by the presence of the tumor and/or the stress associated with cancer diagnosis or treatment. In this study, we aimed to evaluate the diagnostic performance of serum biomarker from patients presenting with ovarian cancer. We especially desired to investigate PRL levels for possible assistance in screening, diagnosis, and follow-up of ovarian cancer patients.

Materials and methods

Patients

A total of 90 Sudanese ladies age range (16-80) years attending gynecological oncology clinics in Omdurman Military hospitals, Khartoum state from May 2015 to December 2016 were included in the study. This was an analytical comparative cross-sectional study. The sample population was divided into two main groups; study group including 53 (58.9%) ovarian cancer patients with an age of 16 to 80 years, and control group including 37 (41.1%) age matched apparently healthy individuals. Patients diagnosed with other cancer types rather than ovarian cancer were excluded from the study. History and background data were collected from participants using verbal interviews and pre-designed questionnaire. Clinical presentation included an enlarged ovary on a pelvic exam, and ascites. Informed and written consents were obtained from all participants prior to involvement in the study. Ethical release to proceed in the study was obtained from the ethical committee of the Faculty of Medical Laboratory Sciences at Alneelain University.

Histological evaluation

Histopathological examinations were performed to assess the tumor type, ovarian cancer type, and staging of the disease. The metastatic status of the cancer was also evaluated.

Serum prolactin level evaluation

Five to 10 ml blood samples were collected from each participant. Sera were separated, and then stored at -20 ºC for subsequent testing. The concentration of PRL was evaluated quantitatively by AIA-600 II automated immunoassay system (Tosoh Bioscience).

The ST AIA-PACK PRL was a two – site immune enzymometric assay which was performed entirely in the ST AIA- PACK PRL test cups. PRL present in the tested sample was pound with the monoclonal antibodies immobilized on magnetic solid phase and enzyme- labeled monoclonal antibodies in test cups. The magnetic beads were washed to remove unbound enzyme. Labeled monoclonal antibodies were then incubated with a fluorogenic substrate, 4-methylelumbelliferyl phosphate (4MUP). The amount of enzyme- labeled monoclonal antibodies that were bound to the beads was directly proportional to the cancer antigen 125 (OVCA125), PRL, and 17-beta-estradiol (E2) concentration in the test sample.

The calibrator of the PRL was prepared gravimetrically and compared to internal reference standard and stability of the curve up to 90 days, which was monitored by quality control performance and was dependent on proper reagent handling and TOSHO AIA system maintenance according to manufacturer's instructions.

Statistical analysis

Raw data were entered into a spread sheet of SPSS statistical package program. Descriptive analysis was performed to all study variables.

Data was analyzed using SPSS version 21. The results were expressed as mean, standard deviation, median, frequency and percentage. Descriptive statistic was performed to obtain the frequencies and percentages of the study variables and clinical data. Independent–sample T-test was used to compare the mean concentration of PRL in ovarian cancer versus healthy individuals. Graphs were done using Microsoft excel and Graph Pad Prism version 6. P value ≤ 0.05 was considered as significant. All statistics tests were done in 95% confidence interval.

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Results

Clinical evaluation

Ninety Sudanese ladies were enrolled in this study. They were distributed into two groups: study group including 53 (58.8%) newly diagnosed ovarian cancer patients with age ranging from 16 to 80 years, and control group including 37 (31.2%) age matched apparently healthy individuals. Study group included 32% in the reproductive age (< 40 years).

The frequency and percentage of signs and symptoms are summarized in Table 1. Accordingly, abdominal pain was the most prevalent symptom with 85% prevalence, followed by abdominal bloating (79%), increased abdominal size (70%), frequent urination (68%), loss of appetite (62%), and irregular bowel movement (57%). About 51% of the study group were para and multi-parous compared with 49% nulliparous. 45% of the study group patients were suffering from ascites when clinical examination was done. The presence of ascites was confirmed by ultrasonography that also revealed the percentage of left, right, and bilateral ovarian mass as 19%, 34%, and 47%, respectively.

Histopathological results

About 97% of the ovarian cancers were epithelial cell origin and only 3 % were germ cell origin. Figure 1 shows the stage distribution among ovarian cancer patients with stage 4 being the most prevalent.

Serum prolactin analysis

Table 2 and figure 2 represent the serum PRL levels in case and control groups. Accordingly, no statistical difference was observed between the 2 groups. Similarly, no statistical difference was observed among different parity groups or different cancer stages (Tables 3 and 4).

The sensitivity of serum PRL assessment was 65%), the specificity was 64%) while positive and negative predictive values were 62% and 61%, respectively.

Table 1. Frequency and percentage of common symptoms among ovarian cancer patients

Variables	Frequency	Percentage (%)
Abdominal bloating	42	79%
Loss of appetite	33	62%
Frequent urination	36	68%
Irregular bowel movement	30	57%
Increased abdominal size	37	70%
Abdominal pain	45	85%
History of ovarian cancer	0	0%
Use of contraceptive pills	7	13%
Use of estrogen	2	4 %
Caesarean section	4	8 %
Ascites	24	45%

Table 2. Prolactin serum levels among study and control groups

Parameter	Case (Mean±SD)	Median	Control (Mean±SD)	Median	P-value
Prolactin (ng/ml)	20.40±2.28	12.50	20.21±3.65	10.35	0.966

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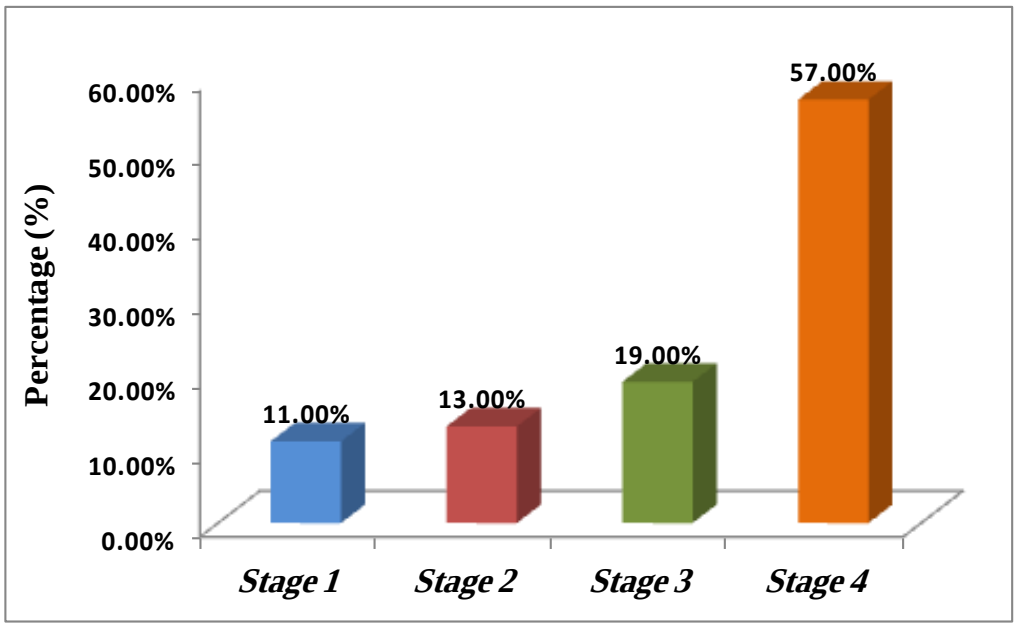

Figure 1. Staging of ovarian cancer among study group.

Table 3. Prolactin serum levels among parity subgroups

Parameter	Para/ multi parity (Mean±SD)	Nulliparous (Mean±SD)	P-value
Prolactin (ng/ml)	22.45±3.58	18.26±2.79	0.141

Table 4. Prolactin serum levels among different ovarian cancer staging groups

Parameter	Stage 1 (Mean±SD)	Stage 2 (Mean±SD)	Stage 3 (Mean±SD)	Stage 4 (Mean±SD)	P-value
Prolactin (ng/ml)	23.23±5.51	28.17±19.73	14.72±10.60	19.91±17.88	0.416

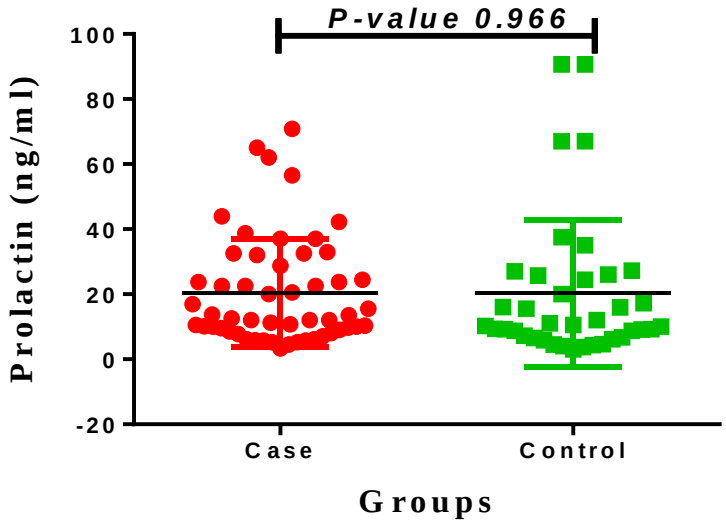

Figure 2. Variation of prolactin levels among ovarian cancer patients and healthy subjects.

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Discussion

Amongst all gynecological cancers, ovarian cancer is the most lethal malignancy worldwide. Aggressive local invasion and the lack of sensitive early screening methods, are the most important barriers to early diagnosis. Furthermore, its high mortality rate has made it one of the most investigated fields in gynecological oncology. During 2016 ovarian cancer ranked fifth in cancer deaths among women in USA (14). A woman's risk of getting ovarian cancer during her lifetime is about 1.5%, and there is 1% lifetime chance of dying from ovarian cancer (1).

Even though ovarian cancer mainly develops in older women, younger age range was reported by Adam et al. (15). Among Sudanese ovarian cancer patients who agreed to participate to the present study 32% were within reproductive age.

Around 57% of all ovarian cancers included in this study were diagnosed at an advanced stage, and only 11% were in early stage. The five-year survival rate for patients with clinically advanced ovarian cancer was reported to be only -15-20%, in striking contrast to a five-year survival rate of over 90% for patients with stage 1 disease (16, 17).

In the present study, we found the common symptoms among ovarian cancer patients which were abdominal bloating, pelvic pain, abdominal pain, increased abdominal size, and vaginal discharge, while vaginal bleeding was observed at a low frequency. These findings are similar to cancer facts published in 2017 by American cancer society. Ultrasonography as a non-invasive diagnostic test in women with pelvic, bilateral, and ascites is helpful in predicting the malignant likelihood of the mass (18). Ovarian tumors were unilateral in 53% of cases and bilateral in 47% with right side predominance. This also corroborates with the findings of Kancherla et al. (19).

Histopathological distribution in our study group is similar to many published works (20, 21) (US Preventive Services Task Force, 2014; American college of Obstetricians and Gynecologists, 2007). Ovarian epithelial cell was the most common form which was present in different age ranges. Germ cell neoplasm was less frequent, and was observed among younger age patients., Relatively, Kancherla et al. reported that surface epithelial tumors were most common (80%) followed by germ cell tumors (16%) (18).

Grosdemouge et al. found a significant difference in PRL level between ovarian cancer and normal individuals (22). Levina et al. found that there was elevated levels of serum PRL in ovarian cancer (13). Several studies reported that higher levels of circulating PRL among women with ovarian cancer vs. benign condition or healthy controls suggest that PRL may be associated with increased risk of ovarian cancer (10, 13) while Clendenen et al. found a non-significant association between circulating PRL levels and ovarian cancer (10) which is similar to the results obtained in the present study. The reason for this discrepancy is not clear from the data presented, but it may be due to the presence of several PRL receptor isoforms that have been identified in the ovaries and the fact that varied expression and dimerization of these receptors may influence the effects of the PRL ligand on ovarian cancer risk. Studies have shown that there are also several variant forms of PRL. Our immunoassay was not able to distinguish between different isoforms or structural variants of PRL which may have different bio-availabilities and biological actions (10).

Further studies are needed to elucidate the mechanisms of action of PRL in ovarian cancer induction.

Conflict of interest

The authors declared no conflict of interest.

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