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EVALUATION OF SERUM PROLACTIN LEVELS IN NEWLY DIAGNOSED EPITHELIAL OVARIAN CANCER

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ABSTRACT

Introduction: Ovarian cancer (OC) ranks eighth in cancer deaths among women, representing more deaths than any other cancer of the female reproductive system. The high mortality rate is due to the difficulty of diagnosis and delayed detection of the disease until late stages, making the search for an effective strategy for early detection an urgent necessity. Many recent studies have shown that prolactin (PRL) has a greater role than previously thought in the pathological mechanisms of ovarian cancer development. Therefore, high PRL levels has been highlighted as a potential risk factor for the incidence of OC. Due to the low sensitivity of CA-125 at early stages of OC, several panels have been proposed to improve diagnostic sensitivity and specificity, and PRL was one of the most prominent of these chemical tests. This study aimed to evaluate serum PRL levels in patients newly diagnosed with OC and in first-degree female relatives, and to study the relationship between PRL and the tumor stage and histological type. **Materials and Methods:** This is a case-control study of 47 female patients attending the Department of Gynecology and Oncology at Tishreen University Hospital in Lattakia in the period between 2022-2024, in addition to 22 first-degree female relatives and 30 healthy controls. PRL was measured by enzymometric immunoassay and patient demographic data were recorded. **Results:** The average age of patients was 56 years and more than half were nulliparous. The mean PRL value for patients was 32.18 ng/ml, while for controls it was 11.88 ng/ml ($p < 0.001$), while it was 17.6 ng/ml, ($p= 0.007$) in female relatives group. PRL values were high in 64% of patients, indicating a lower sensitivity than CA-125, but it showed good sensitivity in early stage patients compared to CA-125. All patients had epithelial ovarian cancer, and there was no association between PRL levels and the histological type. The majority of patients were diagnosed at stages III and IV, and there was no correlation between PRL levels and tumor stage. **Conclusion:** Serum PRL levels are higher in OC patients and in female relatives. This confirms the association between PRL and development of OC and indicates that this increase is a predisposing factor for tumor growth and not due to the tumor itself, which suggests measuring PRL levels in high-risk patients.

KEYWORDS: Ovarian cancer (OC)- prolactin (PRL)– CA-125- epithelial ovarian cancer.

INTRODUCTION

With approximately 314,000 new cases diagnosed in 2020, ovarian cancer ranks eighth in terms of prevalence in women, accounting for 3.4% of all tumors in women. It also ranks eighth in terms of women's deaths, according to 2020 data, with 207,000 deaths, (approximately 4.7%) of all cancer-related deaths.[1] Ovarian cancer is characterized as a cancer of advanced ages, as it rarely occurs at an age younger than 40 years. Approximately 90 % of patients are diagnosed after menopause, and the average age at diagnosis is 63 in most developed countries[2], Persistent ovulation has been suggested as one of the underlying causes of epithelial ovarian cancer. Ovarian epithelial cells proliferate after ovulation, which may induce mutations and lead to carcinogenesis. The process of ovulation is itself implicated in the neoplastic transformation of the epithelium. It was found that suppressing ovulation in age group of 20–29 years reduces the risk of ovarian cancer.[3] Nulliparity is also a proven risk factor for the occurrence of ovarian cancer, as the risk of incidence in women who have given birth decreases by 30-60%.[4]

There are two familial neoplastic syndromes, of which ovarian cancer is a part: familial breast and ovarian cancer syndrome and Lynch syndrome (nonpolyposis colon and rectal cancer), which constitute 10% of the causes of epithelial ovarian cancer and often cause cancer to occur at earlier ages.[5,6] Many studies have reported a 3-4 times higher rate of ovarian cancer in first-degree relatives diagnosed with OC.[7] Previous studies have shown that the relative risk of ovarian cancer in

sisters of patients who were diagnosed before the age of 55 was 5.2 compared to 3.6 for those diagnosed after the age of 55 (this is an indication that in patients with a family history, the tumor occurs earlier.[8] Ovarian cancer has three main types: epithelial (most common), germ cell, and sex-cord-stromal. There are four primary histological subtypes of epithelial ovarian cancer; serous carcinoma, endometrioid carcinoma, mucinous carcinoma, and clear cell carcinoma.[9] New classification divided it into two classes; Type I tumors which behave in an indolent behavior include low-grade serous carcinomas (LGSCs), mucinous carcinomas, endometrioid carcinomas, clear cell carcinomas, and transitional cell carcinomas, while type II tumors comprise high-grade serous carcinomas (HGSC), undifferentiated, and mixed carcinomas, and are suggested to be more aggressive, are found at advanced stages, and are genetically highly unstable; the majority have TP53 mutations.[10]

Ovarian cancer is clinically classified according to the FIGO into four basic stages. At stage I, the tumor is limited to one of the ovaries and fallopian tubes or both, while at stage II the tumor extends to the pelvis, and at stage III, confirmed spread to the peritoneum outside the pelvis and/or metastases to the retroperitoneal lymph nodes, while at stage IV, metastases outside the peritoneum occur.[11] Overall survival rates are 65%, 44%, and 36% at 2, 5, and 10 years, respectively. Five-year survival rates were for stage I 89%, stage II 70%, stage III 36% and stage IV 17%.[12] Trans-vaginal ultrasound is used to diagnose ovarian cancer, as it allows direct visualization of the uterus and appendages and detection of morphological changes. However, one of its limitations is that it is difficult to apply in some cases, and some aggressive tumors develop metastases before they become detectable by ultrasound.[13] The tumor antigen CA125, also known as mucin 16, is a large membrane glycoprotein that belongs to the mucin family. It is widely used in the treatment follow-up of patients with ovarian cancer and monitoring of recurrence. It is also found in the epithelium of many tissues in the body and on the surface of ovarian cancer cells.[14] However, its effectiveness in screening is limited because it is not specific and increases in other cases, where an elevated concentration of serum CA125 was found in approximately 1% of healthy population and in patients with other cancers and in endometriosis and many other diseases.[15] it also lacks sensitivity for early detection (its sensitivity in the early stages is low, reaching approximately 50% at stage I).[16]

The diagnosis of ovarian cancer is often delayed until late stages because of nonspecific symptoms, in addition to the limitations of current diagnostic methods. Therefore, the measurement of multiple serum protein markers has been proposed in order to improve the sensitivity of early tumor detection. One marker that has been suggested to be used for screening and diagnosing ovarian cancer is prolactin, a hormone that is mainly secreted by lactotroph cells of the anterior pituitary gland. This secretion is mainly under inhibitory control by hypothalamic dopamine and is regulated in a negative feedback manner. The major isoform is a 23-kDa single-chain protein with 199 amino acids.[17]

Recently, prolactin has also been secreted from many extrapituitary sites, such as reproductive organs and immune cells. In addition to its role in promoting milk synthesis and maintaining postpartum lactation, prolactin also has numerous functions. It acts as a cytokine and plays an important role in immune response. Prolactin mainly affects the reproductive system by inhibiting gonadotropin-releasing hormone (GnRH) secretion, leading to hypogonadotropic hypogonadism. Other biological effects of prolactin include increased beta cell mass during pregnancy and increased water and electrolyte retention.[18] Numerous studies have revealed a close relationship between prolactin and ovarian cancer. Elevated prolactin levels were associated with nulliparity and endometriosis, which are risk factors for ovarian cancer, suggesting that prolactin may be part of the underlying mechanism through which these factors influence risk.[19] Overexpression of prolactin receptors was also found in most ovarian cancer cell lines and was associated with lower overall survival.[20] Prolactin has an important role in supporting tumor proliferation and growth, as ovarian tumor cells of the OVCAR3 lineage show activation of ERK1/2, MEK1, STAT3, and CREB 30 min after stimulation by prolactin.[21] The role of prolactin in inhibiting apoptosis has also been proven, as in a study by *M. Asai-Sato et al.*, the rate of cell death decreased in ovarian cancer cells incubated with cisplatine when treated with prolactin. It was assumed that this was due to prolactin's activation of PI3K/Akt and because prolactin enhances the expression of anti-apoptotic genes, such as Bcl-2, which have been observed in various types of cancers.[22] Moreover, it enhances the migration of tumor cells in ovarian cancer lineages and thus induces metastases.[23] Many previous studies have measured prolactin levels in ovarian cancer, but there is disagreement regarding study population, calibration methods, and conditions. In this research, the goal was to measure prolactin levels immediately after diagnosis and before any treatment intervention, with the calibration conditions standardized between patients as much as possible.

MATERIALS AND METHODS

This is a case-control, study that was conducted in the Gynecology Department and the Oncology Department at Tishreen University Hospital in Lattakia in the period extending between September 2022 and March 2024. The research included 47 patients who met the criteria for inclusion in the study (Primary ovarian cancer prior to any surgical procedure, radiological or chemical treatment). Fasting blood samples were drawn during the morning, and the serum was kept frozen at - 20ºC until the diagnosis was confirmed by tissue biopsy. Venous blood samples were also drawn from the patients' first-

degree relatives (sisters and daughters) and from 30 healthy control women. Any cases diagnosed with hyperprolactinemia (prolactinomas, medications that increase or decrease serum prolactin concentrations), patients diagnosed with other tumors or chronic renal failure, patients on hemodialysis, and hypothyroidism patients were excluded. Demographic data were collected about patients' age, medical history, personal characteristics, body mass index recordings, clinical symptoms and initial CA-125 values before treatment. Informed consent was obtained from all participants in accordance with recognized ethical guidelines of the Declaration of Helsinki (NSHDS).

Serum prolactin measurement

The concentration of PRL was measured quantitatively by **AIA-900II** automated immunoassay system (**Tosoh Bioscience**). The ST AIA-PACK-PRL was a two–site immunoenzymometric assay which was performed entirely within ST AIA- PACK PRL test cups. PRL present in samples was bound with the monoclonal antibodies immobilized on magnetic solid phase and enzyme- labeled monoclonal antibodies in test cups. The magnetic beads were then 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 PRL concentration in the test sample. Calibration curve was monitored by quality control performance according to manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 26. Descriptive statistics included Means, Standard Deviations (SD), Frequency and Percentages. Inferential Statistical based on: Independent T student test for the difference between means of two independent groups, One Way ANOVA test to study the differences in means between more than two groups, Pearson Correlation Coefficient to study the correlation between quantitative variables, also eta correlation ratio was used to study the correlation between nominal and interval variables. P-value < 0.05 was considered statistically significant.

RESULTS

The patients' ages ranged between 37-73 years. The average age of the ovarian cancer group was 56.1 ± 9.64 years, and 81% of them were postmenopausal. While the median was 50 years in control group. Abdominal pain, abdominal bloating increased abdominal size , frequent urination and loss of appetite were most frequent symptoms.

Histopathological types and staging

All patients had Epithelial Ovarian Cancer. Serous ovarian carcinoma (54%) was the most common among histological subtypes followed by Mucinious carcinoma (16%), Endometrioid carcinoma (12%) and clear cell carcinoma (12%) while undifferentiated types were seen in (6%) of patients. Most patients (66%) were diagnosed at stage III and IV according to FIGO classification. Figure 1 shows distribution of patients by stage of tumor.

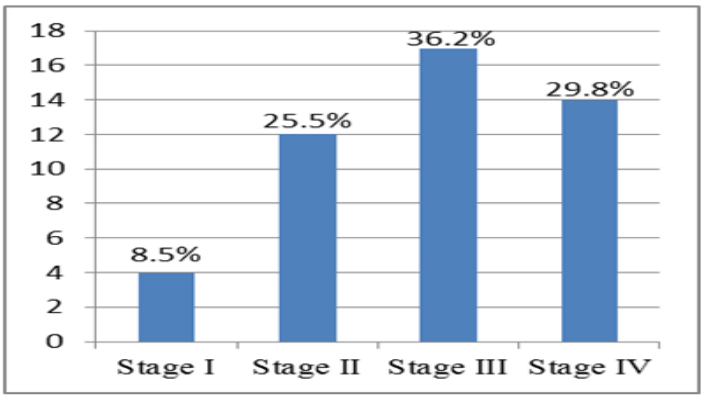

Figure 1: distribution of patients by tumor stage.

Serum Prolactin analysis results

Serum Prolactin Levels were significantly higher in ovarian cancer patients group (mean 32.18 ng\mL) compared with control group (11.88 ng\mL) P value <0.0001. Table 1 shows the difference in prolactin levels between controls and ovarian cancer groups.

Table 1: comparison of prolactin levels between patients and controls.

Group	Mean ng\mL	SD	Mean Differences
Ovarian cancer (n=47)	32.18	14.1	20.3
Controls (n=30)	11.88	6.2	
	P value < 0.0001		

Similarly, prolactin levels were higher in first-degree female relatives of patients (Mean 17.6 ng\mL) compared to controls, P value = 0.007 and this is demonstrated in table 2.

Table 2: comparison of prolactin levels between patient relatives and controls.

Group	Mean ng\mL	SD	Mean Differences
Relatives (n=22)	17.6	6.9	5.8
Controls (n=30)	11.88	6.2	
	P value = 0.007		

As for the means of prolactin according to histological type, by applying the One Way ANOVA test, there was no statistically significant difference between the groups. Table (3) demonstrates Prolactin means of the histological types.

Table 3: prolactin levels according to histological subtype.

Histological subtype	Median ng\mL	Std. Deviation	P value
Serous	34.15	14.76	
Mucinious	30.67	13.3	
Endometrioid	33.25	10.78	
Clear cell	31	18.47	
			0.926

Prolactin levels according to tumor stage

One way ANOVA test was used to evaluate differences in prolactin according to tumor stage and there was no relation between prolactin levels and severity of disease P value 0.56.

Table 4: prolactin levels in tumor stages.

Cancer stage	Mean ng\mL	SD
Stage I	34.9	7.5
Stage II	34.19	14.19
Stage III	28.2	13.35
Stage IV	32.18	16.72
	P value =0.56	

Prolactin levels according to BMI

Patients were distributed into 4 groups. No significant difference was observed in prolactin mean between BMI groups.

Table 5: prolactin levels between BMI groups.

	BMI kg\m²			
	20-25	25-30	30-35	35-40
PRL Mean ng\mL	35.8	27.73	33.11	35.35
SD	12.25	14.16	15	7.36

Correlation between CA-125 levels and tumor stage

In contrast to prolactin, CA-125 has a medium correlation with stage (eta correlation 0.532) where its levels increased in advanced stages. Figure (2) shows the relation between CA-125 and cancer stage.

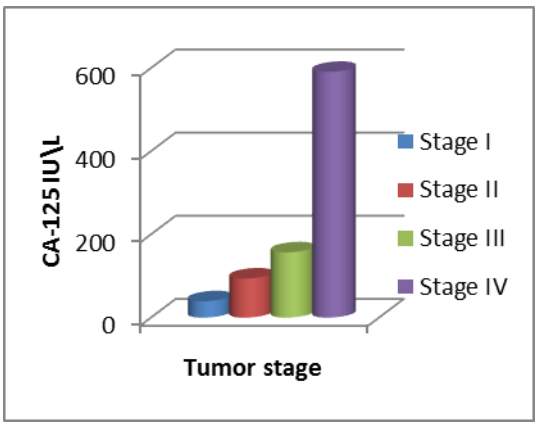

Figure 2 distribution of CA-125 according to tumor stage.

Correlation between prolactin and CA-125 levels

There was no correlation between prolactin levels and CA-125 levels where Pearson correlation = 0.1.

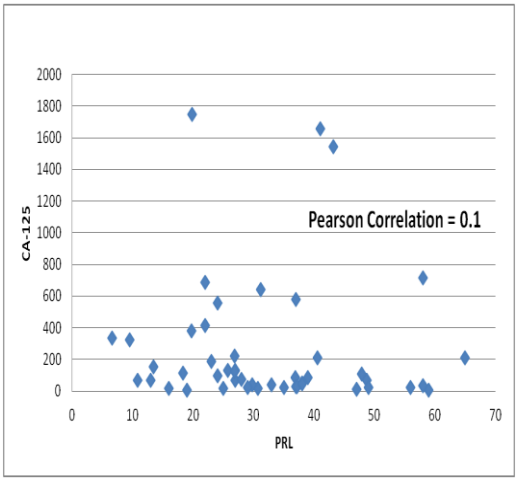

Figure 3 Correlation between prolactin and CA-125.

Diagnostic sensitivity of prolactin in ovarian cancer

The serum prolactin value was high (more than 26 ng/ml) in 30 out of 47 patients, which constitutes 64% of the patient group. While CA-125 values were higher than 33 IU\L in 35 patients, which constitutes 74.4% of patient group. However, at early stages (I and II), prolactin values were higher than normal in 11 out of 16 patients (68.7%).

While the sensitivity of CA-125 in these two groups decreased to 50%, as its value was higher than 33 IU\L in 8 of the patients. Due to the poor correlation between prolactin and CA-125, the combination of a prolactin level above 26 ng/ml and\or a CA-125 above 33 IU/L achieved a sensitivity of 87.5% in these two stages.

DISCUSSION

Ovarian cancer has a high mortality rate due to delayed diagnosis. Much attention has been focused on the possibility of using multiple biomarkers for early screening and diagnosis because of the lack of sensitivity of CA-125 at early stages. Prolactin is one of the proposed protein markers due to several mechanisms linking it to the development and incidence of female reproductive tumors.

60 percent of patients were childless, which supports the fact that nulliparity is a risk factor for ovarian cancer due to continuous ovulatory cycles. Many mechanisms were suggested, as women who have never been pregnant have a higher overall level of exposure to unopposed estrogen, and thus have an increased rate of mitogenic activity in epithelial cells.[24] and This could be due to to the pro-inflammatory response of the distal fallopian tubes during ovulation, which promotes malignant ovarian tendencies.[25]

The mean prolactin concentration in the ovarian cancer patients group was **32.18 ng/ml**, which was clearly higher than the median in the control group that was **11.88 ng/ml**. **P value < 0.0001.** This is consistent with the study done by V. V. Levina *et al*[21], which was conducted on 273 ovarian cancer patients in which the mean value among ovarian cancer patients, **117 ng/ml** and in controls, **12.5 ng/ml** , **P value < 0.0001**, this study also examined serum prolactin levels in a group of patients with other tumors, such as breast and lung cancer. Prolactin levels were significantly higher in ovarian and endometrial cancer groups, and this constitutes additional evidence of the role of prolactin as a carcinogenic factor in sexual cancers and these high serum values are not due to stress accompanying the presence of tumors. Similar results were also found in a study by G. Mor *et al.*[26] which was conducted on 100 patients, in which the median in the group of patients was found to be 40 ng/ml.

The discrepancy between the values may be due to the difference in the measurement method, as G. Mor *et al* used ELISA and in the current study an automated enzymometric immunoassay was used, in addition to the difference in the size of study population.

The prolactin mean in the group of first-degree relatives was 17.6 ng/mL which is higher than levels in control group, and this is consistent with V. V. Levina *et al* study in which it was 16.4 ng/mL which is significantly higher than its levels in control group and with G. Mor *et al*. As it is known that family history is a proven risk factor for ovarian cancer.

Prolactin levels are higher in patients compared to controls, in addition to the absence of correlation of prolactin levels with the stage of tumor, which provides evidence that this increase is not due to the stress accompanying the tumor. The increase in these levels in first-degree relatives also indicates that high prolactin is not a result of the carcinogenesis, but rather may be

related to the mechanism of tumor formation and predisposition to carcinogenesis.

This is consistent with what has been found in many studies that prolactin has stimulating effect on tumor growth by inducing migration, invasion, resistance to treatment, and inhibition of apoptosis, all through the activation of signal transmission pathways and specific proteins.[20,27]

The reason for elevated serum prolactin levels may be due to the autocrine growth loop of prolactin in ovarian cancer, as Tan et al found that both prolactin and multiple types of its receptors were expressed in ovarian cancer cells, and the viability of tumor cells was reduced when incubated with prolactin inhibitors or with prolactin receptor antagonists. [23]

The study contradicted in its results with R. A. Gurashi et al study in Sudan 2019[28], which was conducted on 53 patients and 37 controls. Where the mean of prolactin in patients was 20.40±2.28 ng/ml and in controls 20.21±3.65 with a P value of 0.966. What is noteworthy is the high levels of prolactin in controls group In contradiction with both the current study and V. V. Levina *et al*. This discrepancy may be due to racial differences between study populations.

There was no difference between prolactin values among the histological subtypes of cancer, and they were also similar according to the High Grade and Low Grade classification, as high prolactin was a predictor of tumor growth regardless of the type, and this is close to what was found by A. Hasenburg *et al.*[29] where Prolactin levels were elevated in both benign and malignant ovarian tumors and it has therefore been suggested that it is useful as an indicator of the presence of an ovarian tumor regardless of its type.

There was no statistically significant difference between prolactin levels in the different BMI categories in the control and patient groups, in contrast to a study by J. Liu *et al* in which the median prolactin concentration in the obese group was 17.75 compared to 13.57. This may be due to the fact that the average ages are higher in the current study.[30]

The overall sensitivity of prolactin in diagnosing ovarian cancer was lower than the sensitivity of CA-125, and therefore it cannot be used alone as a diagnostic indicator, as prolactin values were within the normal range in 36% of patients. The reason for this may be due to the fact that there are other mechanisms of carcinogenesis in which prolactin does not interfere and signaling pathways that lead to tumor growth can be activated by other compounds.

However, unlike CA-125 whose levels were correlated with tumor stage and its sensitivity was low at early stages, there was no correlation between prolactin levels and the tumor stage, and its sensitivity was intermediate in stages I and II. Due to the small number of samples in these two stages, it was not possible to find a model to determine its optimal value, to help distinguish the presence of an ovarian tumor.

CONCLUSION

This study provided additional evidence of the involvement of prolactin in the process of tumor growth in ovarian cancer through the rise in prolactin levels in both female patients and first-degree relatives. The absence of a correlation between prolactin levels and tumor stage supports that this increase is due to the pathological mechanism of carcinogenesis and not a result of the stress accompanying the tumor, which it emphasizes the importance of studying high prolactin as a risk factor for the occurrence of ovarian cancer in high-risk patients. Accordingly, there is a need for more attention in research targeting anti-prolactin treatment in ovarian cancer, and more research on larger samples is required in order to incorporate the serum prolactin assay into screening strategies for early detection of ovarian cancer especially at early stages.

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