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ORIGINAL ARTICLE

Evaluation of LH, FSH, Oestradiol, Prolactin and Tumour Markers CEA and CA-125 in Sera of Iraqi Patients With Endometrial Cancer

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Abstract

Background/Aim: Endometrial cancer is one of the most prevalent gynaecologic cancers in advanced nations and act as the largest proportion of tumours occurring in the uterine corpus. The aim of the study was to identify potential diagnostic biomarkers for endometrial cancer among the evaluated hormones and tumour markers to enhance early detection and improve patient outcomes.

Methods: A comparison was made between two groups of women: 30 individuals who were healthy and 30 individuals who had endometrial cancer. The participants in both groups were carefully selected to ensure that they were similar in terms of age and body mass index (BMI). Luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol (E2), cancer antigen 125 (CA-125) and carcinoembryonic antigen (CEA) were analysed.

Results: As compared to healthy individuals, females diagnosed with endometrial tumour and cancer exhibited notably elevated levels of LH, FSH, E2, CA-125 and CEA. Conversely, they demonstrated significantly reduced levels of prolactin in their serum.

Conclusions: Endometrial cancer patients had significantly raised concentrations of LH, E2, FSH, PRL, CEA and CA-125 in their serum, indicating hormonal dysregulation in the development of endometrial cancer. It is not advisable to rely solely on LH, E2, FSH, PRL, CA-125 or CEA as screening markers for endometrial cancer. Instead, they should be considered as part of a comprehensive screening panel that needs to be developed in the future.

Key words: Endometrial cancer; CA-125; CEA; FSH; LH; Oestradiol; Prolactin.

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Introduction

Endometrial cancer is one of the most prevalent gynaecologic cancer in advanced nations and act as the largest proportion of tumours occurring in the uterine corpus.[1] While there have been notable improvements in detecting and treating gynaecological cancers, it appears that the morbidity ratio related to endometrial cancer is on the rise along with the gradual increase in the number of new cases reported each year.[2] Endometrial cancer commonly presents as abnormal vaginal bleeding, including postmenopausal bleeding, bleeding between periods and the pres-

ence of watery or bloody vaginal discharge. Additional symptoms may include pelvic pain, pain during urination or difficulty urinating and unexplained weight loss.[3] The lack of effective and dependable screening analysis for asymptomatic women at moderate risk of endometrial cancer has highlighted the importance of screening programs and clinical approaches for prognostic assessment.[4] Research efforts have been dedicated to the creation of a biochemical panel that can detect early-stage endometrial cancer and identify individuals with a less favourable outlook.[5]

Endometrial cancer is frequently observed in women who have reached menopause and this condition is often linked to higher levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH) in their bloodstream.[6] The release of LH and FSH is regulated in part by gonadotropin-releasing hormone (GnRH) generated by the hypothalamus. Importantly, it is worth mentioning that recurrent endometrial cancer can be managed using GnRH analogues as a potential treatment approach.[7] Oestradiol (E2), a type of oestrogen hormone, plays a pivotal turn in the expansion and maintenance of the reproductive system in female. However, elevated levels of E2, particularly when not balanced by other hormones, can potentially raise the harm of endometrial cancer.[8]

E2 promotes the growth and proliferation of the endometrial tissue. In a normal menstrual cycle, the endometrium grows and thickens under the influence of oestrogen and then sheds during menstruation. However, if the balance between E2 and progesterone is disrupted, such as in cases of excess E2 or insufficient progesterone, the endometrium may grow too much and become abnormal. This unopposed E2 stimulation may drive to the development of endometrial hyperplasia, a precancerous condition that may progress to endometrial cancer.[9]

Prolactin (PRL) is a polypeptide hormone generated by the pituitary gland in the brain. Its primary role is to stimulate milk production in the breasts after childbirth. PRL have a pivotal turn in the expansion of hormonally sensitive malignancies, including breast tumours as well as cancers affecting the pancreas, lungs, ovaries and endometrium.[10]

Yamaguchi et al proposed that PRL could potentially promote the growth of endometrial tissue, thereby raising the likelihood of developing cancer. Conditions characterised by prolonged exposure to high oestrogen levels, such as polycystic ovary syndrome (PCOS) or oestrogen-producing tumours, might also stimulate the production of PRL. Consequently, this increased PRL production could potentially participate to the onset of endometrial cancer.[11] Yurkovetsky and colleagues conducted a study that revealed increased levels of PRL in endometrial carcinoma. They suggested that PRL may work as a worthy diagnostic marker for the earlier detection of cancer in this context.[12]

Cancer antigen 125 (CA-125) is commonly utilised as a tumour marker in gynaecological conditions, including endometrial cancer, which targets the uterine lining (endometrium). Moreover, it's substantial to know that CA-125 is not exclusively specific to endometrial cancer but is also connected with different factors like ovarian cancer, fallopian tube cancer and certain non-cancerous gynaecological conditions.[13] Elevated levels of CA-125 in the bloodstream have been linked to the advancement of endometrial cancer. Consequently, CA-125 may work as a reliable marker to assess the presence of cancer beyond the uterus, providing an independent indication of disease progression.[5, 14]

Kanat-Pektas and colleagues suggested that both CA-125 and PRL lack specificity when used as individual markers for endometrial cancer.[15] Due to the natural fluctuations in PRL levels, its measurement alone has limited effectiveness in the earlier-stage diagnosis of endometrial cancer. Consequently, relying solely on either PRL or CA-125 as a single marker for endometrial cancer screening poses challenges. The study further indicated that incorporating both markers in a biochemical screening panel should be considered in future approaches.[15]

Carcinoembryonic antigen (CEA) glycoprotein have a molecular mass of 200-kDa.[16] CEA was identified by the antigen which was shown in both fatal colon and colon adeno-carcinoma, but which was shown to disappear in the normal adult colon.[17] Serum CEA is a commonly utilised tumour marker that has been found to be increased in numerous types of cancer, including colon and rectal, bladder, breast, liver, stomach, lung, pancreatic, thyroid, prostate and ovarian cancers.[18, 19] In spite of CEA expression were inspected in endometrial cancer, discussion is still open about its relationship with malignancy.[20, 21] The aim of the study was to identify potential

diagnostic biomarkers for endometrial cancer among the evaluated hormones and tumour markers to enhance early detection and improve patient outcomes.

Methods

Study population

This was prospective case-control study performed from November to December 2023. The population study was divides into two groups: patients and controls. The patient group contained 30 patients with endometrial cancer, aged 35-55 years. The individuals diagnosed with endometrial cancer were evaluated by a specialist at the Oncology Teaching Hospital, Medical City, Baghdad, Iraq. The control group comprised 30 healthy individuals, carefully matched in terms of age and gender to the patient group. Participants did not have a history of smoking, alcohol consumption or pregnancy. Additionally, individuals with another medical factors like diabetes, hypertension, hyperthyroidism and psoriasis were not included in the study, focusing solely on patients with endometrial cancer.

Specimen collection

Each participant in the study, including both patients and controls, had 10 mL of blood drawn from a vein using disposable plastic syringes. The blood was collected in special tubes containing a gel. After collection, the gel tubes were putted in a centrifuge and spun at a speed of 3000 rpm for 10 minutes. This operation separated the serum from the other components of the blood. The obtained serum was then stored at a temperature of -20 °C until it could be analysed. Serum concentrations of LH, E2, FSH and PRL were assessed utilising the protocol outlined in Wondfo Finecare Laboratory kits provided by *Wondfo company*, Huangpu, Guangzhou, China. CA-125 and CEA were determined using VIDAS kits and instruments which are based on (ELFA) technology, supplied by *Biomérieux*, France.

Statistical analysis

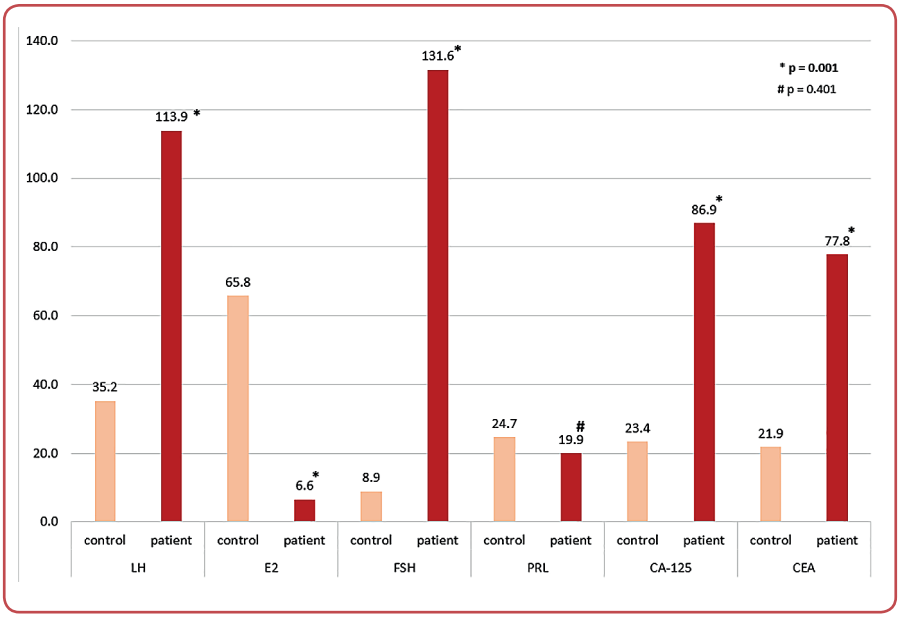
The analysis utilised version 25.0 of the IBM SPSS Statistics software. Descriptive statistics were employed for data analysis and the results are shown by means ± standard deviation (SD). To evaluate mean differences between the patient and healthy groups, t-test was applied to have a compare between the groups. Statistical significance was considered at $p < 0.05$ with a 95 % confidence interval (CI) and highly significant at $p \leq 0.01$ with a 99 % CI.

Results

The patient group exhibited significant differences in LH, E2, FSH, CA-125 and CEA compared to the control group ($p < 0.05$) (Figure 1).
ROC curve illustrates the results of a binary classification model at different threshold settings (Figure 2, Table 1). The area under the curve (AUC) was perfect (1.000) for LH, FSH, CA-125 and CEA, indicating excellent discrimination between the control and patient groups, which indicates that these markers are highly effective. The AUC was 0.000 for E2, which is unusual and might indicate an issue with the test or data. It suggests that E2 might be poor discrimination and not be a strong predictor for distinguishing between the control and patient groups. The AUC was 0.340 for PRL, suggesting fair discrimination between the control and patient groups. However, the $p = 0.033$, indicate that the AUC was significantly different from 0.5, but the performance is not as strong as the variables with an AUC of 1.000.

Pearson correlation matrix indicated strong positive linear relationships among LH, FSH, PRL, CA-125 and CEA for the patient group (Table 2). E2, on the other hand, did not show strong correlations with other variables in this context. The highly significant p-values suggest that these correlations were not likely due to random chance. LH was perfectly positively correlated with FSH ($r = 0.990$), PRL ($r = 0.997$), CA-125 ($r = 0.996$) and CEA ($r = 0.997$) ($p < 0.01$). FSH was highly positively correlated with PRL ($r = 0.997$) and CA-125 ($r = 0.997$), both at the 0.01 significance level. FSH had a strong positive correlation with CEA ($r = 0.987$), also highly significant. Also, PRL was positively correlated with CA-125 ($r = 0.999$) and CEA ($r = 0.996$) ($p < 0.01$). CA-125 was positively correlated with CEA ($r = 0.996$) ($p < 0.01$) (Figure 3).

E2 had a weak negative correlation with LH ($r = -0.031$) and the correlation was not significant ($p > 0.01$). E2 had weak negative correlations with FSH ($r = -0.117$), PRL ($r = -0.073$), CA-125 ($r = -0.066$) and CEA ($r = -0.033$), but none of these were significant at the 0.01 level.



LH: luteinising hormone; E2: oestradiol; FSH: follicle-stimulating hormone; PRL: prolactin; CA-125: cancer antigen 125; CEA: carcinoembryonic antigen; patient: 30 patients with endometrial cancer; control: 30 healthy females.

Figure 1: The means of the parameters used in this study

Table 1: Area under the curve for parameters in this study

Test Variable	Area	SE	p-value	95 % CI
LH	1.000	0.000	0.000	1.000 – 1.000
E2	0.000	0.000	0.000	0.000 – 0.000
FSH	1.000	0.000	0.000	1.000 – 1.000
PRL	0.340	0.071	0.033	0.201 – 0.479
CA-125	1.000	0.000	0.000	1.000 – 1.000
CEA	1.000	0.000	0.000	1.000 – 1.000

LH: luteinising hormone; E2: oestradiol; FSH: follicle-stimulating hormone; PRL: prolactin; CA-125: cancer antigen 125; CEA: carcinoembryonic antigen; SE: standard error; CI: confidence interval;

Table 2: Pearson correlation for the patient group

Variable	LH	E2	FSH	PRL	CA-125	CEA
LH	1.000	0.031	0.990 **	0.997 **	0.996 **	0.997 **
E2	0.031	1.000	0.117	0.073	0.066	0.033
FSH	0.990**	0.117	1.000	0.997 **	0.997 **	0.987 **
PRL	0.997**	0.073	0.997 **	1.000	0.999 **	0.996 **
CA-125	0.996**	0.066	0.997 **	0.999 **	1.000	0.996 **
CEA	0.997**	0.033	0.987 **	0.996 **	0.996 **	1.000

*** Correlation was highly significant at the 0.01 level; LH: luteinising hormone; E2: oestradiol; FSH: follicle-stimulating hormone; PRL: prolactin; CA-125: cancer antigen 125; CEA: carcinoembryonic antigen;*

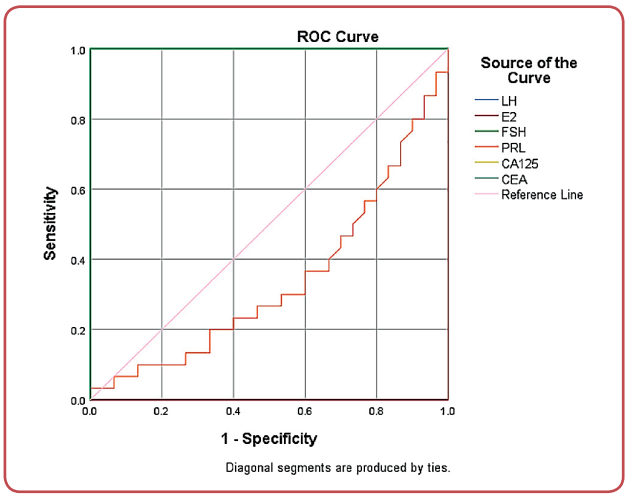


Figure 2: ROC curves for parameters in this study

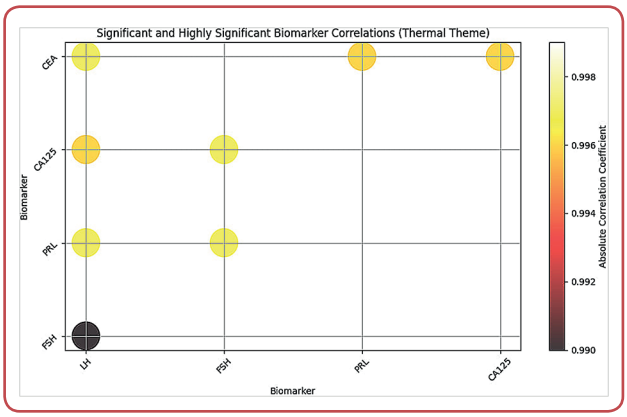


Figure 3: Correlation between different biomarkers

A dot plot showing the significant and highly significant biomarker correlations, where the size and colour of the dots represent the absolute value of the correlation coefficients. LH: luteinising hormone; FSH: follicle-stimulating hormone; PRL: prolactin; CA-125: cancer antigen 125; CEA: carcinoembryonic antigen.

Discussion

The purpose of this research was to understand the relevance of the observed changes in hormonal and tumour marker profiles, address possible implications for diagnosis and treatment and offer areas for future study in endometrial cancer in the Iraqi population. Endometrial cancer poses a significant challenge in the field of gynaecological oncology today because there is currently no reliable and non-invasive screening method available for its detection.[22, 23]

The comparison between participants with endometrial cancer and healthy controls revealed significantly elevated concentrations of FSH, LH and CA-125 in the serum. Previous research has also reported lower levels of FSH and LH, indicating potential hypothalamus disorders in the development of endometrial cancer. This theory gains further support from the observation that both FSH and LH exhibit moderate to high sensitivity, enabling them to differentiate individuals with endometrial cancer from asymptomatic women within a group.[24]

Earlier studies on the levels of LH in women having endometrial cancer have yielded inconsistent findings and these studies were conducted before the advent of highly sensitive bio-assays and radio-immuno-assays. The measurement of pituitary gonadotropin excretion, using the mouse uterine weight assay, did not indicate an elevation in women having endometrial cancer.[25] Dilman et al discovered that women having endometrial cancer had elevated concentrations of immune reactive LH, which they measured using the hemagglutination inhibition method.[26] Litviakova et al on the other hand, employed a distinct method involving the measurement of ventral prostate weight to assess bio-active LH concentrations in urine. Their findings indicated that LH concentrations were elevated in the urine of women having endometrial cancer.[27] Varga and Henriksen conducted a similar bio-assay and found that nearly 30 % of women characterised with endometrial cancer exhibited higher levels of LH in their urine.[28] PRL has been proposed as a potential indicator for endometrial cancer and old studies have noted raised levels of PRL in individuals with a diagnosis of endometrial carcinoma.[29] These results are not consistent with the results of presented study. The raised concentrations of PRL may be due to excessive PRL released from the endometrial cancer cells.[15] Previous studies have uncovered an interesting link between the severity of tumours and the levels of specific hormones, including LH, E2, PRL and CA-125. The intriguing finding is that there is an inverse relationship between tumour stage and E2, implying that an absence of E2 may not have a substantial turn in the expansion of endometrial cancer, particularly in type B tumours known for their higher grades and more offensive behaviour. From another side, decreased levels of E2 could be attributed to increased concentrations of LH, that may arise from a hypothalamic harm connected with the development of endometrial cancer,[24, 30] as opposed to the reverse correlation diagnosed to the survey of Mongia et al.[31]

CA-125 is a glycoprotein present on cell surfaces and is commonly employed as a tumour marker to predict endometrial adenocarcinoma. When CA-125 levels are elevated, it indicates the release of tumour cells into the peritoneal cavity, which suggests aggressive tumour behaviour or a higher grade of the tumour.[32] Elevated levels of CA-125 in the bloodstream have been connected to the spread of endometrial cancer beyond the uterus and involvement of lymph nodes. This suggests that the disease has reached an advanced stage and indicates a less favourable prognosis. While CA-125 is considered an important and independent prognostic factor for endometrial cancer patients, it is essential to show that some patients may have a lot of advanced disease than what is indicated solely by their preoperative CA-125 levels. Moreover, the limited sensitivity of CA-125 presents a challenge, that could be addressed by joining CA-125 with other biochemical markers.[33, 34] Despite the abundance of studies highlighting the value of CA 125 in the characterisation of ovarian tumours, there is a lack of research examining its turn in endometrial cancer. However, presented study demonstrates that individuals with endometrial cancer have elevated concentration of CA 125 compared to healthy individuals. These findings are consistent with previous research, which suggests that the elevated production of CA 125 by endometrial tumour cells is the underlying cause of this increase.[35, 36] In a comprehensive study conducted by Jiang et al, the researchers examined the significance of preoperative CA 125 concentrations, old, menopausal condition and tumour histology in a substantial

cohort of 995 patients with endometrial cancer. The results of the study revealed a noteworthy correlation between CA 125 concentrations and both age and menopausal status. However, no significant connection was observed between CA 125 levels and tumour histology.[37] CA 125 levels can be raised in both harmless physiological and pathological circumstances, including the menstrual cycle, pregnancy and endometriosis. However, elevated CA 125 levels can also indicate the presence of malignant conditions like endometrial carcinoma.[38]

CEA, a tumour marker commonly used for gastrointestinal tract tumours, is not considered specific for endometrial cancer. Its changes are not frequently reported in relation to endometrial cancer. In a previous study done by Kanat-Pektas et al, no significant differences in CEA levels were observed between participants with endometrial cancer and normal peoples serving as controls.[15] According to the current study, levels of CEA show a significant raise in cases of endometrial cancer compared to the general health of women. While CEA is commonly associated with colorectal cancer, elevated CEA levels have also been observed in different types of epithelial-derived carcinomas, including lung adenocarcinoma, ovarian carcinoma and endometrial adenocarcinoma. However, a study done by Kozakiewicz et al demonstrated that elevated CEA concentrations were not sufficiently sensitive and specific for the diagnosis and monitoring of healed in endometrial cancer.[39]

Conclusion

Presented study investigated the hormonal and tumour marker profiles associated with endometrial cancer in Iraqi female patients. It was discovered that endometrial cancer patients had significantly raised concentrations of LH, E2, FSH, PRL, CEA and CA-125 in their serum, indicating hormonal dysregulation in the development of endometrial cancer. This suggests that these markers could potentially be used for diagnosing and predicting the prognosis of endometrial cancer. However, it is substantial to say that CA-125 is not specific to endometrial tumours and can be elevated in other types of cancer as well. Similarly, the influence of physiological factors on PRL secretion raises doubts about its reliability as an early diagnostic marker for endometrial tumours.

It is not advisable to rely solely on LH, E2, FSH, PRL, CA-125 or CEA as screening markers for endometrial cancer. Instead, they should be considered as part of a comprehensive screening panel that needs to be developed in the future. It is crucial to conduct further research with larger cohorts to validate these findings and investigate the underlying mechanisms of hormonal imbalances, tumour marker expression and disease progression in endometrial cancer, particularly in the Iraqi population.

Ethics

The study was approved by the Ethics Committee of the Oncology Teaching Hospital, Medical City, Baghdad, Iraq, the decision No 44265, dated 21 November 2023. Written consent has been obtained from all study subjects prior to their participation and a questionnaire was filled by the patients.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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