DOI: https://doi.org/10.53350/pjmhs2023173214

ORIGINAL ARTICLE

Is Serum Human Epididymis Protein HE4, More Specific than Cancer Antigen 125 in Patients with Benign Gynecological Diseases?

SONIA AZIZ[1], SAHAR SALAHUDDIN AMIR[2], IHSANULLAH[3], HINA SHAMS[4], UMAIR AMIR KHAN[5], SABA SHAMS[6]
[1,4,5,6]*Department of Pathology, Gajju Khan Medical College, Bach Khan Medical Complex, Swabi*
[2]*Department of histopathology Shaikh Zayed Hospital Lahore*
[3]*Department of Hematology, Gajju Khan Medical College, Bach Khan Medical Complex, Swabi*
Correspondence to: Sonia Aziz, Email: aziz_sonia@yahoo.com, Cell: 03305982438

ABSTRACT

Background: The cancer antigen 125 "CA125" and Human Epididymis protein 4 "HE4" are among some well worked out markers for recognition of malignancy in ovarian tumors. Their different cutoffs are determined and reported by various studies and mostly used recommended cutoffs are 35.0 U/mL for CA125 and 140pmol/L for HE4. They are both reported to recognize the malignancy well, but how specific they are for benign gynecological diseases is still needed to be worked out.

Aim: To determine and compare the performance of CA125 and HE4 for benign gynecological pathologies.

Methodology: A cross-sectional study was performed at Gajju Khan Medical College in collaboration with Armed forces Institute of pathology (AFIP). A total of 76 women of age above 18 years age, with benign ovarian pathology, confirmed through histological evaluation were enrolled. All these were examined on both markers, i.e. CA125 and HE4. Standard cutoffs of CA125 >35.0 U/mL and HE4>140 pmol/L were used to see if the case was labeled malignant, incorrectly. SPSS 20.0 was used to manage and analyze the data. Performance of the two markers were compared by using some descriptive analysis and using chi-square test. P-value ≤0.05 was considered significant.

Results: The median age of these women was 40 years ranging between 18 and 71. Majority (86.8%) was premenopausal, The CA125 had no difference between pre and post-menopausal women but HE4 had a significant difference with p-value 0.029. there were 10.5% incorrect labeling of malignancy when evaluated for CA125, while only 2.6% incorrect on HE4. This difference was found statistically significant between two markers with p-value 0.05.

Conclusion: HE4 is better and more specific marker for benign gynecological pathologies as compared to CA125

Keywords: Benign Ovarian Epithelial, Human epididymisprotein (HE4), Cancer Antigen 125 (CA125), Specificity

INTRODUCTION

Ovarian cancer is one of the high mortality rate cancers, having relatively poor prognosis particularly in low-resourced settings (1). It is therefore important to continually examine the burden of ovarian cancer to identify areas of disparities. Currently Pakistan is reported to have 6% of incidence with 80% being diagnosed on advance stages(2). Misdiagnosis can lead to unnecessary laparoscopy/laparotomies(3).

As it is important to diagnose the malignancy, so important is to be specific while diagnosing the cancer as it is quite expensive and many unnecessary removals are done with only suspecting malignancies. In USA at the time of hysterectomy 23% of the women 40-44 years age and 45% of 45-49 year age women go for hysterectomy to prevent ovarian cancer (4). The removal of ovaries in premenopausal period may cause endocrine disturbance, anxiety and depression(5), cardiovascular diseases(6), cognitive disorders and dementia (7) and many other problems.

The Cancer Antigen 125 (CA125) is the most used marker, for last four decades for diagnosis of ovarian cancer and its traditional cutoff used is 35.0 U/mL (8). In a systematic review the median of CA125 for benign ovarian masses was reported between 16 and 54 U/mL, which shows lot of variation. In premenopausal women it is reported to be underperforming as compared to HE4(9). The HE4 was first named by Kirchhoff et al (10). HE4's ability to distinguish benign diseases from malignancies (i.e., its sensitivity) affords it with an advantage over CA-125 alone in OC detection is well discussed in literature and specifically among women in premenopausalstate (11).

A very specific marker is required precisely for benign gynecological diseases and this study has tried to asses and compare HE4 with CA125 among such cases.

MATERIAL AND METHODS

This descriptive study was carried out in the Gajju Khan Medical College, Swabi in coordination Chemical Pathology Department of Armed Forces Institute of Pathology (AFIP), Rawalpindi,after approval from the institutional ethical review committee. Research was carried out from March 2019- March 2020.

A total of seventy six (76) women of age greater than 18 years were included. Women with suspected ovarian malignancy admitted in gynecology ward of Gajju Khan Medical College, Bach Khan Medical Complex, Swabi were considered. All patients underwent imaging by pelvic/abdominal ultrasound to document their presence of ovarian mass. And those confirmed as benign according to WHO classification 2003 by specialized histo-pathologist were considered for this study (2).

A blood sample (5ml) was obtained preoperatively into serum or serum separator tubes and centrifuged, aliquoted and frozen within 4 hours. The samples were stored at -20C until biochemical analysis. Blood samples were taken by trained personnel under strict hygienic conditions. Personal information of the participants were kept confidential and procedure of blood collection was explained to the patients in detail before taking the sample. CA125 assay was performed on automated analyzer VITROS. The reference range used for CA125 was 35U/ml(8). HE4 assay was performed on automated analyzer ARCHITCT and the reference range of HE4 was taken 140 pmol/L (9).

Data was entered and analyzed in SPSS (version 20.0). Mean ± SD was calculated for quantitative variables like age, CA125 and HE4 levels. Median along range and interquartile range were used for pre and postmenopausal women as well as for all. Frequencies and percentages were calculated for qualitative variables like ovarian cancer, status as per cutoffs of CA125 and HE4 and specificity of markers. Mann Whitney U test was used to compare markers between premenopausal and postmenopausal women. Labelling of cases as per marker cutoffs were presented for each benign type as well as overall and comparison of specificity was done by using McNemar test. P-value ≤0.05 was considered significant.

RESULTS

It was observed that the mean age of 40.4 years and range was 18 to 71 years. Majority of the cases (86.8%) were observed with premenopausal status. The mean CA15 level was 22.28 with a standard deviation of 36.9 and median level was 14.05 with a range of 3.6 to 241.0 U/mL. For same cases the HE4 had an average of 59.3 with a smaller standard deviation of 19.42. The

median HE4 was recorded 58.5 with maximum value of 143.5. (Table 1)

Table 1: Characteristics of patients with benign ovarian pathologies

	Category / measure	Value
Age, years	Mean (SD)	40.4 (12.0)
	Median (range)	40 (18.0–71.0)
Menopausal status	Pre, n (%)	66 (86.8)
	Post, n (%)	10 (13.2)
CA125 (U/mL)	Mean (SD)	22.28 (36.9)
	Median (range)	14.05 (3.6 –241.0)
HE4 (pmol/L)	Mean (SD)	59.33 (19.42)
	Median (range)	58.5 (36.80–143.50)

CA125, cancer antigen 125; HE4, human epididymis protein 4; SD, standard deviation

Further when the markers were measured for pre and post-menopausal women, The CA125 for pre-menopausal women was 14.4 with interquartile range of (8.1 – 21.8) and for post-menopausal women was 6.6(5.4 – 25.3) the difference between pre and post-menopausal women was insignificant with p-value 0.148. For HE4 the median level for pre and post-menopausal women were 53.5 and 67.0 respectively and this difference was found significant with p-value 0.029. (Table 2)

Table 2: Comparison of two marker between pre and post-menopausal status

Menopausal status	CA125	HE4
	Median (Q_1 – Q_3)	Median (Q_1 – Q_3)
Total (n = 76)	14.05 (7.8 - 24.10)	58.5 (46.4 - 67.0)
Pre (n = 66)	14.4 (8.1 - 21.8)	53.5 (42.5 - 63.4)
Post (n = 10)	6.6 (5.4 - 25.3)	67.0 (61.8 - 70.0)
P-value	0.148	0.029

Table 3: Status of the benign cases presented as malignant by two markers on standard cutoffs

Benign pathology	Total cases	CA125 > 35.0		HE4 >140.0	
		n	%	n	%
Cyst adenoma	8	2	25.0	2	25.0
Endometriotic cyst	8	2	25.0	0	0.0
Desmoid cyst	4	0	0.0	0	0.0
Leiomyoma	26	2	7.7	0	0.0
Other benign	30	2	6.7	0	0.0
Total	76	8	10.5	2	2.6

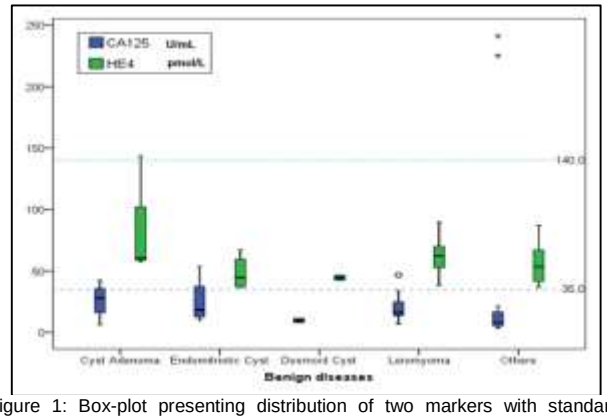

Figure 1: Box-plot presenting distribution of two markers with standard cutoffs

When standard cutoffs of 35.0 U/mL of CA125 and 140.0 pmol/mL for HE4 were used it was observed that 8(10.55) of benign cases were labeled as malignant, while only 2(2.6%) by HE4. Here it was important to be noted that, all 8 cases presented malignant by CA125 were of premenopausal status while 2 presented by HE4 were of postmenopausal status. So it can be concluded thatcyst adenoma was one of the benign type which had 50.0% cases labeled as malignant 25.0% by CA125 and 25.0% by HE4, one marker in premenopausal and other in post-menopausal. Among other benign types HE4correctly labeled all cases as benign while CA125 labeled 2(25.0%) of endomitriotic cyst, 2(7.7%) of Leiomyoma and 2(6.7%) of other benign pathologies as malignant.

DISCUSSION

The benign ovarian diseases are mostly found among premenopausal women, and this study had majority 86.8% of the women with premenopausal status. The median age was noted around 40 years which shows that 50% of the women might be still in family making process, so a misdiagnosis may effect this objective of the patient in terms of ovary removal (3).

The human epididymis protein 4 (HE4), under investigation in this study was expressed significantly different among premenopausal and postmenopausal women, which is in line with the study performed earlier (11).

The CA125 also showed a very wide range 3.5 – 241.0 with a median level of 14.05, and was not different between pre and post-menopausal women. This shows the inconsistency of CA125 on menopausal status, while HE4 had a significant difference, indicating its utility as per menopausal status. Specifically the benign diseases being the phenomena of premenopausal age HE4 may play important role in diagnosis (11).

Also 10.5% of the cases were labeled malignant for its traditional cutoff of 35.0 U/mL which makes its specificity as 89.5% which is also reported by other study (9), while HE4 was reported to have only 2 (2.6%) misdiagnosis as malignant cases measuring its specificity as 97.4%, quite close to the demand made by (11). If we dig in a little deep for premenopausal women only then all 8 cases misdiagnosed by CA125 were among premenopausal women which measures specificity of 87.9%, whereas the 2 misdiagnosed cases by HE4 were both in group of postmenopausal women, hence the specificity of HE4 among premenopausal women was 100.0%.

Hence it further strengthens the idea that HE4 on its conventional cutoff of 140 pmol/L may perform better and more specific (to correctly diagnose benign cases) among ovarian disease than the CA125 with its traditional cutoff of 35 U/mL. And when it becomes to premenopausal women HE4 seems to clearly outperforming CA125.

CONCLUSION

Human epididymis protein with its traditional cutoff of 140 pmol/L may be preferred over CA125 at cutoff of 35.0 U/mL in general and among premenopausal women specifically for ensuring benign gynecological diseases.

REFERENCES

1. Cabasag CJ, Fagan PJ, Ferlay J, Vignat J, Laversanne M, Liu L, et al. Ovarian cancer today and tomorrow: A global assessment by world region and Human Development Index using GLOBOCAN 2020. International Journal of Cancer. 2022;151(9):1535-41.
2. Sonia Aziz EHK, Mohsin Shaffi. erum level of Human epididymis Protein 4 and Cancer Antigen 125 in Different Histological Types of Ovarian Cancer. The Medical Forum. 2018;29(6):88 - 92.
3. Verdicts M. Misdiagnosis leads to unnecessary hysterectomy. 2002;14(6):90, 2.
4. Erickson Z, Rocca WA, Smith CY, Rocca LG, Stewart EA, Laughlin-Tommaso SK, et al. Time trends in unilateral and bilateral oophorectomy in a geographically defined American population. Obstetrics and gynecology. 2022;139(5):724.
5. Rocca WA, Grossardt BR, Geda YE, Gostout BS, Bower JH, Maraganore DM, et al. Long-term risk of depressive and anxiety

symptoms after early bilateral oophorectomy. Menopause. 2008;15(6):1050-9.
6. Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. bmj. 2017;356.
7. Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis. Psychoneuroendocrinology. 2019;106:9-19.
8. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and ovarian cancer: a comprehensive review. Cancers. 2020;12(12):3730.
9. Dikmen Z, Colak A, Dogan P, Tuncer S, Akbiyik F. Diagnostic performances of CA125, HE4, and ROMA index in ovarian cancer. European journal of gynaecological oncology. 2015;36(4):457-62.
10. Bingle L, Singleton V, Bingle CD. The putative ovarian tumour marker gene HE4 (WFDC2), is expressed in normal tissues and undergoes complex alternative splicing to yield multiple protein isoforms. Oncogene. 2002;21(17):2768-73.
11. Li J, Dowdy S, Tipton T, Podratz K, Lu W-G, Xie X, et al. HE4 as a biomarker for ovarian and endometrial cancer management. Expert review of molecular diagnostics. 2009;9(6):555-66.