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List of Abbreviations

AUC : Area under the curve

CA125 : Cancer antigen 125

CEA : Carcinoembryonic antigen

CI : Confidence interval

EOC : Epithelial ovarian cancer

HE4 : Human epididymis protein 4

HNPCC : Hereditary nonpolyposis colorectal cancer

LN : Natural logarithm

LR : Likelihood ratio

MES : Mesothelin

NPV : Negative predictive value

OC : Ovarian cancer

OSE : Ovarian surface epithelium

PPV : Positive predictive value

RMI : Risk malignancy index

ROC : Receiver operating characteristic

ROMA : Risk ovarian malignancy algorithm

SE : Standard error

WAP : Whey acidic protein

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Prediction of Malignancy in Women with Ovarian Mass Using the Risk of Ovarian Malignancy Algorithm

Thesis

Submitted for Partial Fulfillment of
Master Degree in Obstetrics and Gynaecology

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التنبؤ بالسرطان فى النساء المصابة بورم بالمبيض بإستخدام خوارزمية احتمال سرطان المبيض

رسالة

توطئة للحصول على درجة الماجستير فى أمراض النساء والتوليد

مقدمة من

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Prediction of malignancy in women with ovarian mass using the risk of ovarian malignancy algorithm

Protocol of a study submitted for partial fulfillment of

MS Degree in Obstetrics and Gynaecology

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خطة بحثية للحصول على درجة الماجستيير فى أمراض النساء والتوليد

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Introduction:

Ovarian cancer is the second diagnosed gynaecologic malignancy in the United States; it is also the most deadly because over 70% of women are diagnosed with advanced stage disease. In advanced stage disease cure rates are only 20-30% ***(Jemal et al, 2007).*** According to current estimates, 1.4% (1 in 72) of women born today will be diagnosed with ovarian cancer at some point in their lifetime ***(Ries et al, 2008)***. In clinical practice discrimination between a benign disease and a malignant ovarian tumour in patients with an adnexal mass still remains a challenge for the gynaecologist (**Nolen et al, 2010**).

The main goals being a timely diagnosis and early surgical and/or chemotherapeutic treatment due to the high mortality rate in patients diagnosed with advanced cancer (**Dunleavey, 2006**). Early stage ovarian cancer has an excellent prognosis if treated. Given the limitation of treatment for advanced ovarian cancer and the success of treatment for early stage disease, a screening test is intuitively appealing (**Schink, 1999**).

Prior attempts to establish population based screening protocols for ovarian cancer have employed CA125, ultrasound and new biomarkers and statistical approaches (**Bast et al, 1981**).

The serum tumour marker CA125 is commonly used to predict the presence of a malignancy in women with a pelvic mass, but CA125 measurement has limitations. CA125 is elevated in less than half of early-stage epithelial ovarian cancer patients and in approximately 80% of women with epithelial ovarian cancer, potentially leaving 20% of ovarian cancer patients without a useful serum biomarker for the management of their disease (**Bast et al, 1983;Jacobs et al, 1989**). In addition, many premenopausal women with common benign gynaecologic disorders will have an elevated serum CA125 level, and many medical conditions affecting postmenopausal women can also elevate serum CA125,resulting in the reduction of sensitivity and specificity of CA125 (**Jacobs et al, 1989**).

The sensitivity and specificity of CA125 are far from ideal as its levels are raised in approximately 80% of all epithelial ovarian cancers (EOC) and in only 50% of stage I EOC (**Zurawski et al, 1988**). Therefore, CA125 is rarely used as a unique parameter in the prediction of malignancy. Usually, a combination of a patient's medical history, clinical examination results, imaging data and tumour marker profile is used to differentiate malignant ovarian masses from their benign counter parts (**Van Holsbeke et al, 2009**).

The combination of serum CA125 levels and pelvic sonography improves the sensitivity and specificity for predicting the presence of ovarian cancer in patients with a pelvic mass (**Jacobs et al, 1990**).

Nearly 20 years ago, Jacobs et al. developed the Risk of Malignancy Index (RMI), a diagnostic model for the assessment of patients with adnexal masses that combined CA125 concentrations, imaging score and menopausal status. However, this approach improved the invasive malignancy prediction only in post-menopausal women, primarily because of the low diagnostic accuracy of the serum CA125 assay in pre-menopausal women (**Vanden et al,2010**). For example, CA125 increases in endometriosis and other benign conditions and is more prevalent in pre-menopausal compared with postmenopausal women (**Strigini et al, 1996**).

The use of novel biomarkers such as HE4 alone or in combination with CA125 has been intensively studied to improve the sensitivity and specificity of ovarian cancer diagnosis. **(Hellstrom et al, 2003; Havrilesky et al, 2008).**

Human epididymis secretory protein 4 (HE4) gene was found to be over expressed in ovarian cancer (**Schummer et al, 1999**). It is a member of the Wey acidic protein gene family (Bouchard et al, 2006), and is expressed in normal tissues of the reproductive and respiratory tract (**Bingle et al, 2002; Galgano et al, 2006**). The first report mentioning HE4 as a potential serum biomarker for ovarian cancer was published in 2003 (**Hellstrom et al, 2003**). When CA125 was combined with HE4, the prediction rate was higher, showing a sensitivity for detecting malignant disease of 76.4% at a specificity of 95% (**Moore et al, 2007**).

It is plausible to assess the tumour marker levels of both HE4 and CA125 in patients with different forms of benign and malignant ovarian masses, and to establish the diagnostic performance of the risk of ovarian malignancy algorithm (ROMA) to discriminate benign and malignant ovarian tumours in pre-menopausal and postmenopausal women.

1. Protocol Outline

1.1. Title :

Prediction of malignancy in women with ovarian masses using the risk of ovarian malignancy algorithm (ROMA).

1.2. Study site :

Ain-Shams University Maternity Hospital.

2. Study Objectives

Evaluating the performance of the predictive model ROMA (Risk of Ovarian Malignancy Algorithm), which utilizes the combination of human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) values to assess the risk of malignancy in women with an ovarian mass.

3. Study Design:

Women with an ovarian mass, who will be scheduled to have surgery, will be enrolled in a prospective study.

Preoperative serum levels of HE4 and CA125 will be measured.

The performance of each of the markers, as well as that of ROMA, will be analysed.