Evaluation of Serum Mesothelin in Malignant and Benign Ovarian Masses

Thesis

Submitted for the Partial Fulfillment of Master Degree in Obstetrics and Gynecology

Presented By

Amira Mohsen Abd El Hakem

M.B., B.Ch.

Al Azhar University

Under Supervision of

Prof./Ayman Abd El-Razek Abd El-Rahem Abo El-Noor

Professor of Obstetrics and Gynecology

Faculty of Medicine

Ain Shams University

Dr./Ahmed M. Bahaa El Din Ahmed

Lecturer of Obstetrics and Gynecology

Faculty of Medicine

Ain Shams University

Faculty of Medicine - Ain Shams University

2013

Acknowledgement

I would like to express my deepest gratitude to ***Prof. Dr. Ayman Abd El Razek Abd El Rahem Abo El Noor,*** *Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his great help, continuous advices and instructive supervision through the performance of this work.*

My profound gratitude and extreme thanks to ***Dr. Ahmed Mohamed Bahaa ELdin Ahmed,*** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his close generous supervision, energetic help, pushing this work forwards.*

No words can express my sincere thankfulness and deep appreciation to ***Prof. Dr. Ahmed Mohamed Ibrahim, Prof. Dr. Usama Ahmed El Tohamy and Prof. Dr. Mostafa Ibrahim Ibrahim*** *Assistant Professors of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his advices and remarks that have been of most help. they gave me a lot of their valuable time to improve the quality of this work.*

My profound gratitude and extreme thanks to ***Dr. Mohamed Ahmed Faris,*** *Assistant Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his close generous supervision, in statistical analysis help, pushing this work forwards.*

Finally, and not the last, I must mention my patients gratefully, being the source of knowledge and practice, asking God to give them a long healthy life all happy as can be.

Amira

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
AFP	Alphafetoprotein
AGR2	Anterior gradient protein 2
AMH	Antimullerian hormone
AUC	Area under curve
BMI	Body mass index
CA125	Cancer Antigen 125
CA19.9	Cancer Antigen 19.9
CEA	Carcinoembryonic antigen
CT	Computed tomography
DM	Diabetes mellitus
ECG	Electrocardiography
ELISA	Enzyme-linked immunosorbent assay
EOC	Epithelial ovarian cancer
FI	Flow index
FVI	Vascualrization flow index
GCR	Granulose cell tumour
GIT	Gastrointestinal tract
HE4	Human epididymis protein
HGF	Hepatocyte growth factor
hK	Human kallikreins
HP-α	Haptoglobin-α
HRT	Hormonal replacement therapy
HS	Highly significant
Ht	Height
IQR	Interquartile range
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
LRG1	Leucine-rich alpha-2 glycoprotein-1
M	Menopausal score
MAb56%	Monoclonal antibodies 56%
MCS-F	Macrophage colony stimulating factor
MPF	Megakaryocyte potentiating factor
MPF	Megakaryocyte potentiating factor
MRI	Magnetic resonance imaging
MUC16	Mucin 16

NACB	National academy of clinical biochemistry laboratory medicine
NK cells	Natural Killer cells
NPV	Negative predictive value
NS	Non significant
OD	Optical density
OPN	Osteoponin
PAI	Photoacostic imaging
PDA	Power Doppler angiography
PET	Positron emission tomography
PI	Pulsatility index
PID	Pelvic inflammatory disease
PPV	Positive predictive value
PPV	Positive predictive value
RI	Resistance index
RMI	Risk of malignancy index
ROC	Receiver operator characteristics
ROMA	Risk of ovarian malignancy algorithm
SAGE	Serial analysis of gene expression
SD	Standard deviation
SMRP	Soluble mesothelin releasing protein
TAA	Tumour associated antigens
TVS	Transvaginal ultrasound
TVUS	Transvaginal ultrasonography
U	Ultrasound scores
U/S	Ultrasound
USA	United States of America
VEGF	Vascular endothelial growth factor
VI	Vascularization index
VMS	Vascular morphology score
VOCAL	Virtual organ computer aided analysis
WT	Weight
2D	Two dimensional
3D	Three dimensional
3DPD	Three dimensional power Doppler
4-PL	Four parameter logistic

INTRODUCTION

Each year in the United States over 15.000 women die from epithelial ovarian cancer (EOC) and 22.000 are diagnosed with the disease. The incidence of ovarian cancer has remained stable over the past decade. Survival has improved steadily ***(American Cancer Society, 2009)***.

The increase in survival rates can be attributed to the advances in surgical management, development of effective cytotoxic drugs and the intraperitoneal administration of chemotherapy. Ovarian cancer survival rates could also be improved through screening and early detection. Historically the goal of a screening test was to achieve a positive predictive value (PPV) greater than 10% in order to be considered cost effective and have an acceptable risk for the population being screened ***(Moore et al., 2010)***.

Assays measuring tumor markers in serum or other body fluids have the advantage of being non invasive, simple to perform and relatively cheap. An acceptable screening assay would require a sensitivity of 75% and specificity of around 99.7% to obtain minimally tolerable positive predictive value of 10% for

the detection of ovarian carcinoma ***(Hellstrom and Hellstrom, 2011)***.

Mesothelin is a new tumor marker in patients with mesothelioma and ovarian cancers ***(Grigoriu et al., 2008)***.

Mesothelin is a cell surface protein present on normal mesothelial cells lining the pleura, pericardium and peritoneum. Msothelin is highly expressed in several cancers (tumor differentiation antigen) including virtually all epithelial mesotheliomas and pancreatic adenocarcinomas and approximately 70% of ovarian cancers and 50% of lung adenocarcinomas ***(Hassan et al., 2010)***.

As a high molecular weight glycoprotein, CA125 is normally expressed in a variety of epithelial cell types. These range throughout adult tissues derived from Mullerian (endocervical, endometrial, and tubal) and coelomic (peritoneum, pericardium, and mesothelial cells of the pleura) epithelia ***(Gupta and Lis, 2009).***

CA125 antigen is the most commonly used biochemical marker in ovarian cancer diagnosis.

However, it is associated with a higher false positive rate among women with benign gynecological conditions ***(Huhtinen et al., 2009).***

Increased serum CA125 can also be detected during the menstrual phase and in the premenstrual phase in women with anovulatory cycles, as well as during the first trimester of pregnancy. Cyclic combined hormone replacement therapy (HRT) might also be associated with increased CA125. Conversely, regular smoking and caffeine consumption decrease CA125 concentration. Finally, ethnic differences have also been observed, for example, African and Asian women have CA125 concentrations lower than that of Caucasian women ***(Montagnana et al., 2011a).***

CA125 has very low sensitivity in identifying patients with early stage ovarian cancer ***(Terry et al., 2004)***.

A recent study presented evidence that mesothelin binds CA125 and may, therefore, play a role in the dissemination ovarian cancer in the peritoneal cavity ***(Rump et al., 2004)***.

Soluble mesothelin related peptides are members of the megakaryocyte potentiating factor (MPF) family and have been detected in both the serum and urine of patients with ovarian cancer ***(Scholler et al., 1999)***.

AIM OF THE WORK

To evaluate the ability of serum mesothelin concentration to differentiate between benign and malignant ovarian masses.