OSTEOPONTIN IN PATIENTS WITH ENDOMETRIAL CANCER

Thesis
Submitted for partial fulfillment of M. Sc. Degree in
Obstetrics & Gynecology

BY

Neveen Mohamed Abd El Aal El Mamlouk
M.B.B.Ch (1998)

Under Supervision of

Professor. Amr Hassan El Shalakany
Professor of Obstetrics & Gynecology
Faculty of Medicine – Ain Shams University

Dr. Abd El Megeed Ismaeel Abd El Megeed
Asst.Professor of Obstetrics & Gynecology
Faculty of Medicine – Ain Shams University

Professor. Moustafa Mohamed El Rasad
Professor of Biochemistry
Faculty of Medicine – Ain Shams University

Faculty of Medicine – Ain Shams University
2006

بسم الله الرحمن الرحيم

(قالوا سبحانك لا علم لنا إلا ما علمتنا
أنك أنت العليم الحكيم)

صدق الله العظيم

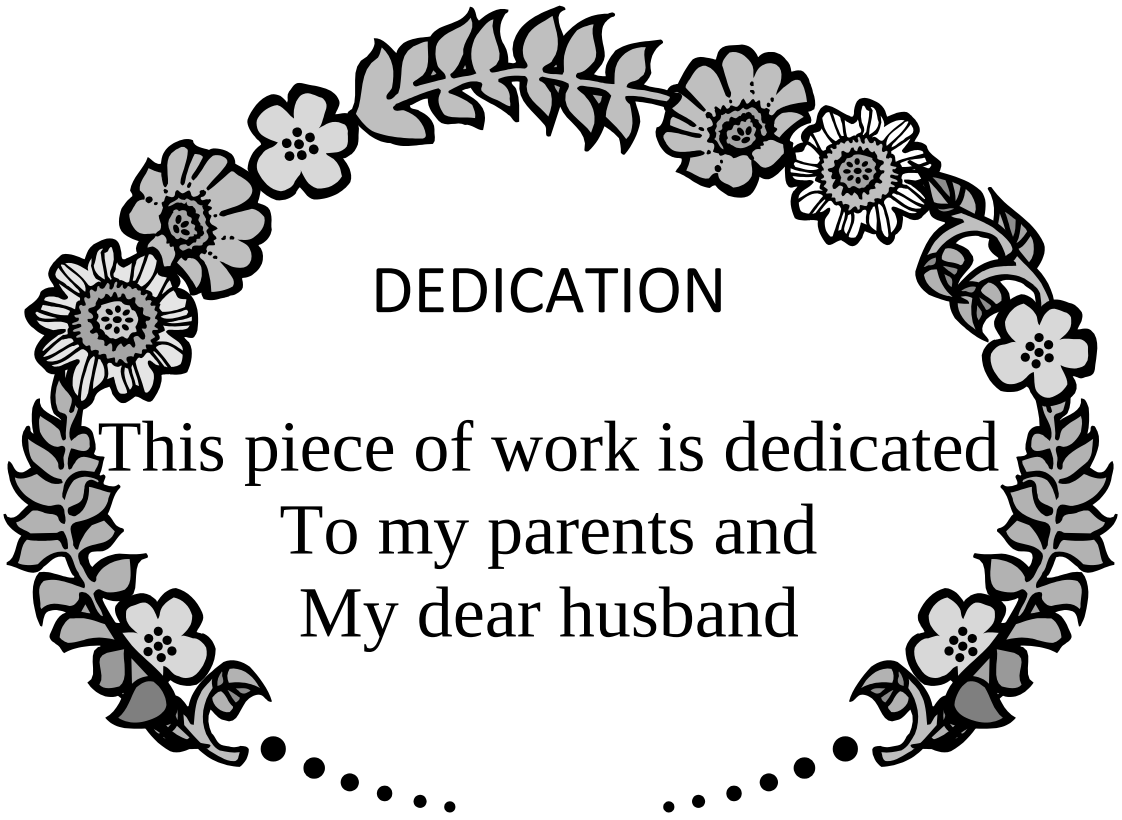
Acknowledgment

At first and foremost thanks to "**Allah**" who gave me the power to finish this work.

I find no words by which I can express my deepest thanks and profound respect to my honored professor, **Prof. Dr. Amro Hassan El Shalakany** , Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University for the continous kind encouragement, guidance and support he gave me throughout the whole work. It has been an honor and a privilege to work under his generous supervision.

I owe special gratefulness to **Dr. Abd El Megeed Ismaeel Abd El Megeed**, Assistant Professor of Obstet and Gynaecol, Faculty of Medicine, Ain Shams University, who supported, encouraged, and directed my efforts throughout this work.

Also, I would like to express my deepest thanks and appreciation to **Prof. Moustafa Mohamed El Rasad**, professor of Biochemistry, Faculty of Medicine, Ain Shams University, for hisgenerosity, kindness and humanity are unique and everlasting.



DEDICATION

This piece of work is dedicated
To my parents and
My dear husband

List of contents

	Page
List of abbreviation ……	—
List of tables……	—
List of figures…….	—
Introduction and aim of the work……..	1
Review of literature……	4
Endometrial cancer ……	4
Osteopontin…….	83
Subjects and methods……	104
Results……	112
Discussion……..	132
Conclusions and recommendations……..	142
Summary……	143
References……..	148
Arabic summary……	—

List of abbreviations

ACS	:	American cancer society
BMI	:	Body mass index
CA125	:	Cancer antigen 125
CCC	:	Clear cell carcinoma
CDC	:	Centers for disease control
CI	:	Confidence interval
CT	:	Computed tomography
D&C	:	Dilatation &curettage
EBM	:	Evidence based medicine
ECM	:	Extracellular matrix
ECPI	:	Endometrial carcinoma prognostic index
EE	:	Endometrial epithelium
EEC	:	Endometrioid endometrial carcinoma
ELISA	:	Enzyme linked immunosorbent assay
ERT	:	Estrogen replacement therapy
FIGO	:	International federation of gynaecology and obstetrics
FN	:	Standard for false negative cases

List of abbreviations (cont.)

FSH : Follicle-stimulating hormone

GIN : Glandular intraepithelial neoplasia

GOG : Gynaecologic oncology group

GTD : Gestational trophoblastic disease

HNPCC : Hereditary non-polyposis colorectal cancer

HPV : Human papilloma virus

HR : Hazard ratio

HRT : Hormonal replacement therapy

ISGP : International society of gynaecological pathologists

IUCD : Intrauterine contraceptive device

LH : Luetinizing hormone

LSD : Least significant difference

MDD : Minimum detectable dose

MRI : Magnetic resonance imaging

NCI : National cancer institute

NEEC : Non-endometrioid endometrial carcinoma

OCPs : Oral contraceptive pills

List of abbreviations (cont.)

OPN : Osteopontin

OS : Overall survival

PCOS : Polycyctic ovarian syndrome

PFS : Progression free survival

PMB : Postmenopausal bleeding

QOL : Quality of life

RCTs : Randomized controlled trials

ROC : Receiver operating characteristic

RR : Relative risk

RT-PCR: Reverse transcription polymerase chain reaction

SEER : Survillance , Epidemiology , and End Results

SHBG : Sex hormon-bound globulin

SPP1 : Secreted phosphoprotein 1

TN : Standard for true negative cases

TP : Standard for true positive cases

TVS : Transvaginal scanning

List of abbreviations (cont.)

UPSC : Uterine papillary serous carcinoma

WHO : World health organization

List of tables

Table	Title	Page
(1)	Comparison between type I (EEC) and type II (NEEC) endometrial carcinoma ……..	41
(2)	FIGO surgical staging for endometrial carcinoma 1988 ...	44
(3)	Grading of tumour differentiation (FIGO 1988) ……	44
(4)	Comparison between the studied groups as regards age	117
(5)	Comparison between the studied groups regarding to mean parity (No) ……	118
(6)	Comparison between the two study groups (malignant vs benign) regarding history of DM and hypertension ……	119
(7)	Comparison between the two study groups (malignant vs. benign) regarding contraception history ……	120
(8)	Comparison between the two study groups (malignant vs. benign) regarding BMI (kg/m^2)……..	121
(9)	Comparison between malignant group and benign group as regards endometrial thickness (mm) …….	122
(10)	Comparison of osteopontin levels among the three studied groups (ng/ml) …….....	123

List of tables (cont.)

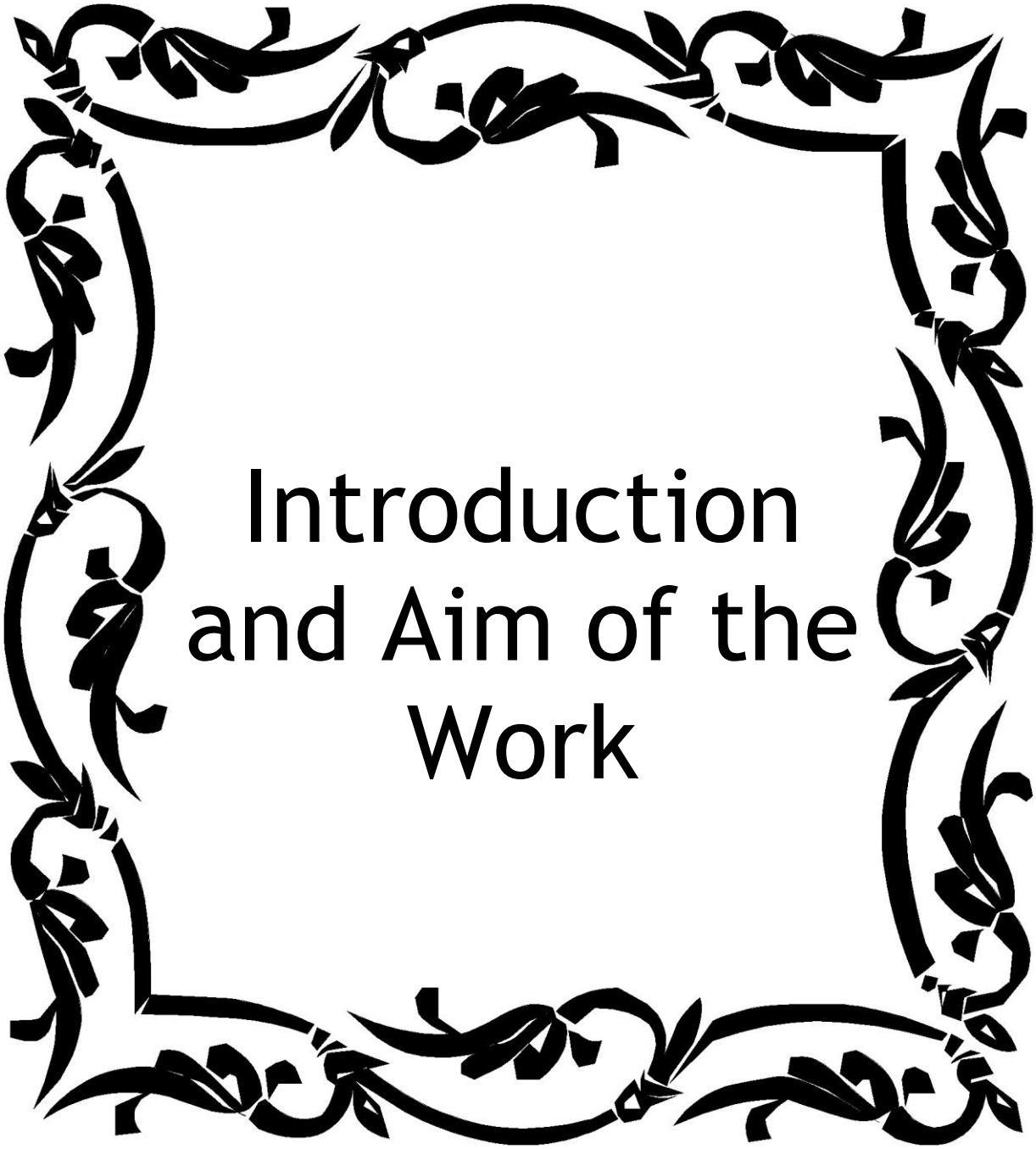
Table	Title	Page
(11)	OPN levels (at cut off limit of > or < 38 ng/ml) in the studied groups ……	125
(12)	Histopathology , staging and grading of malignant group….	126
(13)	OPN level (ng/ml) according to the tumour grade in malignant group ……	128
(14)	OPN levels (ng/ml) in early (I & II) vs. late stages (III & IV) in malignant group …….	129
(15)	Predictive value (%) of serum osteopontin as a marker in diagnosis of malignant endometrial tumour at two different cut off values (38 , 23 ng/ml) ……	130

List of figures

Figure	Title	Page
(1)	GIN-I …….	31
(2)	GIN-Π ……....	31
(3)	GIN-ΙΙΙ…….	31
(4)	FIGO grade I endometrial adenocarcinoma …….	37
(5)	FIGO grade Π endometrial adenocarcinoma ……...	37
(6)	FIGO grade ΙΙΙ endometrial adenocarcinoma ……	37
(7)	Well-differentiated adenocarcinoma with foci of benign squamous metaplasia …….	38
(8)	Adenosquamous carcinoma ……...	38
(9)	Papillary serous adenocarcinoma ……..	39
(10)	Clear cell adenocarcinoma …….	39
(11)	OPN levels (ng/ml) among the three studied groups ……..	124
(12)	Histopathology of the malignant group…….	127
(13)	OPN levels (ng/ml) according to the tumour grade in malignant group …….	128
(14)	OPN levels (ng/ml) in early (I, Π) vs. late stages (ΙΙΙ, IV) in malignant group……	129

List of figures (cont.)

FIGURE	TITLE	PAGE
(15)	Frequency distribution of OPN levels in the three studied groups at the cut off value of (38 ng/ml) ……	130
(16)	ROC curve for plasma OPN in diagnosis malignant endometrial tumour ……	131



Introduction and Aim of the Work

Introduction

Endometrial cancer is the most common gynecologic malignancy & the 4th most common cancer in women in U.S.A and the 8th most common malignant neoplasm world wide. Incidence ranges from 5.9 per 100.000 in China, to 44 per 100.000 in U.S.A **(Randall and Trimble 1999)**.

The etiology of endometrial cancer is hypothesized to be a hormone mediated process, through long standing stimulation of endometrium by unopposed estrogen. **(Randall and Trimble, 1999).**

Seventy percent of cases are presented early (stage I) and of good prognosis while 30% of cases present late (stage IV) and of bad prognosis **(Randall and Trimble, 1999).**

The key stone for diagnosis of endometrial cancer in women with post menopausal bleeding is endometrial biopsy through fractional uterine curettage or office hysteroscopy. This is followed by surgical staging according to 1988 FIGO criteria to determine the extent of the disease hence of surgery and the selection of any adjuvant treatments. (**Randall and Trimble, 1999).**

So there is still a place for diagnostic and prognostic markers to search for to help us for early detection and hence good prognosis of endometrial cancer. **(Randall and Trimble, 1999).**

Of these potential markers suggested a single-chain polypeptide sialoprotein called osteopontin (OPN) with a molecular weight of approximately 32,600 Dalton. It is glycosylated, highly phosphorylated and sulphated **(Chang and Prince, 1991).**

OPN is an acidic protein which exhibits a high amino acid homology between species (mouse, rat, human and pig) **(Prince et al., 1987).**

Osteopontin was originally identified in the mineralized matrix of bovine bone (**Franzen and Heinegard, 1985)** but has subsequently been reported in a variety of human organs, including female reproductive tissues such as the ovary