

THE ROLE OF EPIDERMAL GROWTH FACTOR EXPRESSION AND CYTOKERATINS IN NORMAL, HYPERPLASTIC AND CARCINOMA OF ENDOMETRIUM

Thesis

Submitted for Partial Fulfillment of M.D. Degree in Pathology

6/6. A.

By

Reem Abdel Azeem Hussein

M.B., B.Ch., M.Sc. (Pathol.)

Under Supervision of

Prof. Dr. Ahmed El-Taweel

Professor of Pathology
Faculty of Medicine - Ain Shams University

Prof. Dr. Nafissa M. A. El-Badawy

Professor of Pathology Faculty of Medicine - Ain Shams University

Dr. Magda Hassan A. Nasr El-Dig

Assistant Professor of Pathology Faculty of Medicine - Ain Shams Universit

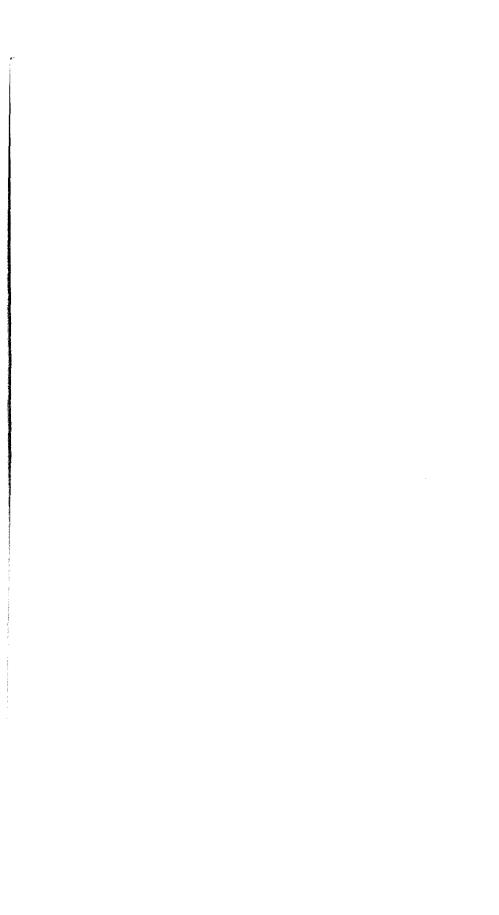
Dr. Hala Sobhy Cousha

Assistant Professor of Pathology Faculty of Medicine - Ain Shams University

> Faculty of Medicine Ain Shams University 1999



ACKNOWLEDGEMENT



ACKNOWLEDGEMENTS

It gives me a great pleasure and honor to present my deepest gratitude to Professor Dr. Ahmed El-Taweel, Professor of Pathology, Faculty of Medicine, Ain Shams University, for accepting the supervision of my work and for his helpful guidance, directions and encouraging attitude throughout this work. To him, I feel greatly indebted.

My sincere thanks and gratitude are due to Professor Dr. Nafissa El-Badaway, Professor of Pathology, Faculty of medicine, Ain Shams University, for her meticulous supervision, constructive criticism and valuable efforts, which are highly appreciated.

I would like to express my sincere gratitude and deepest appreciation to Dr. Magda Hassan, Assistant Professor of Pathology, Ain Shams University, who spared no effort in helping me throughout this work, her valuable advice and efforts are unforgettable.

Indeed I would like to express my deepest thanks to Dr. Hala Sobhy, Assistant Professor of Pathology, Ain Shams University, for her fruitful suggestions and keen supervision.

Particular thanks are to Professor Mohammed El-Shawarby, Professor of Pathology, Ain Shams University for his greatly appreciated help.

Great thanks are also to members of the Early Cancer Detection Unit, Ain Shams University, particularly Professor Dr. Mohammed Ezz El-Din Azzam, Professor of Gynecology and Obstetrics, Ain Shams University and Head of the Unit.

CONTENTS

	Page
ACKNOWLEDGEMENTS	i
LIST OF TABLES	v
LIST OF FIGURES	vi
LIST OF ABBREVIATIONS	viii
INTRODUCTION	X
AIM OF THE WORK	xii
REVIEW OF LITERATURE	1
Histology of Normal Endometrium	1
Endometrial Hyperplasia	6
◆ Introduction	6
 Definition and Classification of Endometrial Hyper- 	7
plasia	
 Clinical Profile of Endometrial Hyperplasia 	8
◆ Pathologic Criteria of Endometrial Hyperplasia	9
Behavior of Endometrial Hyperplasia	12
Endometrial Carcinoma	14
◆ Introduction	14
 Etiology & Predisposing Factors 	14
 Classification of Endometrial Carcinoma 	18
 Gross Picture of Endometrial Carcinoma 	19
Microscopic Grading	21
Surgical Pathological Staging	23
◆ Variants of Endometrial Carcinoma	24
◆ Immunohistochemical Findings in Endometrial Carcinoma	37
Prognostic Factors of Endometrial Carcinoma	39

 Immunohistochemistry 	
Intermediate Filaments	
 Definition and Types 	55
 Structure of Intermediate Filaments 	56
 Cytokeratins 	58
◆ Formation of Keratin Filaments	59
 Applications of Cytokeratins 	62
 Cytokeratins in the Female Genital Tract 	64
Cytokeratins in Endometrium	66
Growth Factors	69
Biological Effects of Growth Factors	72
 Growth Factor Receptors 	72
• Epidermal Growth Factors (EGF) and Epidermal Growth	76
Factor Receptors (EGFR)	
◆ Introduction	76
Structure of EGF	76
Biological Effects of EGF	78
 Mechanism of Action of EGF 	78
 Epidermal Growth Factor Receptor (EGFR) 	80
Structure of EGFR	81
 EGF and its Receptors in the Female Genital Tract 	85
 EGF and EGFR in the Endometrium 	86
MATERIAL AND METHODS	92
RESULTS	100
DISCUSSION	139
SUMMARY	152
CONCLUSION	158
RECOMMENDATIONS	
REFERENCES	161

LIST OF TABLES

		Page
Table 1	Classification of Non-invasive Endometrial Proliferation.	7
Table 2	Endometrial Carcinoma: Two Types.	15
Table 3	Classification of Endometrial Carcinoma	18
Table 4	Architectural Grading of Endometrial Carcinoma	21
Table 5	Nuclear Grading of Endometrial Carcinoma	21
Table 6	International Federation of Gynecology and Obstetrics (FIGO) Staging of Endometrial Cancer (1988)	24
Table 7	Types and Distribution of the Epithelial Keratins	59
Table 8	Major patterns of cytokeratin expression in relation to epithelial differentiation	62
Table 9	Growth Factors	70
Table 10	The mean age for the four studied groups.	102
Table 11	The mean parity for the four different groups	103
Table 12	The distributions of histopathological type and grade among the endometrial carcinoma group	105
Table 13	The distributions of Histopathological type and the various stages of endometrial carcinoma group.	106
Table 14	The mean score for EGFR among the four studied groups	110
Table 15	The difference of EGFR score between carcinoma & MMMT on one hand and normal and hyperplasia group on the other hand.	111
Table 16	EGFR score among the normal endometrial group.	111
Table 17	The score of EGFR in simple and complex hyperplasia.	112
Table 18	The histopathological type and EGFR score among the endometrial carcinoma group.	114
Table 19	The mean score for EGFR in different histopathological grades of endometrial carcinoma.	115
Table 20	The correlation between the EGFR score and stage of endometrial carcinoma	115
Table 21	The mean score for EGFR in different histopathological grades of	116



LIST OF FIGURES

		Page
Fig. 1	Structure of Intermediate Filaments	57
Fig. 2	Schematic illustration of fibrillar organization and keratin filament assembly and architecture.	61
Fig. 3	Signal transduction and epidermal growth regulation by growth factor and its receptors.	69
Fig. 4	Models of delivery of growth factors.	72
Fig. 5	Structure and amino acid of EGF, a 53 amino acid polypeptide with three disulfide bonds.	77
Fig. 6	Model for the structure of the EGF receptors.	84
Fig. 7	Schematic representation of the variation in the number of EGF	89
	receptor binding sites throughout the menstrual cycle.	
Fig. 8	Proliferative endometrium	117
Fig. 9	Simple hyperplasia	117
Fig. 10	Complex hyperplasia	118
Fig. 11	Well differentiated endometroid adenocarcinoma	118
Fig. 12	Villoglandular endometroid carcinoma	119
Fig. 13	Endometrioid adenoacanthoma	119
Fig. 14	Papillary serous carcinoma	120
Fig. 15	Clear cell carcinoma	120
Fig. 16	Malignant Mixed Mullerian Tumor (MMMT)	121
Fig. 17	MMMT	121
Fig. 18	Proliferative endometrium. Cytokeratin positively stained endometrial glands with negative stroma.	122
Fig. 19	Proliferative endometrium. Fibrillary network of cytokeratin between	122
	the nuclei and cell membrane.	
Fig. 20	Simple hyperplasia. Positive cytokeratin stain in the glands	123
Fig. 21	Well differentiated endometroid adenocarcinoma.	123
Fig. 22	Villoglandular endometroid carcinoma	124
Fig. 23	Secretory endometroid carcinoma	124
Fig. 24	Papillary serous carcinoma	125
Fig. 25	Well differentiated endometroid carcinoma	125
Fig. 26	Endometrioid adenoacanthoma. Positive cytokeratin stain in the glands and squamous elements.	126
Fig. 27	Endometrioid adenoacanthoma. Heavy stain in the squamous elements	126

Fig. 28	Poorly differentiated carcinoma. Positive cytokeratin stain	127
Fig. 29	Endometrial stromal sarcoma. Negative cytokeratin stain	127
Fig. 30	Omental metastases from adenocarcinoma. Positive cytokeratin stain	128
Fig. 31	MMMT. Cytokeratin stain highlight areas of carcinoma among	128
	negatively stained areas of sarcoma	
Fig. 32	Another case of MMMT. Positive cytokeratin stain in epithelial	129
	elements	
Fig. 33	Proliferative endometrium. Light stain EGFR	129
Fig. 34	Secretory endometrium. Negative stain of EGFR	130
Fig. 35	Simple hyperplasia. Light stain of EGFR	130
Fig. 36	Simple atypical hyperplasia. EGFR stain is light	131
Fig. 37	Complex hyperplasia. Heavy stain of EGFR	131
Fig. 38	Well differentiated endometroid adenocarcinoma	132
Fig. 39	Glands of endometroid adenocarcinoma	132
Fig. 40	Endometrioid adenocarcinoma. Negative stain for EGFR	133
Fig. 41	Endometrioid adenocarcinoma. Positive EGFR stain	133
Fig. 42	Moderately to poorly differentiated endometroid carcinoma. Positive EGFR stain	134
Fig. 43	Poorly differentiated carcinoma. Positive EGFR stain.	134
Fig. 44	Endometrioid adenoacanthoma. Positive EGFR stain	135
Fig. 45	Papillary serous carcinoma. Positive EGFR stain	135
Fig. 46	Clear cell carcinoma	136
Fig. 47	Endometrioid Carcinoma deeply infiltrated in the myometrium	136
Fig. 48	Metastatic endometroid carcinoma (Omentum)	137
Fig. 49	MMMT. Positive EGFR stain	137
Fig. 50	Another case of MMMT Negative EGFR stain	138

LIST OF ABBREVIATIONS

CK: Cytokeratin

CIN: Cervical Intraepithelial Neoplasia

D & C: Dilatation and Curretage

DAB: Diamenobenzidine Chromogen Solution

EGF: Epidermal Growth Factor

EGF: Epidermal Growth Factor

EGF: Epidermal Growth Factor

EGFR: Epidermal Growth Factor Receptor

FGF: Fibroblast Growth Factor

FIGO: International Federation of Obstetrics and Gynecology

GF: Growth Factors

Gr. Fract.: Growth Fraction

GTP: Guanithedin Tri Phosphate

H & E: Heamatoxylin and Eosin

HMK: High Molecular Weight Keratin

IGF-I: Insulin-like Growth Factor type I

IGF-II: Insulin-like Growth Factor type II

IHC: Immunohistochemistry

ISGP: International Society of Gynecological Pathologist

LMK: Low Molecular Weight Keratin

MAB: Monoclonal Antibody

viii

MIF: Macrophage Inhibitory Factor

MMMT: Malignant Mixed Mullerian Tumor

NGF: Nerve Growth Factor

PBS: Phosphate Buffer Saline

PCNA: Proliferating Cell Nuclear Antigen

PDGF: Platelet Derived Growth Factor

TGF-α: Transforming Growth Factor-α

TGF-β: Transforming Growth Factor-β

VIN: Vulval Intra-epethelial Neoplacia

WHO: World Health Organization