Endometrial Histopathology, Estrogen Receptor and Progesterone Receptor Expression in Women with Abnormal Uterine Bleeding in the Reproductive Age: A Cross-Sectional Comparative Study

Thesis

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By

Ahmed Mahmoud Ibrahim Mostafa

M.B.,B.Ch Ain Shams University 2014

Resident of Obstetrics&Gynecology in Dar Elshefa hospital

Supervised by

Dr. Alaa El-Din Hamed El-Feky

Professor of Obstetrics & Gynecology

Faculty of Medicine, Ain Shams University

Dr. Ragaa Amin Fawzy

Professor of Pathology

Faculty of Medicine, Ain Shams University

Dr. Nashwa El-Said Hassan

Professor of Obstetrics & Gynecology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2018

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Ahmed Mahmoud Ibrahim Mostafa

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List of Abbreviations

AF.....	Activation function
AF1.....	Activation function 1
AF2.....	Activation function 2
AUB	Abnormal uterine bleeding
AUB-A.....	Abnormal uterine bleeding due to adenomyosis
AUB-C.....	Abnormal uterine bleeding due to coagulopathies
AUB-E	Abnormal uterine bleeding due to local causes in the endometrium
AUB-I.....	Iatrogenic abnormal uterine bleeding
AUB-L....	Abnormal uterine bleeding due to leiomyoma
AUB-M…….	Abnormal uterine bleeding due to Malignancy and hyperplasia
AUB-N.....	Not classified abnormal uterine bleeding
AUB-O.....	Abnormal uterine bleeding due to ovulatory dysfunction
AUB-P.....	Abnormal uterine bleeding due to polyps
bFGF	Basic fibroblast growth factor
CDKs.....	Cyclin dependent kinases
DNA.....	Deoxyribonucleic acid
DUB…….	Dysfunctional uterine bleeding
E1	Estrone
E2	Estradiol
EIN.....	Endometrial intraepithelial neoplasia
eNOS.....	Endothelial nitric oxide synthase

List of Abbreviations(Cont.)

ER	Estrogen receptor
ERs	Estrogen receptors
ERT	Estrogen replacement therapy
ER-α	Estrogen receptor alpha
ER-β	Estrogen receptor beta
ESR1	Estrogen receptor gene 1
ESR2	Estrogen receptor gene 2
FIGO	International Federation of Gynecology and Obstetrics
FOS	A gene on chromosome 14q24.3 named after Finkel-Biskis JinkinsmurineOsteogenicsarcoma
FSH……..	follicle stimulating hormone
GNRH	Gonadotrophin releasing hormone
H&E	Hematoxylin and eosin stain
hCG	Human chorionic gonadotrophins
hIFN-β.....	Human interferon beta
hpf…….	High power filed
HSP 90	Heat shock protein 90
IUD.....	Intrauterine device
kDa	Kilo Daltons
miRNA	Micro ribonucleic acid
mRNA	Messenger ribonucleic acid
PA.....	Pure progesterone receptor antagonists
PBS.....	Phosphate buffered saline
PDGF	PLATELET derived growth factor

List of Abbreviations (Cont.)

PGE……..	Prostaglandin E
PGF……..	Prostaglandin F
pH.....	Percentage hydrogen
PR	Progesterone receptors
PR-A.....	Progesterone receptor A
PR-B.....	Progesterone receptor B
PRM	Progesterone receptor modulators
SD.....	Standard deviation
SERMs	Selective estrogen receptor modulators
SPRM.....	Selective progesterone receptor modulators
Src	is a family of non-receptor tyrosine kinases
TAF3	Transcription activating factor 3
U/S	Ultrasonography
VEGF	Vascular endothelial growth factor
WHO	World health organization

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PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE INOBSTETRICS & GYNECOLOGY

Title of the Protocol: Endometrial Histopathology and Estrogen Receptor, Progesterone Receptor Expression in Womenwith Abnormal Uterine Bleeding in the Reproductive Age: A crosssectional comparative study

Postgraduate Student: Ahmed Mahmoud Ibrahim Mostafa

Degree: M.B.B.Ch

DIRECTOR: ALAA EL.DIN HAMED EL.FEKY

Academic Position: Professor

Department: Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University

Co-DIRECTOR: RAGAA AMIN FAWZY

Academic Position: Professor

Department: Pathology, Faculty of Medicine, Ain Shams University

Co-DIRECTOR: NASHWA EL.SAID HASSAN

Academic Position: Assistant Professor

Department: Obstetrics &Gynecology, Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2017

What is already known on this subject? AND

What does this study add?

Abnormal uterine bleeding may be associated with different histo-pathological patterns and change in the Estrogen and Progesterone receptors expression**.**

This study will differentiate between histopathology and estrogen and progesterone receptors expression in normal women versus women with abnormal uterine bleeding**.**

1. INTRODUCTION

Abnormal uterine bleeding formerly known as dysfunctional uterine bleeding is irregular uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy thus reflecting a disruption of the normal cycling pattern of the ovulatory hormones (**Takreem et al**., **2009**)**.**

Abnormal uterine bleeding is one of the most common morbidities that require women to seek medical attention in gynecology outpatient clinics**.** It is unlike the menstrual bleeding in duration and amount**.** Most commonly in the form of menorrhagia (32%) and perimenopausal bleeding (28 %) (**Nicula et al., 2017**)**.**

Abnormal uterine bleeding can be presented as menorrhagia, polymenorrhagia, metrorrhagia, menometrorrhagia or spotting**.** Menorrhagia represents bleeding at regular intervals but in larger amounts and longer duration than normal cycle**.**Polymenorrhagia represents bleeding at shorter intervals than normal and also in

excessive amounts**.** Meanwhile, Metrorrhagia is irregular bleeding pattern**.** Menometrorrhagia mixed irregularity in pattern and excessiveness**.**

In June 2011 International Federation of Gynecology and Obstetrics (FIGO) gave PALM COEIN classification of abnormal uterine bleeding for non-gravid women in reproductive age groups**.**

PALM stands for **P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy and hyperplasia**.**

COEIN stands for **C**oagulopathy, **O**vulatory Disorder **E**ndometrium, **I**atrogenic and **N**ot Classified **(Munro et al., 2011).**

PALM group is structural and can be diagnosed by imaging techniques, and/or by histopathology**.** However, **COEIN** group contains entities that cannot be diagnosed by imaging or histopathology alone

Other investigations and proper clinical history will help in further classifying the COEIN group**(Munro et al., 2011).**

AUB**.**E is diagnosis of exclusion and at present no specific test is available to diagnose this group**.** It is mostly due to any one of these mechanisms: Estrogen breakthrough bleeding, Estrogen withdrawal bleeding or Progesterone breakthrough bleeding **(Speroff et al., 1994).**

Estrogen and progesterone hormones are mainly produced by the ovary in fluctuating patterns throughout the ovarian cycle under the effect of the gonadotrophic FSH, LH hormones released from the anterior pituitary gland**.** They directly control the uterine cycle with their effect on the endometrium during its proliferative and secretory

phase respectively**.**

They work by acting on specific nuclear receptor proteins; Estrogen Receptor (ER) and Progesterone Receptor (PR)**.** These receptors are present in endometrial stromal and glandular cells **(Clark, 1979).**

Estrogen (ER) and Progesterone (PR) receptors are placed in nuclear steroid receptor superfamily **(Mylonas et al., 2005).** They mediate their effect through intraand extranuclear receptors**.**

ER exists in 2 main forms, ER-αand ER-β**(Klinge, 2001).**

PR receptor occurs in PR A and PR B **(Clark, 1979).**

Assessment of the receptors can be done by Immunohistochemistry IHC technique, which aids in assessing tissue distribution and intensity of the receptors in glandular and stromal cells **(Press, 1988).**

IHC may be a useful investigation, which can be used along with pelvic ultrasound and histopathology of endometrial biopsies in diagnosis and management of AUB in reproductive age group**.**

2.**AIM/ OBJECTIVES**

To compare between the histomorphological classification and the estrogen and the progesterone receptors distribution in the endometrium of normal women vs**.** women with abnormal uterine bleeding**.**

3. METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods

Womenbetween the age of **20 and 40 years** will be included in this study**.**

Type of the study

Cross sectional comparative study**.**

Study settings

The study will be conducted at Ain Shams University maternity hospital inpatient units and the gynecology outpatient clinic**.**

Sample size

60: 30 cases per group

Sample size justification

Sample size was calculated using PASS®version 11 program, setting the type one error (α) at 0**.**05 (95% confidence interval and the power (1**.**β) at 0**.**8 results from a previous study **(Pieczyńska et al., 2011)**showed that ER score among control was 5**.**5 ± 3**.**6, while among RPL it was 12**.**1±7**.** calculation according to this values produced a minimal sample size of 15 cases per group **(Hintze et al., 2011).**

Study population

60 patients will be included in this study