

# بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ



HOSSAM MAGHRABY



# شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



HOSSAM MAGHRABY

# جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم  
قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغييرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HOSSAM MAGHRABY



بعض الوثائق

الأصلية تالفة



HOSSAM MAGHRABY



بالرسالة صفحات

لم ترد بالأصل



HOSSAM MAGHRABY

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

"وقل رب زدني علما"

بِسْمِ اللَّهِ  
الرَّحْمَنِ الرَّحِيمِ

**GONADOTROPINS STEP-DOWN  
PROTOCOL FOR OVULATION  
INDUCTION IN POLYCYSTIC  
OVARIAN DISEASE**

B 1449E

*Thesis*  
*submitted to the Faculty of Medicine,*  
*University of Alexandria,*  
*in partial fulfillment of the requirements*  
*of the degree of*

**MASTER OF  
OBSTETRICS AND GYNAECOLOGY**

*By*  
**AMR MAHMOUD KHALIL**  
MBBCh Alex

*FACULTY OF MEDICINE*  
*UNIVERSITY OF ALEXANDRIA*

**2000**

## ***SUPERVISORS***

***Prof. Dr. Hassan Ahmed El-Damarawy***

*Professor of Obstetrics and Gynaecology,*

*Faculty of Medicine*

*University of Alexandria.*

***Prof. Dr. Moustafa Abdel Monem kamal***

*Professor of Obstetrics and Gynaecology,*

*Faculty of Medicine*

*University of Alexandria.*

***Dr. Emad El-Din Abdel Rhman Kalifa***

*Assistant Professor of Obstetrics and Gynaecology,*

*Faculty of Medicine,*

*University of Alexandria.*

# ACKNOWLEDGMENT

*Praise to be done to ALLAH, most merciful and most compassionate, without his help nothing could be reached.*

*Words cannot adequately express the feelings of gratitude I have for All those who helped me to complete this work,*

*I wish to express my deepest gratitude and appreciation to Prof. Dr. Hassan El Damarawy, Professor of obstetrics and Gynecology, Faculty of Medicine, University of Alexandria, for supervising this work, for his valuable advises, and his fatherly attitude.*

*I gratefully acknowledge Prof. Dr. Moustafa Kamel, Professor of obstetrics and Gynecology, Faculty of Medicine, University of Alexandria, for his meticulous supervision, intellectual stimulation and encouragement were of major help in the accomplishment of this work,*

*I wish to thank cordially and express my gratitude to Ass. Prof. Dr. Emad Kalifa, Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, University of Alexandria, for his encouragement throughout the research program, and for the time spent and interest shown in all aspects of this work whether technical details or theoretical background.*

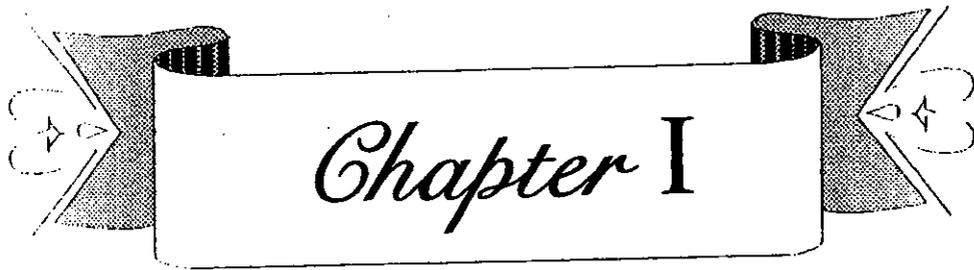
*Lastly my gratitude to all members of my Family, their heartily support which helped me to accomplish this work,*

# CONTENTS

<b>Chapter</b>	<b>Page</b>
I. INTRODUCTION . . . . .	1
II. AIM OF THE WORK . . . . .	37
III. MATERIALS . . . . .	38
IV. METHODS . . . . .	40
V. RESULTS . . . . .	45
VI. DISCUSSION . . . . .	65
VII. SUMMARY . . . . .	74
VIII. CONCLUSION AND RECOMMENDATIONS . . . . .	79
IX. REFERENCES . . . . .	81

PROTOCOL

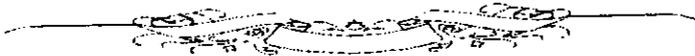
ARABIC SUMMARY



*Chapter I*



# **INTRODUCTION**



# INTRODUCTION

## Reproductive Physiology

Follicular growth and development is a dynamic process beginning from infancy and continuing up to around menopause. There is a large reservoir of primordial follicles stored within each ovary and these follicles undergo a continuous process of growth and atresia, which is independent of gonadotrophic hormonal influences. From this large pool of ovarian primordial follicles only 400 follicles will ovulate during the woman reproductive years.<sup>(1)</sup>

With the beginning of each new cycle trophic hormones and autocrine/paracrine peptides sequentially stimulate the ovarian pool of inactive follicles leading to recruitment of a cohort of primordial follicles which will undergo initial growth. After serious competition only one follicle will succeed, it is the leading follicle. It will pass through a series of stages from a primordial follicle, preantral, antral to the preovulatory follicle which is destined to ovulate.<sup>(2)</sup>

## Follicular Phase

The demise of the corpus luteum in the luteal follicular transition results in a nadir in the circulating levels of estradiol, progesterone and inhibin-A.<sup>(3)</sup> The decrease in the circulating level of Inhibin-A removes a suppressing influence on the FSH secretion in the pituitary.<sup>(4)</sup>

The decrease in the progesterone and estradiol allow a progressive rapid increase in the frequency of GnRH pulsatile secretion and a removal of the pituitary from negative feedback suppression.<sup>(5)</sup>

**Activin** is a peptide related to inhibin but has an opposite action to inhibin. Activin secretion from the immature follicles begins in the late luteal phase to reach a peak in the early follicular phase.<sup>(6)</sup>

The late luteal corpus luteum decline of steroidogenesis and inhibin-A secretion is associated with early follicular increase production of activin and all these factors favor increased secretion of FSH a few days before menses.<sup>(7)</sup> The rising level of FSH will recruit a cohort of follicles. Without the appearance and persistence of an increase in the circulating FSH level, this cohort of follicles will be doomed to atresia and apoptosis (programmed

cell death, which is a physiological mode of natural cell death in contrast to the pathological cell death of necrosis).<sup>(8)</sup>

The gonadotropin independent follicular development results in an increase in the size of the primordial follicle, a process of maturation rather than growth. Primordial follicle is then transformed into primary preantral follicle. This process of follicular growth is continuous under all physiological circumstances, independent on FSH, and is correlated with increased production of estrogen and inhibin B.<sup>(9)</sup> Inhibin B begin to be secreted by the granulosa cells in the early follicular phase and reach a midfollicular peak then decreases in the late follicular before ovulation.<sup>(10)</sup>

The binding of FSH to its receptors on the granulosa cells stimulates their growth and initiates steroidogenesis via activation of the aromatase enzyme (converts androgens to estrogen) and mediation the expression of multiple mRNAs (encodes for the proteins responsible for cell proliferation).<sup>(11)</sup>

Together FSH with estrogen exert a mitogenic action on the granulosa cells stimulating their proliferation which in turn causes rapid accumulation and increase in the number of FSH receptors.<sup>(12)</sup> Despite the fact that only a subpopulation of granulosa cells can bind the FSH via their receptors,

signal is transmitted to the neighbouring cells with initiation of FSH actions in these cells. This system of communication promote synchronous and coordinated performance throughout the follicle.<sup>(13)</sup>

Under the synergistic effect of both FSH (Gonadotropin dependant stage) and estrogen there is continued follicular growth with development of the antral follicle containing the primary oocyte. The antral follicle is filled with follicular fluid containing a high concentration of estrogen, and is surrounded by multilayers of granulosa cells, well established theca interna and externa cell layers.<sup>(14)</sup>

### **The Two cell, Two Gonadotropin system**

As FSH stimulates preantral follicular development into antral follicle in the midfollicular phase it induce the expression of theca cells genes for synthesis of LH receptors, P450 scc and 3 B-hydroxysteroid dehydrogenase enzyme system formation.<sup>(15)</sup> This action is primed by activin which increases the follicle receptivity by inducing both FSH and LH receptors formation on the granulosa and thecal respectively.<sup>(6)</sup>

The rising estradiol produced from the preantral follicle exerts a positive stimulatory feedback effect on LH which in turn begins to act on its newly formed receptors.<sup>(16)</sup> The LH receptors are present only on the