

**Augmentation of Folliculogenesis by the Use
of Micro-Dose Human Chorionic
Gonadotropin (HCG) In Resistant Polycystic
Ovary Syndrome (PCOS) Patients**

*Thesis
Submitted for partial fulfillment of
Master Degree in Obstetrics and Gynecology*

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٢٠٠٨

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LIST OF ABBREVIATIONS

AC	<u>A</u> denylyl <u>C</u> yclase
ASNs	<u>A</u> drenal <u>A</u> ndrogen <u>S</u> ecreting <u>N</u> eoplasm
ASRM	<u>A</u> merican <u>S</u> ociety for <u>R</u> eproductive <u>M</u> edicine
AES	<u>A</u> ndrogen <u>E</u> xcess <u>S</u> ociety
AACE	<u>A</u> merican <u>A</u> ssociation of <u>C</u> linical <u>E</u> ndocrinologists
AUC	<u>A</u> rea <u>U</u> nder the <u>C</u> urve
17 β -HSD	17 β <u>h</u> ydroxysteroid <u>d</u> ehydrogenase
17 β –HSD	17 β - <u>h</u> ydroxysteroid <u>d</u> ehydrogenase enzyme
cAMP	<u>c</u> yclic <u>A</u> denosine <u>M</u> ono <u>P</u> hosphate
CBG	<u>C</u> orticosteroid- <u>B</u> inding <u>G</u> lobulin
CC	<u>C</u> lomiphene <u>C</u> itrate
CRA	<u>C</u> C- <u>R</u> esistant <u>A</u> novulation
CCF	<u>C</u> C <u>F</u> ailure
COS	<u>C</u> ontrolled <u>O</u> varian <u>S</u> timulation
DNA	<u>D</u> eoxyribo <u>n</u> ucleic <u>a</u> cid
ESHRE	<u>E</u> uropean <u>S</u> ociety for <u>H</u> uman <u>R</u> eproduction and <u>E</u> mbryology
E γ	<u>E</u> stradiol

FSH	<u>F</u>ollicular <u>S</u>timulating <u>H</u>ormone
GnRH	<u>G</u>onadotropin <u>R</u>eleasing <u>H</u>ormone
GnSAF	<u>G</u>onadotropin <u>S</u>urge-<u>A</u>ttenuating <u>F</u>actor.
GDP	<u>G</u>uanosine <u>d</u>iphosphate
GTP	<u>G</u>uanosine <u>t</u>riphosphate
GLUT-4	<u>G</u>lucose <u>t</u>ransporter 4
GC	<u>G</u>ranulosa <u>c</u>ells
HDL-C	<u>H</u>igh <u>D</u>ensity <u>L</u>ipoprotein <u>C</u>holesterol
hMG	<u>h</u>uman <u>M</u>enopausal <u>G</u>onadotropin
hCG	<u>h</u>uman <u>C</u>horionic <u>G</u>onadotropin
IGF-1	<u>I</u>nsulin-like <u>G</u>rowth <u>F</u>actor 1
IRS-1	<u>I</u>nsulin <u>R</u>eceptor <u>S</u>ubstrate 1
IGFBP-1	<u>I</u>nsulin-like <u>g</u>rowth <u>f</u>actor-<u>b</u>inding <u>P</u>rotein-1
KEGG	<u>K</u>yoto <u>E</u>ncyclopedia of <u>G</u>enes and <u>G</u>enomes
LH	<u>L</u>eutinising <u>H</u>ormone
LDL-C	<u>L</u>ow <u>D</u>ensity <u>L</u>ipoprotein <u>C</u>holesterol
LEO	<u>L</u>aparoscopic <u>E</u>lectrocautery of the <u>O</u>varies
LIF	<u>L</u>eukemia <u>I</u>nhibitory <u>F</u>actor
mRNA	<u>M</u>essenger <u>R</u>ibonucleic <u>A</u>cid
MMP	<u>M</u>atrix <u>M</u>etalloproteinases
NCAH	<u>N</u>onclassic <u>A</u>drenal <u>H</u>yperplasia
NIH	<u>N</u>ational <u>I</u>nstitutes of <u>H</u>ealth
NICHD	<u>N</u>ational <u>I</u>nstitute of <u>C</u>hild Health and <u>H</u>uman <u>D</u>evelopment
NICE	<u>N</u>ational <u>I</u>nstitute for <u>C</u>linical <u>E</u>xcellence

OHSS	<u>O</u> varian <u>H</u> yperstimulation <u>S</u> ndrome
P ₄₅ ·scc	<u>C</u> holesterol <u>s</u> ide <u>c</u> hain <u>c</u> leavage
P ₄₅ ·arom	<u>A</u> romatase enzyme
PKA	<u>P</u> rotein <u>k</u> inase <u>A</u>
PCOS	<u>P</u> olycystic <u>O</u> vary <u>S</u> ndrome
PI ³ K	<u>P</u> hosphatidylinositol <u>γ</u> - <u>k</u> inase
P ₄	<u>P</u> rogesteron
RCOG	<u>R</u> oyal <u>C</u> ollege of <u>O</u> bstetricians and <u>G</u> ynaecologists
RPSGB	<u>R</u> oyal <u>P</u> harmaceutical <u>S</u> ociety of <u>G</u> reat <u>B</u> ritain
ROC	<u>R</u> eciever <u>O</u> perating <u>C</u> haracteristics
RCT	<u>R</u> andomized <u>C</u> ontrolled <u>T</u> rials
rFSH	<u>R</u> ecombinant FSH
rLH	<u>R</u> ecombinant LH
rhCG	<u>R</u> ecombinant hCG
SHBG	<u>S</u> ex <u>H</u> ormone- <u>B</u> inding <u>G</u> lobulin
SNPs	<u>S</u> ingle <u>N</u> ucleotide <u>P</u> olymorphisms
TIMP	<u>T</u> issue inhibitors of <u>m</u> atrix-metalloproteinases
uFSH	<u>u</u> rinary FSH
VEGF	<u>V</u> ascular <u>E</u> ndothelial <u>G</u> rowth <u>F</u> actor
WHO	<u>W</u> orld <u>H</u> ealth <u>O</u> rganization

LIST OF TABLES

Table No.	Title	Page No.
۱	Criteria for defining PCOS	۳۸
۲	Candidate genes demonstrating some evidence of linkage or association with PCOS or component traits of PCOS.	۵۳
۳	History of important developments in the production of exogenous gonadotropins.	۱۰۶
۴	Socio-demographic data of group ۱ & ۲	۱۳۱
۵	Base line hormonal profile (FSH, LH & Prolactin) in the second day of the cycle of group ۱ & ۲	۱۳۳
۶	Estradiol level at time of hCG triggering or cycle cancellation (ovulatory and total) in group ۱ & ۲	۱۳۵
۷	Progesterone level at time of hCG triggering or cycle cancellation (ovulatory and total) and progesterone level at ۲۱ st day of the cycle (ovulatory and total) in group ۱ & ۲	۱۳۳
۸	Endometrial line (mm) (ovulatory & total) and Day of follicle reaching ۱۸-۲۰ mm	۱۳۹
۹	Ovulation rate and Pregnancy rate in group ۱ & ۲	۱۴۱
۱۰	Number of follicle reaching ۱۸-۲۰ mm in group ۱ & ۲	۱۴۳

LIST OF FIGURES

Fig. No.	Title	Page No.
١	Control system of the menstrual cycle. Modified from Mammakarzinom-info.de (٢٠٠٦).	١١
٢	Model scheme for LH synthesis and release.	١٧
٣	Model scheme for FSH synthesis and release.	١٧
٤	Follicular development, modified from Mammakarzinom-info.de (٢٠٠٦)	٢٢
٥	Two cell theory (Chabbert-Buffet and Bouchard, ٢٠٠٢).	٢٢
٦	KEGG PATHWAY Database, ٢٠٠٦	٣٠
٧	Phenotypes of PCOS: Relationship between degree of B cells functions but not severity of insulin resistance	٤٢
٨	Pharmacodynamics of Clomiphene Citrate	٨٧
٩	A nomogram predicting live birth after clomiphene citrate (CC) treatment in normogonadotropic anovulatory infertility	١٠٢

LIST OF FIGURES (Conten.)

Fig. No	Title	Page No.
୧୦	Hypothetical model of hCG directly regulating human implantation	୧୨୦
୧୧	Socio-demographic data of group ୧ & ୨	୧୨୨
୧୨	Base line hormonal profile (FSH, LH &Prolactin) of group ୧ & ୨	୧୨୧
୧୩	Estradiol level (total & ovulatory) at time of hCG triggering or cycle cancellation	୧୨୩
୧୪	P ^୧ levels at time of hCG triggering or cycle cancellation (ovulatory & total) and at ୨୧ st day of the cycle (ovulatory & total).	୧୨୪
୧୫	Endometrial line (mm) (ovulatory & total) and Day of follicle reaching ୧୪-୨୦ mm	୧୨୫
୧୬	Ovulation rate, Pregnancy rate in group ୧&୨	୧୨୬
୧୭	Number of follicle reaching ୧୪-୨୦ mm in group ୧&୨	୧୨୭

LIST OF CONTENTS

Title	Page No.
Acknowledgment.....	I
List of Abbreviations.....	III
List of tables.....	VI
List of figures.....	VII
English Protocol.....	X
Arabic Protocol.....	XXVII
Introduction.....	١
Aim of the work.....	٨
Review.....	٩
Patients & Methods.....	١٢٥
Results.....	١٢٩
Discussion.....	١٣٨
Summary & Conclusion.....	١٤٩
Recommendations.....	١٥٥
References.....	١٥٦
Arabic Summary.....	١٧٧

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٢٠٠٧

INTRODUCTION

Most couples desire pregnancy after marriage, but only 80 to 90% of them can achieve pregnancy within 12 to 18 months of regular unprotected intercourse. (Kelestimur *et al*, 2000)

There are numerous causes of infertility, approximately 40% of infertility is due to female factor, and anovulation constitutes about 40% of female infertility. (Sperof *et al*, 1999)

The WHO had classified anovulatory women into three categories:

Group I (hypogonadotropic hypo gonadal anovulation): Those for whom the ovaries fail to function properly because of decreased signals from the brain (Hypothalamic or Pituitary). Typically the pituitary hormone FSH is low in these patients. This may be due to excessive exercise, disorders of inadequate weight such as Anorexia nervosa, tumors of the hypothalamus or pituitary, or a rare disorder called Kallman's syndrome.

Group II (Normogonadotropic normoestrogenic anovulation): Patients with Polycystic Ovary Syndrome (PCOS).

Group III (Hypergonadotropic hypoestrogenic anovulation): Patients with intrinsic ovarian failure. These patients will have an elevated FSH and may include premature ovarian failure, prior surgery or irradiation, or advancing age. **(Stephen, ٢٠٠٠)**

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with a prevalence of approximately ٤-٦%. Its cardinal features are hyperandrogenism and polycystic ovaries. **(Laven *et al*, ٢٠٠٢)**

Clinically, PCOS is characterized by menstrual irregularities, hyperandrogenism, hyperinsulinemia, and long-term metabolic disturbances such as diabetes mellitus, cardiovascular disease, and dyslipidemias. **(Dunaif, ١٩٩٥)**

During the Rotterdam Conference of ٢٠٠٣, a revision of the diagnostic criteria the US National

Institutes of Health conference initially proposed in 1990 was made in order to include the findings of polycystic ovaries and recommended that at least two of the following three features are required for PCOS to be diagnosed:

1-Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea.

2-Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess).

3-Polycystic ovaries (as defined on ultrasonography as 12 or more follicles in at least 1 ovary measuring 2-9 mm in diameter or a total ovarian volume of $>10\text{ cm}^3$). (**Fauser et al, 2004**)

How polycystic ovary syndrome (PCOS) is associated with anovulatory cycles has not been completely elucidated. Two associations with this disease entity are theorized to be at least somewhat responsible for its development. The first is the persistent elevation of LH levels in these patients; the second is the apparent arrest of antral follicle development at the antral to

10-mm stage and consequent failure to enter the preovulatory phase of the cycle. This evidence indicates that the disturbance is mainly a central defect that initiates the cascade of events leading to its onset. (Franks *et al*, 1998)

The most common prescribed drug for anovulation is clomiphene citrate (CC). It is a triphenylethylene and is a nonsteroidal estrogenic-like compound distantly related to diethylstilbestrol. Paradoxically, these compounds are both estrogen agonists and antagonists. However, in almost all circumstances, clomiphene acts purely as an antagonist or antiestrogen. The similarity to estrogen, however, is sufficient to achieve uptake and binding by estrogen receptors. Clomiphene acts to modify the hypothalamic activity and ultimately reduce the concentration of intracellular estrogen receptors by inhibiting the process of receptor replenishment. When exposed to clomiphene, the hypothalamic-pituitary axis becomes blind to the endogenous estrogen levels in circulation, negative feedback is diminished and the neuroendocrine mechanism for GnRH secretion is