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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LIST OF ABREVIATIONS

AC	**Adenylyl Cyclase**
ASNs	**Adrenal Androgen Secreting Neoplasm**
ASRM	**American Society for Reproductive Medicine**
AES	**Androgen Excess Society**
AACE	**American Association of Clinical Endocrinologists**
AUC	**Area Under the Curve**
٣β-HSD	**٣ β hydroxysteroid dehydrogenase**
١٧β –HSD	**١٧ β -hydroxysteroid dehydrogenase enzyme**
cAMP	**cyclic Adenosine MonoPhosphate**
CBG	**Corticosteroid-Binding Globulin**
CC	**Clomiphene Citrate**
CRA	**CC-Resistant Anovulation**
CCF	**CC Failure**
COS	**Controlled Ovarian Stimulation**
DNA	**Deoxyribonucleic acid**
ESHRE	**European Society for Human Reproduction and Embryology**
E٢	**Estradiol**

FSH	**Follicular Stimulating Hormone**
GnRH	**Gonadotropin Releasing Hormone**
GnSAF	**Gonadotropin Surge-Attenuating Factor.**
GDP	**Guanosine diphosphate**
GTP	**Guanosine triphosphate**
GLUT-٤	**Glucose transporter ٤**
GC	**Granulosa cells**
HDL-C	**High Denisty Lipoprotien Cholesterol**
hMG	**human Menopausal Gonadotropin**
hCG	**human Chorionic Gonadotropin**
IGF-٢	**Insulin-like Growth Factor ٢**
IRS-١	**Insulin Receptor Substrate ١**
IGFBP-١	**Insulin-like growth factor-binding Protein-١**
KEGG	**Kyoto Encyclopedia of Genes and Genomes**
LH	**Leutinising Hormone**
LDL-C	**Low Denisty Lipoprotien Cholesterol**
LEO	**Laparoscopic Electrocautery of the Ovaries**
LIF	**Leukemia Inhibitory Factor**
mRNA	**Messenger Ribonucleic Acid**
MMP	**Matrix Metalloproteinases**
NCAH	**Nonclassic Adrenal Hyperplasia**
NIH	**National Institutes of Health**
NICHD	**National Institute of Child Health and Human Development**
NICE	**National Institute for Clinical Excellence**

OHSS	**Ovarian Hyperstimulation Syndrome**
P٤٥٠ scc	**Cholesterol side chain cleavage**
P٤٥٠arom	**Aromatase enzyme**
PKA	**Protein kinase A**
PCOS	**Polycystic Ovary Syndrome**
PI٣K	**Phosphatidylinositol ٣-kinase**
P٤	**Progesteron**
RCOG	**Royal College of Obstetricians and Gynaecologists**
RPSGB	**Royal Pharmaceutical Society of Great Britain**
ROC	**Reciever Operating Characteristics**
RCT	**Randomized Controlled Trials**
rFSH	**Recombinant FSH**
rLH	**Recombinant LH**
rhCG	**Recombinant hCG**
SHBG	**Sex Hormone-Binding Globulin**
SNPs	**Single Nucleotide Polymorphisms**
TIMP	**Tissue inhibitors of matrix-metalloproteinases**
uFSH	**urinary FSH**
VEGF	**Vascular Endothelial Growth Factor**
WHO	**World Health Organization**

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Augmentation of folliculogenesis by the use of micro-dose human chorionic gonadotropin (hCG) in resistant polycystic ovary syndrome (PCOS) patients

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INTRODUCTION

Most couples desire pregnancy after marriage, but only ٨٥ to ٩٠% of them can achieve pregnancy within ١٢ to ١٨ months of regular unprotected intercourse. (**Kelestimur *et al*, ٢٠٠٠**)

There are numerous causes of infertility, approximately ٤٠% of infertility is due to female factor, and anovulation constitutes about ٤٠% of female infertility. (**Sperof *et al,* ١٩٩٩**)

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 ١٩٩٠ 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:

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

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

٣-Polycystic ovaries (as defined on ultrasonography as ١٢ or more follicles in at least ١ ovary measuring ٢-٩ mm in diameter or a total ovarian volume of >١٠ $cm^{٣}$). **(Fauser *et al*, ٢٠٠٤)**

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 ٥- to

١٠-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*, ١٩٩٨**)

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