LETROZOLE INDUCTION OF OVULATION IN WOMEN WITH CLOMIPHENE CITRATE-RESISTANT POLYCYSTIC OVARY

Thesis

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بسم الله الرحمن الرحيم

وَأَنْزَلَ اللهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا

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List of Abbreviations

11β-HSD	*11β hydroxysteroid dehydrogenase*
3β-HSD	*3β hydroxysteroid dehydrogenase*
AA	*Amino acid*
ACTH	*Adrenocorticotropic hormone*
AES	*Androgen Excess Society*
AI	*Aromatase inhibitor*
AKt	*Protein kinase B*
AMH	*Antimullerian hormone*
AMHRII	*Antimullerian hormone receptors type II*
AR	*Androgen receptor*
ART	*Assisted reproduction techniques*
ASRM	*American Society for Reproductive Medicine*
BMI	*Body mass index*
CA	*Cyproterone acetate*
CAH	*Congenital adrenal hyperplasia*
CAPN 10	*Calpain 10*
CC	*Clomiphen citrate*
CNS	*Central nervous system*
COH	*Controlled ovarian hyperstimulation*
CVS	*Cardiovascular system*
CYP11α	*Cytochrome p-45011α*
CYP17	*Cytochrome P-450c17*
CYP17α1	*17α-hydroxylase/17,20 lyase*
DES	*Diethylstilbestrol*
DHEA	*Dehydroepiandrosterone*

DHEA-S	*Dehydroepiandrosterone sulphate*
DM	*Diabetes mellitus*
DUB	*Dysfunction uterine bleeding*
E_1	*Estrone*
E_2	*Estradiole*
EE	*Ethinyl estradiol*
ER	*Estrogen receptor*
ERα	*Estrogen receptor α*
ERβ	*Estrogen receptor β*
ERγ	*Estrogen receptor gamma*
ESHRE	*European Society for Human Reproduction and Embryology*
FDA	*Food and Drug Administration*
FFA	*Free fatty acids*
FSH	*Follicle stimulating hormone*
FST	*Follistatin*
GIT	*Gastrointestinal tract*
GnRH	*Gonadotropin releasing hormone*
GT	*Glucose tolerance*
GT4	*Glucose transporter-4*
H6PD	*Hexose-6-phosphate dehydrogenase*
HA	*Hypothalamic amenorrhea*
HCG	*Human chorionic gonadotropin*
HDL	*High density lipoprotein*
hMG	*Human menopausal gonadotropin*
HSG	*Hysterosalpingography*
IGF-1	*Insulin like growth factor 1*
IGF-1Rs	*Inulin-like growth factor 1 receptors*
IGT	*Impaired glucose tolerance test*

INSR	*Insulin receptor region*
IR	*Insulin receptor*
IRS	*Insulin receptor substrate*
IRS-1	*Insulin receptor substrate 1*
IRS-2	*Insulin receptor substrate 2*
IRα	*Insulin receptor α*
IRβ	*Insulin receptor β*
IUI	*Intrauterine insemination*
IVF	*In vitro fertilization*
IVNTR	*Insulin variable number tandem repeats*
LDL	*Low density lipoprotein*
LH	*Leutinizing hormone*
LOD	*Laparoscopic ovarian drilling*
LOS	*Laparoscopic ovarian surgery*
LP	*Luteal phase*
LPD	*Luteal phase defect*
MAP	*Mitogen activated protein*
MFO	*Multifollicular ovary*
MPA	*Medroxy progesterone acetate*
NIH	*National Institutes of Health*
OCPs	*Oral contraceptive pills*
OGTT	*Oral glucose tolerance test*
OHS	*Ovarian hyperstimulation*
OHSS	*Ovarian hyperstimulation syndrome*
OSA	*Obstructive sleep apnea*
P1	*Initial mid luteal serum progesterone*

P2	*Mid luteal serum progesterone of ovulation induction*
P450 arom	*Aromatase cytochrome P450*
P450 C17	*17α hydroxylase-17, 20 lyase*
P450scc	*Cholesterol side chain cleavage*
PAT-1	*Plasminogen activator type 1*
PCOM	*Polycystic ovary morphology*
PCOS	*Polycystic ovary syndrome*
PI3K	*Phosphatidylinositol 3-kinase*
PKA	*Protein kinase A*
PPAR γ	*Peroxisome-proliferator activated receptor γ*
PPP1R3	*Protein phosphatase 1 regulatory subunit*
PR	*Pregnancy rate*
SERM	*Selective estrogen receptor modulators*
SHBG	*Sex hormone binding globulin*
StAR	*Steroid acute regulatory protein*
T	*Testosterone*
TAF-1	*Transcription activation function*
TB	*Tuberculosis*
TGF-β	*Transforming growth factor β*
TNFa	*Tumor necrosis factor α*
TSH	*Thyroid stimulating hormone*
TVS	*Transvaginal sonography*
US	*Ultrasound*
VLDL	*Very low density lipoprotein*

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility, affects 4-7% of women ***(Ehrmann, 2005).***

It is by far the most common cause of hyperandrogenic anovulatory infertility and was described more than half a century ago, the underlying cause of this disorder is still uncertain ***(Yen, 1999).***

The classic symptoms of the disease are due to increased ovarian androgen production and chronic anovulation ***(Tsilchorozidou et al., 2004).*** There are several clinical and laboratory criteria such as obesity, acanthosis nigricans, oligomenorrhea, hirsutism, acne and resistance to ovulation induction with clomiphene citrate (CC) ***(Mor et al., 2004; Ciampelli et al., 2005).*** Also, there may be an increase luteinizing hormone to follicle-stimulating hormone ratio (LH/FSH), as well as decreased ovulatory rate ***(Eisenhardt et al., 2006).***

Clomiphene citrate has been the front line therapy for ovulation induction ***(Holzer et al., 2006).*** Failure to respond to clomiphene citrate occurs in up to 20% of cases which may require the use of injectable gonadotropines as a second line ***(Mitwally and Casper, 2001).***

The drawbacks of this approach include its high cost, the potentially life threatening ovarian hyperstimulation syndrome and the significant risk of high order multiple gestations ***(Holzer et al., 2006).***

Recent research has focused on the successful use of aromatase inhibitors (AIs) as letrozole for ovulation induction ***(Mitwally and Casper, 2006).***

Aromatase is a cytochrome P-450 hemoprotein containing enzyme complex (the product of the CYP19 gene) that catalyzes the rate-limiting step in the production of estrogens which is the conversion of androstenedione and testosterone via three hydroxylation step to estrone and estradiol ***(Cole and Robinson, 1990; Akhtar et al., 1993).***

Aromatase activity is present in many tissues such as the ovaries, adipose tissue, muscle, liver, breast tissue, and in malignant breast tumours. The main sources of circulating estrogens are the ovaries in premenopausal women and adipose tissue in postmenopausal women ***(Cole and Robinson, 1999).***

There are two types of aromatase inhibitor (AIs): Steroidal (type I) and non-steroidal inhibitors (type II) ***(Bhatnagar et al., 1990; Plourde et al., 1994).*** Type II non-steroidal AIs exert their function through binding to the heme moiety of the cytochrome P450 enzyme ***(Brodie and Njar, 1996).***

Anastrozole and letrozole are third generation selective (non steroidal) AIs, available for clinical use for treatment of postmenopausal breast cancer, they are reversible, competitive AIs, which are highly potent and selective ***(Okman et al., 2003).***

The high affinity of AIs for aromatase is thought to reside in the N-4 nitrogen of the triazole ring that coordinates with the heme iron atom of the aromatase enzyme complex ***(Buzdar et al., 1996***; ***Dowett, 1996; Bergh et al., 1997; Marty et al., 1997)***.

Letrozole is rapidly absorbed from the gastrointestinal tract and excreted by the kidney. The elimination half-life of letrozole is about 2 days ***(Mitwally and Casper, 2001).***

AIs can be applied for ovarian stimulation as its administration early in the follicular phase can induce ovulation by releasing the hypothalamus or pituitary from estrogen negative feedback on GnRH and gonadotropin secretion, leading to an increase in gonadotropin production which would stimulate ovarian follicular development ***(Lidor et al., 2000).***

AIs prevent the Androgen-Estrogen conversion and therefore interfere with the negative feedback at the level of the hypothalamus-pituitary. The increased pituitary gonadotropin out- put will in turn stimulate the ovaries ***(Mitwally et al., 2005).***

Also, they act locally in the ovary to increase follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens, since conversion of androgen substrate to estrogen is blocked. Recent data support a stimulatory role for androgens in early follicular growth ***(Al-Omari et al., 2001; Metawie, 2001).***

In some studies, letrozole in contrast to C.C is better as it increases endometrial thickness by upregulation of estrogen receptors, so it increases pregnancy rate and also it decreases incidence of multiple pregnancy ***(Fatemi et al., 2003; Mitwally et al., 2005).***

AIs reported to be effective in inducing ovulation, increased pregnancy rate, improve uterine environment, endometrial development with favorable cervical mucus ***(Mitwally et al., 2005).***