CLOMIPHENE STAIR-STEP PROTOCOL FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

Thesis
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الْحَمْدُ لِلّهِ الَّذِي هَدَانَا لِهَـذا
وَ مَا كُنَّا لِنَهْتَدِيَ لَوْلاَ أَنْ هَدَانَا اللّهُ

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List of Abbreviations

17-β HSD	17 β hydroxysteroid dehydrogenase
3-β HSD	3 β hydroxysteroid dehydrogenase
ACTH	Adrenocorticotropic hormone
AES	Androgen excess society
AIDS	Aquired immune deficiency syndrome
AR	Assisted reproduction
ART	Assisted reproduction techniques
ASRM	American society foe reproductive medicine
BBT	Basal body temperature
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CC	Clomiphene citrate
CCCT	Clomiphene citrate challenge test
COH	Controlled ovarian hyperstimulation
CVD	Cardiovascular disease
DHEA	Dehydrepiandrsterone
DHEAS	Dehyrdoepiandrosterone sulfate
DHT	Dihydrotestosterone
DP	Douglas pouch
E2	Estradiol
F	Fisher exact test
FAI	Free androgen index
FDA	Food and drug administration
FSH	Follicular stimulating hormone
FSH-GC	Follicular stimulating hormone granulosa cell

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FSHR	FSH receptors
GnRH	Gonadotropins releasing hormone
HAIR-AN	Hyperandrogenic insulin resistant acanthosis nigrans
HCA	Hyperandrogenism and chronic anovulation
HCA-PCO	Hyperandrogenism chronic anovulation and polycystic ovary
HCG	Human chorionic gonadotropin
HLD	High density lipoprotein
HMG	Human menopausal gonadotropine
HPCO	Hyperandrogenism and polycystic ovary
HS	Highly significant
IGF	Insulin like growth factor
IGFBP1	Insulin like growth factor binding protein 1
IGT	Impaired glucose tolerance
INS-1	Inositol
Insl3	Insulin like factor 3
IR	Insulin resistance
IU	International unit
IUI	Intra-uterine insemination
IVF	In vitro fertilization
LDL	Low density lipoprotein
LH	Luteinizing hormone
LHTIC	Luteinizing hormone theca interstitial cell
MMPs	Matrix metalloproteinases
MPA	Medroxyprogesterone acetate
N	Number
NICHD	National institute of child health and human development
NIDDM	Non insulin dependent diabetes mellitus
NIH	National institute of health
NS	non insignificant
OCP	Oral contraceptive pills

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OHSS	Ovarian hyperstimulation syndrome
OV	Ovarian volume
PA	Premature adrenarch
PCO	Polycystic ovary
PCO-CA	Polycystic ovary and chronic anovulation
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
POF	Premature ovarian failure
PPAR	Peroxisome proliferator activated receptor
PPV	Positive predictive value
rFSH	Recombination follicular stimulating hormone
S	Significant
SD	Standard deviation
SHBG	Sex hormone binding globulin
SPSS	Statistical program for social science
T	Test for independent samples
TIMPs	Tissue inhibitors of metalloproyeinases
TSH	Thyroid stimulating hormon
UK	United kingdom
U/S	Ultrasound
USA	United States of America
uFSH	Urinary follicular stimulating hormone
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHO	World health organization
X	Chi square test

Introduction

INTRODUCTION

Infertility is generally defined as the inability of a couple to conceive within a certain period of time that is usually one year, time is seen as the enemy and often the couple feels a sense of personal loss and frustration. Polycystic ovarian syndrome (PCOS) is the commonest cause of anovulatory infertility ***(Aboulghar et al., 2003)***.

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with a prevalence of approximately 4-6%. Its cardinal features are hyperandrogenism and polycystic ovaries ***(Laven et al., 2002)***.

The Rotterdam Conference of 2003, recommended that at least two of the following three features are 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 > $10mm^3$ ***(Fauser et al., 2004).***

The most common prescribed drug for ovulation induction is clomiphene citrate. It is a triphenylethylene and is a nonsteroidal estrogenic-like compound distantly related to

diethylstilbestrol. It acts to modify the hypothalamic activiy 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 activated resulting in rise in circulating levels of FSH and LH ***(Gysler et al., 1982)***.

Clomiphene citrate is easy to use and leads to ovulation in the vast majority of patients, but pregnancy rates are disappointing (50 percent or less) Lower-than-expected pregnancy rates with CC have been attributed to its long half-life and peripheral anti-estrogenic effects, mainly on the endometrium and cervical mucus. In such individuals, who are often classified as "clomiphene resistant", the next step is traditionally the administration of exogenous gonadotropin preparations via injections ***(Hammond et al., 1983)***.

Clomiphene citrate is the drug most commonly used for ovulation induction starting with a daily dose of (50mg) for 5 days beginning on day 3-5 of the menstrual cycle if ovulation achieved this is usually continued for 6 cycles or until pregnancy occurs. However if the patient fails to ovulate on this dose a further increase by (50mg) per day to a maximum of (200-250mg) is used next cycle ***(Manal et al., 2007)***.

A disadvantage with the mentioned traditional protocol that several months may pass to ultimately determine that patient is non responsive to clomiphene.

(Hurst et al., 2009) described a novel clomiphene stair-step protocol that it is hoped to reduce time to ovulation in women with polycystic ovary syndrome, this stair-step protocol is performed as follows: (50mg) clomiphene for 5 days and Ultrasound on days 11-14. When there is no response (no follicle >10mm), (100mg) clomiphene is initiated immediately for 5 days, and Ultrasound is repeated 1 week after the first Ultrasound. If there is no response, (150mg) clomiphene is initiated immediately for 5 days and Ultrasound is performed 1 week after the second Ultrasound ***(Hurst et al., 2009)***. Using this approach, 52% ovulated in response to (50mg), and 22% ovulated in response to (100mg), and 12% responded to (150mg) ***(Hurst et al., 2009)***.

Aim of The Work

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To determine the efficacy of stair-step clomiphene protocol in women with polycystic ovarian syndrome (PCOS) compared to traditional protocol.