A randomized trial of combined letrozole with metformin versus clomiphene citrate with metformin in PCOS patients

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وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ

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Abstract

Polycystic Ovary Syndrome (PCOS) is one of the most common causes of anovulatory infertility**.** Currently, CC is considered first-line therapy for ovulation induction for women with PCOS and infertility

Aromatase inhibitors (AIs) have been introduced as a new treatment option that could challenge CC for ovulation induction

The present study was designed to compare the efficacy of combined aromatase inhibitors (Letrozole) with metformin versus CC with metformin in PCOS patients

This study was done on 100 documented PCOS cases. They were divided to two groups,

The 1st group received CC 50mg twice daily from the 3rd day of cycle for 5 days and repeated for 3 cycles with metformin 500mg 3 times daily as an adjunct with CC and continued for 3 cycles.

The 2nd group received aromatase inhibitor (Letrozole) 2.5 mg twice daily from 3rd day of cycle for 5 days and repeated for 3 cycles with metformin 500mg 3 times daily as an adjunct with letrozole and continued for 3 cycles.

These cases were followed up for three cycles by transvaginal ultrasound folliculometry to document ovulation (size and number of follicles).

The results of the present study revealed both lines of treatment were effective in treatment of PCOS patients, with slight favorability in letrozole group but without statistically significant difference founded between CC group and letrozole group as regard ovulation rate, number of follicles in the end of first, second or third cycles, or as regard the diameter of follicles, i.e., both regimens showed efficacy to the same extent.

Key Words :

PCOS –clomiphene citrate – letrozole -metformin

List of Abbreviations

Abbreviation		Full name
3β-HSD	**:**	**3β-hydroxysteroid dehydrogenase**
ACC	**:**	**Acetyl-CoA carboxylase**
ACTH	**:**	**Adrenocorticotrophic hormone**
ADMA	**:**	**Asymmetric dimethylarginine**
AES	**:**	**Androgen excess society**
AGEs	**:**	**Advanced glycated end products**
Ais	**:**	**Aromatase inhibitors**
AKT	**:**	**Protien kinase B(known as Akt)**
AMH	**:**	**Antimullerian hormone**
AMPK	**:**	**50-AMP-activated protein kinase**
BMI	**:**	**Body mass index**
CAH	**:**	**Congenital adrenal hyperplasia**
CC	**:**	**Clomiphene citrate**
CVD	**:**	**Cardio vascular disease**
CYP 2A6	**:**	**Cytochrome P 450 2A6**
CYP 3A4	**:**	**Cytochrome P 450 3A4**
CYP11A1	**:**	**Cytochrome P450, family 11, subfamily A, polypeptide 1**
CYP17	**:**	**Cytochrome P450, family 17**
CYP19A1	**:**	**Cytochrome P450, family 19, subfamily A, polypeptide 1**

Abbreviation		Full name
CYP-450	**:**	**Cytochrome450**
D	**:**	**Day**
DHEA	**:**	**Dehydroepiandrosteron.**
DHEAS	**:**	**Dehydroepiandrosterone sulphate**
DHT	**:**	**Dihydrotestosterone**
DPP	**:**	**Diabetes prevention program**
E2	**:**	**Estradiol**
EC	**:**	**Endothelial cells**
ER	**:**	**Estrogen receptor**
ERs	**:**	**Estrogen receptors**
ET-1	**:**	**Endothelin-1**
FA	**:**	**Fatty acid**
FBS	**:**	**Fasting blood Sugar**
FDA	**:**	**Food and drug adminstration**
FFA	**:**	**Free fatty acid**
FSH	**:**	**Follicle-stimulating hormone**
FST	**:**	**Follistatin**
G/I	**:**	**Glucose to insulin ratio**
GD	**:**	**Gestational diabetes**
GLUT-4	**:**	**Glucose transporter type 4**

Abbreviation		Full name
GnRH	**:**	**Gonadotrophin-releasing hormone**
GSK-3	**:**	**Glycogen synthase kinase-3**
HA	**:**	**Hyperandrogenic**
HCG	**:**	**Human Chrionic Gonadotropin**
HDL	**:**	**High density lipoprotein**
HGP:	**:**	**Hepatic glucose production**
HOMA	**:**	**Homeostasis model assessment**
HOMA-IR	**:**	**Homeostatic assessment model for insulin resistance**
HSG	**:**	**Hysterosalpingogram**
HUVECs	**:**	**Human umbilical vein endothelial cells**
IGF-1	**:**	**Insulin-like growth factor I**
IGFBP-1	**:**	**Insulin-like growth factor binding protein-1**
IGF-II	**:**	**Insulin-like growth factor II**
IGT	**:**	**Impaired glucose tolerance**
IMGU	**:**	**Insulin-mediated glucose uptake**
IR	**:**	**Insulin resistance**
IRs	**:**	**Insulin receptor substrate**
IUI	**:**	**Intra uterine insemination**
IVF	**:**	**In vitro fertilization**
LDL	**:**	**Low density lipoprotein**

Abbreviation		Full name
LH	**:**	**Luteinizing hormone**
MAP	**:**	**Mitogen-activated protein**
MAPK	**:**	**Mitogen-activated protein kinase**
MFO	**:**	**Multifollicular oocyte**
MS	**:**	**Metabolic syndrome**
NAFLD	**:**	**Non Alcholic Fatty Liver Disease**
NASH	**:**	**Nonalcoholic steatohepatitis**
NASHES III	**:**	**National health and nutrition examination survey three**
NF	**:**	**Nuclear factor**
NIH	**:**	**National institutes of health.**
NO	**:**	**Nitric oxide**
no	**:**	**Number of**
NOS	**:**	**Nitric oxide synthases**
NPY	**:**	**Neuropeptide Y**
OCPs	**:**	**Oral contraceptive pills**
OGTT	**:**	**Oral glucose tolerance test**
OHSS	**:**	**Ovarian hyperstimulation syndrome**
OSA	**:**	**Obstructive sleep apnea**
P1	**:**	**Initial mid luteal serum progesterone.**
P4	**:**	**Progesterone.**

Abbreviation		Full name
P450	**:**	**P450 side-chain cleavage**
PAI-1	**:**	**Plasminogen activator inhibitor-1**
PAT-1	**:**	**Plasminogen activator type 1**
PCOM	**:**	**Polycystic ovarian morphology**
PCOS	**:**	**Polycystic ovary syndrome**
PI3K	**:**	**Phosphatidylinositol 3-kinases**
PKA	**:**	**Protein kinase A**
PKB	**:**	**Protien Kinase B(known as Akt)**
RCT	**:**	**Randomized controlled trial**
RCTs	**:**	**Randomized controlled trials**
SBP	**:**	**Systolic blood pressure**
SHBG	**:**	**Sex hormone binding globulin**
SLE	**:**	**Systemic lupus erythematosis**
SM	**:**	**Skeletal muscle**
StAR	**:**	**Steroidogenic acute regulatory protein**
STK11	**:**	**Serine/threonine kinase 11**
T	**:**	**Testosterone**
T1/2	**:**	**Terminal half-life**
T2DM	**:**	**Type two diabetes mellitus**
TGF-β	**:**	**Transforming growth factor β.**

Abbreviation		Full name
TNF	**:**	**Tumor necrosis factors**
TNF-α	**:**	**Tumor necrosis factor- alpha**
TSH	**:**	**Thyroid-stimulating hormone**
TVUS	**:**	**Trans vaginal ultrasound**
TZDs	**:**	**Thiazolidinediones**
VEGF	**:**	**Vascular endothelial growth factor**
VLDL	**:**	**Very low density lipoproteins**
VSMC	**:**	**Vascular smooth muscle cells**
WC	**:**	**Waist circumference**
WHO	**:**	**World Health Organization**
WHR	**:**	**Waist-to-hip ratio**
Wk	**:**	**Weeks**

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Introduction

Infertility has been attributed to various factors, amongst which anovulation is the cause in about 40% of all female infertility

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

Criteria used for diagnosing Polycystic Ovary Syndrome (PCOS) are the Rotterdam Criteria of which a woman must have two out of the followings:

1: Oligo- or anovulation.

2: Clinical and / or biochemical signs of hyperandrogenism

3: Polycystic ovaries (with the exclusion of related disorders).

-With exclusion of other conditions with similar signs such as androgen-secreting tumors or Cushing's syndrome and thyroid dysfunction and hyperprolactinemia.

- Anti estrogenic drug, such as Clomiphene citrate (CC) is considered the first line treatment for induction of ovulation in women with Polycystic Ovary Syndrome (PCOS). CC is given orally at a dose of 50-100 mg/day from 3rd day of cycle for 5 days. If patients fail to respond to 150 mg/day, they are considered as CC resistant.

- Aromatase inhibitors (AIs) have been introduced as a new treatment option that could challenge CC for ovulation induction **(Casper RF and Mitwally MF (2006)**

Aromatase is a cytochrome P-450 hem protein 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.

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

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 output 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 CC 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).***

-Insulin-sensitizing Agents for example :(Metformin)