L-Carnitine and Clomiphene Citrate for induction of ovulation in women with Polycystic Ovary Syndrome: Randomized controlled trial

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Submitted for Partial Fulfillment of Master Degree in Obstetrics and Gynecology

By

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List of Abbreviations

Abb.	Full term
17-OH-progesterone	17-hydroxyprogesterone
ACS	Acyl-CoA synthases
ADMA	Asymmetric dimethylarginine
BMI	Body mass index
CACT	Carnitine acyl carnitine translocase
СС	Clomiphene citrate
CoA	Coenzyme A
COX	Cyclooxigenase
CPT-1	Carnitine palmitoyl transferase-1
CPT-2	Carnitine palmitoyl transferase-2
ER	Endoplasmic reticulum
FA	Fatty acid
FABPpm	Plasma membrane fatty acid binding
	proteins
FAT/CD36	Fatty acid translocase
FATP	Fatty acid transport proteins
FET	Fetal Embryo transfer
FFA	Free fatty acids
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
GPx	Glutathione peroxidase
GRd	Glutathione reductase
GSH	Reducted glutathione
GSSG	Oxidized glutathione

Tist of Abbreviations

Abb.	Full term
H ₂ O ₂	Hydrogen peroxide
НСҮ	Homocysteine
HSG	Hysterosalpingography
ICSI	Intra-Cytoplasmic Sperm Injection
IFN	Interferon
IL	Interleukin
IMM	Inner mitochondrial membrane
IR	Insulin resistance
IVF	In-vitro fertilization
LC	L-carnitine
LDL	Low-density lipoprotein
LH	Luteinizing hormone
mPTP	Mitochondrial permeability transition
1111 11	pore
NO	Nitric oxide
NOS	Nitric oxide synthase
02-	Superoxide anion
OCTN2	Organic cation transporter novel 2
ОН	Hydroxyl radical
ОМ	Oocyte membrane
OMM	Outer mitochondrial membrane
ON00-	Peroxynitrite
OS	Oxidative stress
oxLDL	Oxidized low-density lipoprotein
PCOS	Polycystic ovary syndrome
PON-1	Paraoxonase 1

Tist of Abbreviations

Abb.	Full term
PRL	Prolactin
ROS	Reactive oxygen species
SHBG	Sex hormone-binding globulin
SOD	Superoxide dismutase
Т	Translocase
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TNF	Tumor necrosis factor
Trigs	Triglycerides
WC	Waist circumference

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Abstract

<u>Objective</u>: The aim of the study was to assess the efficacy of adding L-carnitine to clomiphene citrate for increasing the ovulation and the pregnancy rate in women with PCOS. The primary outcome was the ovulation rate and the secondary outcome was the pregnancy rate.

Materials and Methods: This study was a randomized controlled clinical trial that was conducted on 94 women who attended at the Obstetrics & Gynecology Outpatient Infertility Clinic at Ain Shams University Maternity Hospital, and they were diagnosed with PCOS according to the Rotterdam Criteria (11). The women were distributed randomly into two equal groups; Group L (n=47) received 100 mg of clomiphene citrate plus 3 gm of L-carnitine orally from day 3 to day 7 of the cycle with continuation of L-carnitine till the day of pregnancy test and Group C (n=47) received 100 mg of clomiphene citrate orally from day 3 to day 7 of the cycle.

Results: There was a significant difference (P<0.05) between the two groups regarding the ovulation rate (Group L: 70.2%; Group C: 44.7%). There was no significant difference (P>0.05) between the two groups regarding the pregnancy rate (Group L: 8.5%; Group C: 6.4%). There was a highly significant difference (P<0.01) between the two groups as regards to; the number of mature follicles (Group L: 1.6 ± 1.2 ; Group C: 0.8 ± 0.7), the days needed till hCG injection (Group L: 12.2 ± 1.5 ; Group C: 14.0 ± 1.8), the Endometrial thickness (Group L: 10.4 ± 1.2 mm; Group C: 9.1 ± 0.8 mm). There was no significant difference (P>0.05) between the two groups regarding the level of progesterone after 8 days from the hCG injection.

<u>Conclusion</u>: L-carnitine added to clomiphene citrate for induction of ovulation in PCOS women had a significant effect on the ovulation rate, but it didn't have a significant effect on the pregnancy rate when compared to clomiphene citrate alone.

Keywords: Polycystic ovary syndrome, Induction of ovulation, L-Carnitine, Clomiphene citrate.





PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN OBSTETRICS AND GYNECOLOGY

Title of the protocol:

L-Carnitine and Clomiphene Citrate for induction of ovulation in women with Polycystic Ovary Syndrome: Randomized controlled trial.

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What is already known on this subject? AND What does this study add?

Polycystic ovary syndrome (PCOS) is one of the most common <u>endocrine disorder</u>s and the leading cause of infertility in women of reproductive age, it is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology.

This study will help to add more proof that L-carnitine supplementation has positive effects on PCOS patients as shown by previous studies.

Also, this study will add positive value to PCOS patients' lives because it will increase their chance of becoming pregnant without doing operations on their ovaries.

1. INTRODUCTION/REVIEW

Insulin resistance with compensatory hyperinsulinemia appears to be the most universal feature of the polycystic ovarian disease and has a pathophysiologic role in the hyperandrogenism of the disorder (Samsami et al., 2014).

In most cases ovulation can be induced with clomiphene citrate which constitutes one of the first-line treatments for ovulation induction in PCOS patients, as it is economical, has few adverse effects, and requires little monitoring (Elsamy and Saleh, 2015).





A lot of investigations have revealed that oxidative stress level is significantly increased in patients with PCOS compared with the normal (Zuo et al., 2016).

Oxidative stress is defined as an imbalance derived from excessive formation of oxidants in the presence of limited antioxidant defenses (Murri et al., 2013).

L-Carnitine is a ubiquitous molecule derived from the amino acids lysine and methionine (Maldonado et al., 2016).

A study by Celik et al., in 2017 showed that the women with PCOS had significantly lower L-carnitine levels than those of the healthy controls (Celik et al., 2017).

Carnitine plays a substantial role in weight loss, glucose tolerance, insulin function and fatty acid metabolism (Samimi et al., 2016).

A study by <u>Jamilian</u> et al., in 2017 concluded that carnitine supplementation among patients with PCOS had favorable effects on the biomarkers of oxidative stress (**Jamilian et al.**, 2017).

In addition to a study by Ismail et al., in 2014 where they combined L-carnitine and clomiphene citrate and this significantly improved both ovulation and cumulative pregnancy rates in patients with clomiphene-resistant PCOS (Ismail et al., 2014).





2. AIM/OBJECTIVES

Research hypothesis:

In women with PCOS adding L-carnitine to clomiphene citrate may improve the ovulation process and the pregnancy rate.

Research question:

In women with PCOS does adding L-carnitine to clomiphene citrate improve the ovulation process and the pregnancy rate?

Aim of the study:

This study aims to assess the efficacy of adding L-carnitine to clomiphene citrate for increasing the ovulation and the pregnancy rate in women with PCOS.

Outcome:

- . The main outcome is the success of the ovulation process.
- . The Secondary outcome is the pregnancy rate.





3. METHODOLOGY

Type of the Study:

A Randomized controlled clinical trial.

Study Setting and population:

Women attending at the Obstetrics & Gynecology outpatient infertility clinic in Ain shams university hospital, Cairo, Egypt.

Sample size calculation:

The required sample size has been calculated using the IBM© Samplepower© version 3.3 (IBM© Corp.,Armonk,NY,USA).

The main outcome measures are the ovulation rate and cumulative pregnancy rate. A previous study reported that the ovulation and cumulative pregnancy rates were 64.4% versus 17.4% and 51.5% versus 5.8% in PCO patients receiving L-carnitine with clomiphene citrate or clomiphene citrate alone, respectively (Ismail et al., 2014),

So it is estimated that a sample size of 47 patients in either study group achieves a power of 99% to detect a difference of 47% (64.4% versus 17.4%) between the 2 groups as regards the ovulation rate, and a power of 99.6% to detect a difference of 45.7% (51.5% versus 5.8%) as regards the cumulative pregnancy rate. These calculations used a two-sided chi-squared test with a type I error of 0.01.

Assuming a drop-out rate of approximately 10%, 53 patients will be recruited in either group (total number = 106 patients).