Clomiphene Citrate with Estradiol Valerate versus Clomiphene Only in Treatment of Women with Unexplained Infertility: Randomized Controlled Trial

Thesis

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Enas Mohsen

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List of Abbreviations

Abb.	Full term
AFC	Antral Follicle Count
Alu	Arthrobacter luteus
AMH	Antimüllerian Hormone
Apo-A1	Apolipoprotein A1
ART	Assisted reproductive techniques
ASRM	American Society for Reproductive Medicine
BBT	Basal body temperature
BMI	Body mass index
CAT	Chlamydia Antibody Test
CC	Clomiphene citrate
CC/IUI	Clomiphene citrate with Intrauterine Insemination
CCCT	Clomiphene Citrate Challenge Test
COH	Controlled ovarian hyperstimulation
COH/IUI	Controlled ovarian hyperstimulation with Intrauterine Insemination
COS	Controlled ovarian stimulation
CpGs	5'—C—phosphate—G—3'
DNA	Double Stranded Nucleic acid
DOR	Diminished ovarian reserve
E_2	Estradiol
EBM	Endometrial biopsy
EE	Ethinyle Estradiol
ET	Endometrial thickness
EV	Estradiol Valerate
FASTT	Fast Track and Standard Treatment
FET	Frozen Embryo Transfer
FI	Flow Index
FMR1	Fragile X mental retardation 1
FOXO1	Forkhead box 1
FOXO3	Forkhead box 3

List of Abbreviations Cont...

Abb.	Full term
FSH	Follicle stimulating hormone
FXS	Fragile X syndrome
GA	Gestational Age
GnRH	Gonadotropin releasing hormone
HCG	Human chorionic gonadotropin
HFEA	Human Fertilization and Embryology Authority
HIV	Human immunodeficiency virus
HMG	Human menopausal gonadotropins
HSG	Hysterosalpingography
ICSI	Intracytoplasmic sperm injection
IL	interleukin
IUI	Intrauterine insemination
IVF	In vitro fertilization
IVF/ET	In vitro fertilization/embryo transfer
LBR	Live birth rate
LH	Luteinizing hormone
LIF	Leukemia inhibitory factor
LINE-1	Long interspersed element-1
NCR	Natural cytotoxicity receptor
NICE	National Institute for Health and Care Excellence
NK	Natural killer cells
NPV	Negative predictive value
NSAIDs	Non-steroidal anti-inflammatory drugs
OH	Ovarian hyperstimulation
OHSS	Ovarian hyperstimulation syndrome
OS	Ovarian stimulation
P	Progesterone
P/E_2	Progesterone/ Estradiol ratio

List of Abbreviations Cont...

Abb.	Full term
PC6	Proprotein convertase 5/6
PCO	Polycystic ovary
PCOS	Polycystic ovarIAN syndrome
PI	Pulsatility index
pNK	Peripheral natural killer cells
POR	Poor ovarian response
PPV	Positive predictive value
PRL	Prolactin
PV	Per-vaginal
RPL	Recurrent pregnancy loss
SCH	Subclinical hypothyroidism
SD	Standard deviation
SIS	Saline infusion sonography
THL	Transvaginal hydrolaparoscopy
TMX	Tamoxiphene
TSH	Thyroid stimulating hormone
TV/US	Transvaginal ultrasonography
UI	Unexplained infertility
UK	United Kingdom
uNK	Uterine natural killer cells
US	United States
VEGF-C	Vascular endothelial growth factor C
VFI	Vascularization Flow Index
VI	Vascularization Index
WHO	World Health Organization
αvβ3	Alphavbeta3

INTRODUCTION

Infertility is defined as failure to achieve successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination ***(Practice committee of ASRM, 2013b).*** **Unexplained infertility** (UI) is the infertility in the absence of a definable cause despite a thorough evaluation ***(Practice Committee of ASRM, 2008; Moghissi and Wallach, 1983).***

About 4–17 % of couples have fertility problems resolve their infertility, but generally there are more cases unreported ***(Gibson and Wilkerson, 2017).*** Unexplained infertility affects about 15% - 37% of the couples seeking medical advice ***(Isaksson and Tiitinen, 2004; Aboulghar et al., 2003).***

The American Society of Reproductive Medicine guidelines for standard infertility evaluation includes semen analysis, assessment of ovulation, tubal patency and uterine abnormalities and, if indicated, tests for ovarian reserve and laparoscopy ***(Practice committee of ASRM, 2012a).***

Clinicians should counsel the couples with unexplained infertility about the empiric nature of available treatment options including IVF ***(Gunn and Bates, 2016).***

Spontaneous conception rate in couples with unexplained infertility is more than that in couples with defined causes of infertility. It is about 13-15% during the first year of infertility;

and it increases to 35% during the following two years. Furthermore, the rate may reach 80% in young couples during the next three years of unprotected intercourse without any adjuvant therapy. However it decreases dramatically if the infertility duration is more than 3 years or the women are older than 30 years ***(Gelbaya et al., 2014; Nardelli et al., 2014).*** The goal of the treatment options is to increase the fecundability/ month to reach a closer level to that observed in normally fertile couples ***(Tapia et al., 2008).***

The probability of pregnancy is increased by superovulation through increasing the oocytes number which is suitable for fertilization. In women with unexplained infertility, (CC), the traditional therapy, has been the first line used for induction of ovulation for more than four decades ***(Legro et al., 2012; Pritts, 2010).*** In contrast, current evidence suggests that CC may not be beneficial ***(NICE, 2013).***

CC is a non-steroidal triphenyl ethylene derivative, has estrogen agonist and antagonist properties, but CC estrogenic agonist properties manifest only when endogenous estrogen levels are very low ***(Practice committee of ASRM, 2013a).*** CC binds to the estrogen receptors in the hypothalamus, blocking the estrogen negative feedback mechanism. This decreased feedback stimulates normal compensatory mechanisms that changes the secretion pattern of gonadotropin releasing hormone (GnRH), which increases gonadotropin release from

the pituitary, and in turn development of the ovarian follicles stimulated ***(Speroff and Fritz, 2005).***

Generally CC is a very well tolerated drug. However, relatively some side effects are common, but rare to be persistent or severe enough to enforce the patient to stop the drug before completing the usual 5-day course or next cycle of treatment ***(Practice committee of ASRM, 2013a).***These side effects are mainly due to its antiestrogenic effect, which typically resolve soon after treatment ends ***(Purata et al., 2016).***

About 15%-50% of women who receive CC show thin endometrium and non-trilaminar pattern at midcycle ***(Begum et al., 2009).*** As an explanation, CC has an intrinsic negative effect on the synchronization of glandular development and endometrial stromal maturity by causing glandular density reduction and decreasing the number of vacuolated cells ***(Sereepapong et al., 2000; Unfer et al., 2001).*** In addition CC has been detected to affect the uterine blood flow and endometrial perfusion ***(Hsu et al., 1995; Nakai et al., 2002),*** this leads to lower implantation rates ***(Zhao et al., 2012).***

The relatively long half-life of CC, which is known to be 5 days, augments these negative effects ***(Biljan et al., 2000).***

Consequently, to reverse the anti-estrogenic effect of CC it seems logic to use adjuvant therapies. For this purpose, some investigations have proven a positive role for estrogens as an

adjuvant treatment ***(Gerli et al., 2000; Shahin et al., 2009; Unfer et al., 2001).***

In this study, effect of adding EV to CC will be assessed on the clinical pregnancy rate among women with unexplained infertility.