Effect of Sildenafil Citrate on the Outcome of in vitro Fertilization after Multiple IVF Failures Attributed to Poor Endometrial Development: A Randomized Controlled Trial

Thesis

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By

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Amr El-Sayed Abd El-Hamid

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List of Abbreviations

Abbrev.	Full-term
ART	: Assisted-reproductive technique
ASRM	: American Society for Reproductive Medicine
AUCs	: Area under the curve
BMI	: Body mass index
cAMP	: Cyclic adenosine monophosphate
CAT	: Catalase
CDK	: Cyclin dependent kinase
cGMP	: Cyclic Guanosine Monophosphate
COH	: Controlled ovarian hyperstimulation
CYP	: Cytochromes P
EPDA	: Endometrial power Doppler area
ESHRE	: European society for human reproduction and Embryology
ET	: Embryo transfer
EU	: European Union
FDA	: Food and Drug Administration
FET	: Frozen-thawed embryo transfer
FSH	: Follicle-stimulating hormone
GSH-S-T	: Glutathione S-transferase
hCG	: Human chorionic gonadotropin
HMG	: Human menopausal gonadotropin
ICSI	: Intracytoplasmic sperm injection
IFNγ	: Interferon γ
IL	: Interleukin

IUAs : Intrauterine adhesions
IUI : Intrauterine insemination
IVF : In-vitro fertilization
LH : Luteinizing hormone
LIF : Leukemia inhibitory factor
MDA : Malondialdehyde (MDA)
MRHD : Maximum Recommended Human Dose
MTD : Maximum Tolerated Dose
NO : Nitric oxide
OHSS : Ovarian hyperstimulation syndrome
PAI-1 : Plasminogen activator inhibitor 1
PCOS : Polycystic ovarian syndrome
PDE : Phosphodiesterase
PDZ : Primary decidual zone
PLC : Phospholipase C
ROC : Receiver-operating characteristic
SDZ : Secondary decidual zone
SOD : Superoxide dismutase
SPSS : Statistical package for social science
SRC : Steroid receptor coactivator
SSRIs : Selective serotonin uptake inhibitors
TAC : Total antioxidant capacity
TV : Transvaginal
U/S : Ultrasound
VEGF : Vascular endothelial growth factor
ZD : Zona drilling

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ABSTRACT

Aim of the work: this study aimed to evaluate the effect of sildenafil citrate on endometrial development in women with history of recurrent implantation failure after IVF.

Setting: This study was conducted in obstetrics and gynecology department of Ain Shams University.

Patients and methods: this is a randomized controlled trial on 80 women with previous two or more failed IVF. Women in **group A** (N=40) took oral sildenafil citrate at dose 25mg tab /6h daily from day six of induction of ovulation until day of HCG administration; while those in **group B** (N=40) took placebo tablets. **Outcome measures**: The primary outcome was change in endometrial thickness before and after intervention. **Results**: Endometrial thickness in both groups was statistically insignificant between the two groups when measured in day 6 with p-value 0.070

Endometrial thickness on day of HMG injection measured and found that it was higher in **group A**(Sildenafil Group) than **group B**(Placebo Group) with significantly increased statistically difference between the two groups with p-value <0.001.

Conclusion: sildenafil citrate leads to smooth muscle relaxation and vasodilation. This may enhance endometrial development and increased pregnancy rate in females undergoing IVF which may be attributed to the increase in the endometrial thickness.

Keywords: endometrial thickness, IVF, sildenafil.

Introduction

Embryo implantation depends on the quality of the ovum and endometrial receptivity. Endometrial receptivity is a temporally unique sequence of factors that make the endometrium receptive to embryonic implantation. Implantation window is a period during which the endometrium is optimally receptive to implanting blastocyst ***(Aboubakr et al., 2004).***

Observations suggest that prospective assessment of the quality of decidualization response in the endometrium may be an important tool for predicting the likelihood of successful implantation and pregnancy outcome. Since its introduction into the clinic, ultrasound has been used widely to assess uterine features such as endometrial thickness, endometrial pattern and that may be predictive of pregnancy, especially in the context of assisted reproductive technology ***(Abdallah et al., 2012).***

Endometrial receptivity plays a crucial role in the establishment of a healthy pregnancy in cycles of assisted reproduction. The endometrium as a key factor during reproduction can be assessed in multiple ways, most commonly through transvaginal grey-scale or 3-D ultrasound. It has been shown that controlled ovarian hyper stimulation has a great impact on the uterine lining, which leads to different study results for the predictive value of endometrial

factors measured on different cycle days. There is no clear consensus on whether endometrial factors are appropriate to predict treatment outcome and if so, which one is suited best ***(Heger et al., 2012).***

Significant advances have occurred in the diagnosis and, more importantly, in the treatment of reproductive disorders over the past decade. The overall incidence of infertility has remained stable ***(Stephen and Chandra, 1998)***.

However, the success rates have markedly improved with the widespread use of assisted reproductive technologies. Treatment options and success vary with the cause of infertility. Approximately 15% to 30% of couples will be diagnosed with unexplained infertility after their diagnostic workup ***(Practice Committee of the American Society for Reproductive Medicine, 2006).***

Precise and specific endometrial maturational developmentt is crucial in allowing implantation following assisted reproduction. As endometrial biopsy is invasive and hormonal milieu assessment inaccurate, the need to evaluate endometrial development encouraged the use of high-resolution ultrasonography as an alternative non-invasive method of assessment for uterine receptivity. Ultra sonographic endometrial thickness measurement, endometrial pattern investigation, endometrial volume computation is just some of

the methods that we can utilize to have an idea of uterine receptivity and consequently to better predict pregnancy outcome following assisted reproductive technology cycles ***(Senturk and Erel, 2008).***

There is a correlation between endometrial thickness measured on HCG day and clinical outcome in normal responders with GnRH antagonist administration. The pregnancy rate was lower in patients with endometrial thickness less than 7 mm compared with patients with endometrial thickness more than 7 mm ***(Wu et al., 2014).***

A trilaminar sonographic endometrial pattern of ≥8 mm on the day of human chorionic gonadotrophin (HCG) has been shown to be correlated with a high chance of pregnancy in patients being treated with in-vitro fertilization (IVF) ***(Geoffrey and Jeffrey, 2000).***

Several regimens have been proposed to improve a poor endometrial response, including treatment with estrogens and low dose aspirin ***(Sher et al., 1993; Weckstein et al., 1997).***

A thin endometrium is one of the most difficult problems encountered in assisted reproduction every day practice. Whether a daily dose of 150 IU HCG for 7 days concomitant with estrogen administration in estrogen replacement cycles

can increase the endometrial thickness and improve pregnancy outcome ***(Papanikolaou et al., 2013).***

Previous animal research has demonstrated that NO release leads to the relaxation of vascular smooth muscle through a cyclic guanosine monophosphate (cGMP)-mediated pathway ***(Ballard et al., 1998).***

Endothelial and inducible NO synthase isoforms have also been identified in the vascular endothelium of human endometrium and myometrium ***(Telfer et al., 1997).***

Phosphodiesterase (PDE) is a family of isoenzymes that hydrolyze cAMP and cGMP. Specific inhibitors of PDE subtypes have been identified that can augment the effects of cyclic nucleotides on target tissues, such as human spermatozoa ***(Fisch et al., 1998).***

Sildenafil citrate is a newly developed, type 5-specific PDE inhibitor that prevents the breakdown of cGMP and potentiates the effects of NO on vascular smooth muscle. Since its introduction in 1997, sildenafil has been used with great success in the treatment of vascular smooth muscle through a cGMP-mediated pathway ***(Ballard et al., 1998).***

Aim of the Work

The aim of this study is to evaluate the effect of sildenafil citrate on endometrial development in women with history of recurrent implantation failure after IVF.