

## The Value of Oral Sildenafil in the Treatment of Female Infertility: A Randomized Clinical Trial

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**Abstract:** Background: Sildenafil citrate leads to smooth muscle relaxation and vasodilation. This may enhance endometrial development. The aim of this work is to study the effect of oral sildenafil citrate on pregnancy rate, endometrial thickness and number of follicles in women undergoing induction of ovulation with clomiphene citrate (CC). Patients and methods: this study included 70 infertile patients who were randomly divided into 2 groups. After ovulation induction with CC, patients in the treatment group received oral sildenafil citrate 25 mg 3 times daily from day 8-13 of the cycle and patients in control group received placebo. Results: the pregnancy rate, endometrial thickness and number of follicles were significantly higher in the treatment group. Side effects were significantly more in the treatment group compared to the placebo group ( $p=0.003$ ). Among patients in the treatment group, the most common side effect was headache which was found in 7 patients (20%) versus non in the placebo group. Conclusion: sildenafil citrate increased pregnancy rate in females undergoing induction of ovulation by CC 50 mg which may be attributed to the increase in endometrial thickness and number of follicles.

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### 1. Introduction:

There are many causes of infertility. In the majority of couples, an identifiable male or a female factor explaining their inability to conceive is usually found, in 10–25% there will be no explanation. Within this cohort of patients there is a spectrum of disorders ranging from those patients with a reduced fecundity that will conceive with time to those in whom conception is very unlikely with current medical practice. In women, subfertility may be caused by a diminished ovarian reserve, suboptimal endometrial receptivity or a disorder of oogenesis[1].

Phosphodiesterase (PDE) is a class of isoenzymes hydrolyzing cAMP and cGMP. Specific PDE inhibitors have been identified that can augment the effects of cyclic nucleotides on target tissues, such as human spermatozoa [2]. Sildenafil citrate (Viagra) is a type 5-specific PDE inhibitor preventing the breakdown of cGMP and potentiates the effects of nitric oxide (NO) on vascular smooth muscle. Sildenafil has been used since 1997 with great success in the treatment of male erectile dysfunction [3].

Sildenafil citrate was the first PDE-5 inhibitor approved by the United States Food and Drug Administration (FDA). The mechanism of action for the PDE-5 inhibitors involves increased cGMP levels, causing vasodilation and smooth muscle relaxation. The recent advancing basic and clinical studies suggest some very promising new

applications of PDE-5 inhibitors, far beyond their urological scope [4].

The importance of endometrial appearance as a predictor of outcome in patients undergoing induction of ovulation is well established. However, treatment with oestrogens alone does not appear to improve pregnancy rates significantly in patients with poor endometrial response.

NO is recognized as a mediator of vascular smooth muscle dilatation in many areas of the body. Nitroglycerin (NTG) has long been used for its vasodilatory properties in the treatment of angina, as well as obstetrically, to achieve tocolysis and uterine relaxation. NTG has been successfully used to improve uterine artery blood flow and endometrial lining in in-vitro fertilization (IVF) patients with a previous poor response. However, a high rate of side-effects, including hypotension and headaches was experienced. The use of intravaginal sildenafil suppositories made it possible to decrease the incidence of these side effects by delivering medication in close proximity to the target organ [5].

**The present work aimed** to study the effect of oral sildenafil citrate 25 mg on pregnancy rate as primary outcome and the endometrial thickness and number of follicles as secondary outcome in women undergoing induction of ovulation.

### 2. Patients and Methods

This study is a prospective randomized clinical trial which included 70 infertile patients. Cases were

selected from patients attending the infertility outpatient clinic of Ain Shams University Maternity Hospital from January to July 2012. We included women aged between 18 and 40 years with primary or secondary infertility and with regular menstrual cycles.

The exclusion criteria were: ovarian cysts, abnormal hormonal profile. e.g. hyper prolactinemia,

significant cardiovascular liver or renal disease and women with history of any pelvic pathology.

The patients in this study were divided into two groups by random allocation using sealed envelope: the treatment group (Sildenafil group) and the control group (placebo group) with 35 patients in each group. Figure (1) shows the flow chart of the included patients in this study.

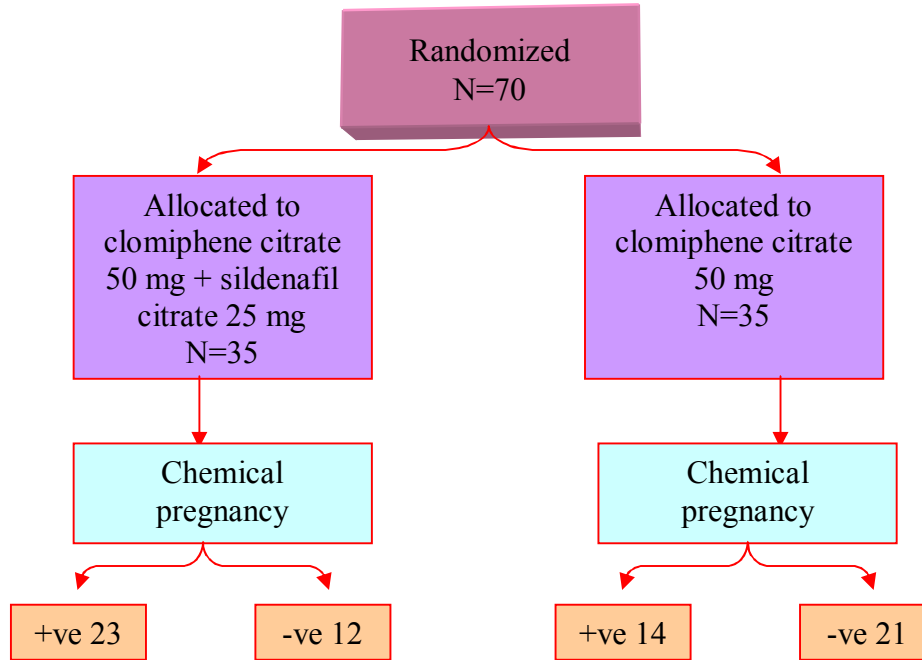


Figure (1): Study flow chart and patient outcome

All the couples were subjected to detailed medical history, general and local examination as well as ultrasound (transvaginal) examination for each studied patient.

#### **Infertility workup:**

Basal hormonal profile (follicle stimulating hormone, leutinizing hormone and prolactin) were measured on day three of menstrual cycle standard specific immunoassay and also at least one hystosalpingography was performed showing patent tubes.

Husbands of all cases were proved to have spermograms within normal as documented by a recent semen analysis. Criteria for normal semen analysis were considered according to the world health organization (WHO) standards that consider the normal semen analysis with the following:

- Volume: > 2.0 mL
- Concentration: at least 20 million spermatozoa/mL

- Motility: at least 50% exhibit good to excellent forward progressive movement within 60 minutes after ejaculation.
- Morphology: < 25% abnormal forms.
- White blood cell count < 1 million/mL.

Each patient received a full explanation of purpose of the study. All patients were enrolled in this study if and only if they gave a free and informed written consent. All the data were manipulated confidentially.

Induction of ovulation in both groups was done with clomiphene citrate (CC) 50mg (clomid, Glopa) orally 3times/day from 3<sup>rd</sup> to 7<sup>th</sup> day of the cycle with intramuscular injection of 5000 IU of human chorionic gonadotrophin (HCG) which was used to trigger ovulation. In addition the study group received sildenafil citrate 25mg (Viagra, Pfizer) orally 3times/day from 7<sup>th</sup> to 11<sup>th</sup> day of the cycle and the control group received placebo.

Folliculometry was assessed by transvaginal ultrasound (the machine used was premedical, 260 corvus with transvaginal transducer 5.0/7.5 MHZ

curved array R 10 endocavitary 150°). It was done on day 13 and/ or 14 of the cycle to detect number of follicles and endometrial thickness.

Pregnancy was confirmed by beta subunit HCG test positive.

### Data Management and Analysis:

The collected data was revised, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Presented data was suitable analysis was done according to the type of data obtained for each parameter.

### 3. Results

The demographic characteristics of the studied patients among the treatment and the control group were presented in table (1). The difference in the endometrial thickness was significant between both groups ( $p=0.01$ ) while other variables were non significant.

As regards chemical pregnancy rate, it was significantly higher in sildenafil group compared to placebo group ( $p=0.03$ ) as  $\beta$ - HCG was positive in 23 patients (65.7%) among treatment group compared to 14 patients (40%) among controls (Table2, Figure 1).

Side effects were significantly more in the treatment group compared to the placebo group ( $p=0.003$ ). Among patients in the treatment group, side effects were encountered in 15 patients (42.9%) with headache representing the most common side effect in 7 patients (20%) flushing in 4 patients (11.4%), blurring of vision and GIT upset in 2 patients (5.7%) for each (Table 3). Among patients in the placebo group, side effects were encountered in 8 patients (22.8%) with flushing in 4 patients (11.4%), blurring of vision and GIT upset in 2 patients (5.7%) for each and no patient in the placebo group had headache (Table 3).

Using logistic regression analysis, age, body mass index, duration and type of infertility, follicle count, endometrial thickness and sildenafil treatment were the variables included in the model with follicular count (odds ratio 3.35, 95% confidence interval 1.145- 9.802,  $p=0.027$ ) and endometrial thickness (odds ratio 3.276, 95% confidence interval 1.674- 6.412,  $p=0.001$ ) were the strongest independent factors affecting pregnancy (Table 4). Although non significant, sildenafil treatment increase the rate of pregnancy by 2.5 times the rate among placebo group (odds ratio 2.538, 95% confidence interval 0.495- 13.005,  $p>0.05$ ).

**Table (1):**Demographic statistics of both study groups.

	Treatment group	Placebo group	P	Sig
Age	28.34±4.13	28.40±3.15	0.948*	NS
Body mass index	28.97±2.64	29.43±1.57	0.374*	NS
Endometrial thickness	10.36±1.40	9.41±1.74	0.014*	S
Total follicles	4.40±1.54	3.77±1.70	0.109*	NS
Average follicle	2.20±0.77	1.89±0.85	0.109*	NS
Duration of infertility	2.55±1.24	2.57±0.93	0.931*	NS
Type of infertility	Primary	25 (71.4)	0.138**	NS
	Secondary	16 (45.7)		

Data presented as mean± standard deviation or number (percentage), \*analysis done using independent Student t test, \*\*analysis done using Chi-Square Test

**Table (2):**Comparison between treatment and placebo groups as regard pregnancy rate:

Pregnancy test	Treatment group	Placebo group	p	odds ratio (95% CI)
Negative	12 (34.3)	21(60)	0.031	2.875 (1.1-7.5)
Positive	23 (65.7)	14 (40)		

Data presented as number (percentage), CI= confidence interval

**Table (3):**Description of side effects among treatment and placebo group

Side effects	Treatment group	Placebo group	p
No side effects	20 (57.1%)	27 (77.1%)	0.003
Headache	7 (20%)	0	
Flushing	4 (11.4%)	4 (11.4%)	
Blurring of vision	2 (5.7%)	2 (5.7%)	
GIT disorder	2 (5.7%)	2 (5.7%)	
total side effects	15 (42.9%)	8 (22.8%)	

**Table (4):** Multivariate analysis for studying independent factors affecting pregnancy rate

	OR	95% CI		p	sig
Age	1.091	0.847	1.405	0.501	NS
BMI	1.248	0.850	1.831	0.258	NS
Duration of infertility	0.686	0.273	1.725	0.423	NS
Type of infertility	0.945	0.096	9.319	0.962	NS
Follicle count	3.350	1.145	9.802	0.027	S
Endometrial thickness	3.276	1.674	6.412	0.001	HS
Treatment	2.538	0.495	13.005	0.264	NS

#### 4. Discussion:

Disorders of ovulation account for approximately 30-40% of all causes of female infertility, but are generally easily diagnosed and are the most treatable causes of infertility [6]. Ovarian stimulation, is a less expensive and less invasive treatment in comparison with other assisted reproductive techniques and has been widely used for the treatment of infertile couples with a variety of indications, such as ovulatory disturbances, mild male factor infertility, and unexplained infertility [7].

Clomiphene citrate (CC) is the first line treatment for induction of ovulation [8]. Despite good results reported with CC induction of ovulation, a high proportion of patients still don't achieve pregnancy. This may be attributed to failure of implantation.

Adequately prepared endometrium has to be built up during the menstrual cycle in order to have successful implantation. Steroid hormones, various growth factors and cytokines regulate endometrial development. Some of the regulatory factors are produced locally and act via paracrine mechanisms and others have to be transferred to the endometrium.

Sufficient blood supply is required for these factors to reach the endometrium as it was previously noticed that women having endometrial thickness less than 6 mm were less likely to become pregnant and it should be at least 7 mm for successful implantation [9]. With its vasodilatation effect, sildenafil citrate leads to vascular relaxation and increased blood flow which may improve the endometrial thickness [10,11].

The current study aimed to evaluate the value of enhancing endometrial thickness using oral sildenafil citrate 25 mg three times daily on the pregnancy rate in women undergoing CC induction of ovulation.

The present study showed that there was a significant statistical difference in endometrial thickness and number of follicles between treatment and placebo group which was higher in the treatment group. Thicker endometrium might be attributed to the vasodilator effect of sildenafil citrate which lead to increase uterine blood flow.

This is in agreement with a study done by *Jerzak et al* [12] who reported that there was a good

correlation between endometrial thickness and the prevalence of conception and that endometrial thickness greater than 9mm as determined by vaginal ultrasound in the late proliferative phase, correlates well with the pregnancy rate.

Also in accordance with our results, *Paulus et al* [5] reported that sildenafil citrate improved uterine artery blood flow and the sonographic endometrial thickness in patients with thin endometrial. Moreover, *Fisch et al* [11] found that sildenafil significantly increases endometrial thickness to >7mm when used from day 8 to day 13 of the cycle.

The effect of sildenafil citrate on endometrial thickness had also been reported using different route. *Fisch and Sher* [13] evaluated the effect of vaginal sildenafil citrate on the outcome of IVF after multiple IVF failure attributed to poor endometrial thickness in a cohort of 105 infertile women, with normal ovarian reserve and at least two consecutive prior IVF. They showed that sildenafil citrate enhanced endometrial development in 70% of the studied cases.

The present study showed that there was a statistical significant difference between treatment and placebo group as regards side effects as it was higher among treatment group. Headache representing the most common side effect between the treatment group (20%), flushing (11.4%), blurring of vision (5.7%), finally, GIT disorder (5.7%).

The main reported side effects for sildenafil citrate are headache, flushing, blurring of vision, nausea and dyspepsia [14]. Side effects to sildenafil citrate are mild to moderate in nature and are dose related [15].

In spite of non statistical significant difference in pregnancy rate between both groups, we found that the pregnancy rate in the treatment group was higher by 2.5 than the placebo group.

Also, *Kim et al* [16] detected that pregnancy rate was two folded higher in the study group although it was also statistically non significant through a prospective randomized study done on twenty-one patient by luteal supplementation of sildenafil citrate 25 mg/day.

This come in agreement with the results of a study done by *Dehghani et al* [4] who reported that

implantation rate was higher in the sildenafil citrate group but not statistically significant through a randomized controlled clinical trial which was conducted on forty patients who were given sildenafil citrate 50 mg tablet daily.

#### Conclusions:

Based on our preliminary results sildenafil citrate increased pregnancy rate in females undergoing induction of ovulation by clomiphene citrate 50 mg which may be attributed to the increase in endometrial thickness and number of follicles.

Future studies to evaluate its effect on fetal outcome in pregnant women are needed.

**Conflict of interest:** No Conflict of interest

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