Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.262762.3112 Volume 30, Issue 8.1, NOV. 2024, Supplement Issue
Manuscript ID ZUMJ-2401-3112
DOI 10.21608/ZUMJ.2024.262762.3112

ORIGINAL ARTICLE

Efficacy of Adding Sildenafil Citrate to Clomiphene Citrate as Adjuvant Therapy in Induction of Ovulation

Khaled Hassan Mohamed Al-Sadek, Youssef Abo Elwan, Walid Abdallah, Ahmed Metwally Mohamed

Obstetrics and Gynecology Department, Faculty of Medicine- Zagazig University

Corresponding author:

Khaled Hassan Mohamed Al-Sadek

Email:

elbakhshawangy@gmail.com.

Submit Date 14-01-2024
Revise Date 18-02-2024
Accept Date 28-02-2024

ABSTRACT

Background: Patients who had thinner endometrium could be managed using sildenafil citrate, which could be efficient in enhancing endometrial development and pregnancy outcomes; clomiphene citrate is the first-line treatment for anovulation. The present study aimed for evaluation of the effectiveness of adding sildenafil citrate to the clomiphene citrate as adjunct treatment line for ovulation induction. **Subjects and methods:** We carried out this randomized controlled clinical trial on 98 cases with primary infertility, 49 cases in every group. From 3rd to 7th day seven, participants in groups A and B took 50 mg CC (Clomid) orally twice daily to induce ovulation. From Day eight until the ovulation was triggered, members of group B also received 25 mg of Sildenafil orally once every 12 hours. The frequency of pregnancies in the two groups was subsequently evaluated. **Results:** This study revealed a significantly higher follicular size on day 9 in group A (15.56 ± 2.39) vs (13.42 ± 2.25) in group B. A statistically significant difference was revealed in the thickness of endometrium between the two studied groups in < 7mm and 7 -13mm (p=0.005 and 0.013, respectively); in group B (clomiphene with sildenafil), 41 patients (83.7%) had endometrium of 7 to 13 mm. We found that the pregnancy rates in group B were 25 cases (51%); 23 patients got pregnant with endometrium thickness from 7-13mm, while only two patients got pregnant with endometrium thickness >13mm, and no pregnancy recorded endometrial thickness less than 7mm. **Conclusion:** Sildenafil citrate could increase pregnancy rates among women who are undergoing ovulation induction using clomiphene citrate by increasing endometrial thickness.

Keywords: Clomiphene Citrate, Sildenafil Citrate, Induction of Ovulation, Infertility

INTRODUCTION

Infertility is described as the failure to conceive after one year of sexual intercourse without protection. Fertility issues can arise from a variety of sources. Implantation and endometrial receptivity have taken center stage as etiology remains a mystery in 10–25 percent of couples, even after extensive diagnostic testing. Endometrial thickness (ET) is an essential factor in implantation success [1]. Clinical pregnancy rates and embryo implantation were substantially higher in patients whose ETs were greater than 9 mm, as shown in multiple studies [2].

Implantation and pregnancy are thought to be more difficult to achieve when the endometrial thicknesses are below 7 mm. There aren't many options for women with a thin endometrium, and the ones that do exist are mostly experimental or based on empirical evidence, such as estrogens, granulocyte colony-stimulating factor (G-CSF), acetylsalicylic acid, human chorionic gonadotrophins (hCG), and

piroxicam. Most of these treatments are based on the idea that an increase in blood supply to the endometrium causes endometrial development and thickness [2,3].

As a first-line treatment for anovulation, clomiphene citrate (CC) is recommended [4]. Clomiphene citrate interacts with estrogen receptors in the hypothalamus, making it an antiestrogen agonist. In a mistaken response, the hypothalamus increases blood levels of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to this signal [5]. Most patients (57–91 percent) have their periods induced by CC, and it is easy to use, but the pregnancy chances are still modest (27-40 percent) [6]. The reason could be that CC has negative effects on endometrial growth during stimulation and on the quality of cervical mucus [7].

As a vasoactive agent, sildenafil citrate has been prescribed to men around the world for erectile dysfunction since 1998. In the penile erectile tissue, this specific phosphodiesterase type 5 inhibitor activates the cyclic guanosine monophosphate (cGMP) pathway, amplifying the relaxing and vasodilatory effects of nitric oxide (NO) [8].

Research on the endometrium of rats and humans has revealed that constitutive NO synthase and certain messenger RNAs cause the same impact. The endometrium grows in response to estrogen, and sildenafil citrate increases blood flow to the uterus [9]. It was revealed that patients with a thin endometrium could benefit from sildenafil citrate because it promotes endometrial development and improves pregnancy outcomes [10, 11].

So, we performed this study aimed for evaluation of the effectiveness of adding sildenafil citrate to the clomiphene citrate as adjunct treatment line for ovulation induction.

PATIENTS AND METHODS

In this randomized controlled clinical trial, which lasted from June 2022 to September 2023, 98 patients who had experienced primary infertility. The patients were recruited from Zagazig University Hospitals, either from Outpatient Infertility Clinics or the Obstetrics and Gynecology Department.

Patients were asked to sign an informed consent form. The study's goal and protocol were explained to every patient. This study complies with the Helsinki Declaration, a code of ethics for research involving human subjects, as established by the World Medical Association. Institutional Review Board (IRB) approved the study protocol (#9543/23-5-2022).

They were implying that the average endometrial thickness was 9.64+8 in the intervention group and 8.47+ 2.4 in the control group. With a power of 80% and a 95% confidence interval, the predicted sample size was 98 participants, with 49 individuals from each group. From 3rd to 7th day, participants in groups A and B took 50 mg CC (Clomid) orally twice daily to induce ovulation. From Day 8 until the ovulation trigger, participants in group B also received 25 mg of Sildenafil orally once every 12 hours.

Cases with the following criteria were included: females aged from 18 to 35 years who were diagnosed with primary infertility, having regular menstrual cycles, and their husbands having normal semen parameters and having body mass index (BMI) less than 30k/m^2.

Cases with the following characteristics were excluded: females aged less than 18 or above 35 years and patients who had any ovarian or uterine pathologies or endocrine, cardiovascular, renal, hepatic, and thyroid disorders, we excluded cases when their husbands had abnormal semen parameters. Also, we excluded cases who had tubal pathology like tubal block, hydrosalpinx or pyosalpinx that was detected by hysterosalpingogram (HSG) or diagnostic laparoscopy, or duration of infertility that was less than 1 years.

Methods of randomization

Group A (clomiphene only) received an even number of patient files, while group B (clomiphene plus sildenafil) received an odd number of files, ensuring a random selection.

The following was performed on every case that fulfilled the inclusion criteria: Patients' complete medical histories were obtained, which included details about any chronic or metabolic disorders they may have had. Detailed medical histories were gathered from all infertile couples before they underwent both general and local exams. To check for male factor infertility, a standard semen analysis was performed and interpreted in accordance with

the standards set out by the World Health Organization in 2021 [8].

Day 3 basal hormonal profile testing (follicle-stimulating hormone, Luteinizing hormone, and Prolactin) was performed on the female spouse. On Day 3, a Transvaginal Scan (TVS) was also performed to measure the basic endometrial thickness and image the uterus and adnexa for any potential abnormalities. Patients who fulfilled the requirements were subsequently scheduled for ovulation induction during the subsequent cycle.

From 3rd day to 7th day of the cycle, 50 mg CC (Clomid) was taken orally once daily to induce ovulation in groups A and B. Group B also received 25 mg of Sildenafil (Silden) vaginally every 12 hours beginning on Day 8 and continuing until the ovulation was triggered.

A TVS scan was conducted to examine the follicles and estimate the thickness of the endometrium (ET). Essentially, on day 3, again on day 9, and every day after that until the leading follicles attain a diameter of 18–20 mm. If the E2 level was below 3500 pg/ml, if the follicular size was 18mm to 20mm, 5000 IU of Human Chorionic Gonadotrophin - hCG was administered intramuscularly to induce ovulation.

On Day 30, testing for the β subunit hCG in urine was used to detect pregnancy. During this time, patients were subject to stringent monitoring for adverse consequences, such as Ovarian Hyperstimulation Syndrome (OHSS) [8].

To detect spontaneous miscarriages, tubal ectopic pregnancies, and multiple gestations, the patients were followed up for eight weeks.

STATISTICAL ANALYSIS

A statistical analysis was performed on the data using IIBM SPSS, version 20.0. (IBM Corporation, Armonk, New York). Percentages and numbers were utilized to convey qualitative data. The qualitative characteristics between the groups were compared using a chi-square test instead of the chi-square test; the Fisher exact test was used when one or more of the anticipated cells were fewer than 5. To compare the two groups concerning the quantitative variable in parameters (SD<50 percent mean), an unpaired t-test was employed.

RESULTS

Table (1) showed no statistically significant differences between the studied groups regarding demographic data, infertility types, and duration (p >0.05).

This study revealed a significantly higher follicular size on day 9 in group A (15.56 ± 2.39) vs (13.42 ± 2.25) in group B (Table 2).

The patients who had endometrial thickness less than 7mm and who had endometrial thickness from 7 to 13 mm differed significantly between both groups (15 patients (30.6%), 30 patients (61.2%) in the clomid only group versus four patients (8.2%), and 41 patients (83.7%) in the clomid plus sildenafil citrate group with p values of 0.05 and 0.013 respectively. Also, statistically significant differences were revealed according to pregnancy groups in < 7 mm & 7 -13mm (p<0.001 and p= 0.002, respectively) (Table 3).

As regards the pregnancy rates in group B, there were 25 cases (51%); 23 patients got pregnant with endometrium thickness from 7-13mm, while only two patients got pregnant with endometrium thickness >13mm, and no pregnancy recorded in endometrial thickness less than 7mm (p=0.003) (Table 4).

While there was no statistically significant difference between pregnant and non-pregnant women with respect to age, body mass index (BMI), or the type or duration of infertility, statistically significant differences were found among the follicle size and endometrial thickness (Table 5 and Figure 1).

Table (1): Demographic data, Duration and Type of infertility of the two studied groups

Variable		Group A CC only (n=49)	Group B CC+sildenafil (n=49)	P
Age (years) Mean ± SD		28.78 ± 3.15 yr.	27.68 ± 3.94 yr.	0.888
BMI (kg/m^2) Mean ± SD		28.18 ± 1.617	28.54 ± 2.76	0.180
Duration of infertility (Years) Mean ± SD		1.49 ± 0.34 yr.	1.533 ± 0.51 yr.	0.879
Type	**1ry**	40 (81.7%)	35 (71.4%)	0.076
	2ry	9 (18.3%)	14(28.6%)	

CC: clomiphene citrate , BMI: Body mass Index p value significant if <0.05

Table (2): Size of dominant follicle of the two studied groups.

Follicle Size (mm)	Group A Cc Only (n=49)	Group B Cc +sildenafil (n=49)	p
On day zero Mean ± SD	9.6 ±1.2	8.7 ±1.0	0.712
On day 3 th Mean ± SD	11.4 ±1.4	9.2 ±1.2	0.051
On day 9th Mean ± SD	15.56 ± 2.39	13.42 ± 2.25	0.011
Follicle >18mm Mean ± SD	2.37 ± .57	2.42 ± .563	0.810

P value is significant if <0.05

Table (3): Endometrial thickness in the two studied groups

Endometrial thickness	Group A Cc only (n=49)	Group B Cc +sildenafil (n=49)	p
< 7mm	15 (30.6%)	4 (8.2%)	**0.005**
7 – 13mm	30 (61.2%)	41 (83.7%)	**0.013**
> 13mm	4 (8.2%)	4 (8.2%)	1
Pregnancy	**Positive (n=35)**	**Negative (n=63)**	**P**
< 7mm	0	19 (30.2%)	<0.001
7 – 13mm	33 (94.2%)	38 (61.9%)	0.002
> 13mm	2 (5.7%)	6 (7.9%)	.912

P value is significant if <0.05

Table (4): Pregnancy rate between the two studied groups after three menses.

	Group A Cc only (n=49)	Group B Cc +sildenafil (n=49)	p
Negative	39 (79.6%)	24 (49%)	**0.003**
Positive	10 (20.4%)	25 (51%)	

Table (5): Comparison of different parameters according to pregnancy. Multi-variant analysis

Variable		t	P
Age (years) Mean ± SD		0.501	0.433
BMI (kg/m^2) Mean ± SD		0.871	0.291
Duration of infertility Mean ± SD		0.614	0.510
Type of infertility	**1ry**	0.502	0.895
	2ry		
Size of follicle	**On day 11th** Mean ± SD	**3.013**	**0.001**
	On day 13th/14th Mean ± SD	**2.153**	**0.002**
Endometrial thickness	**On day 11th** Mean ± SD	**5.171**	**<0.001**
	On day 13th/14th Mean ± SD	**5.104**	**<0.001**

P value is significant if <0.05

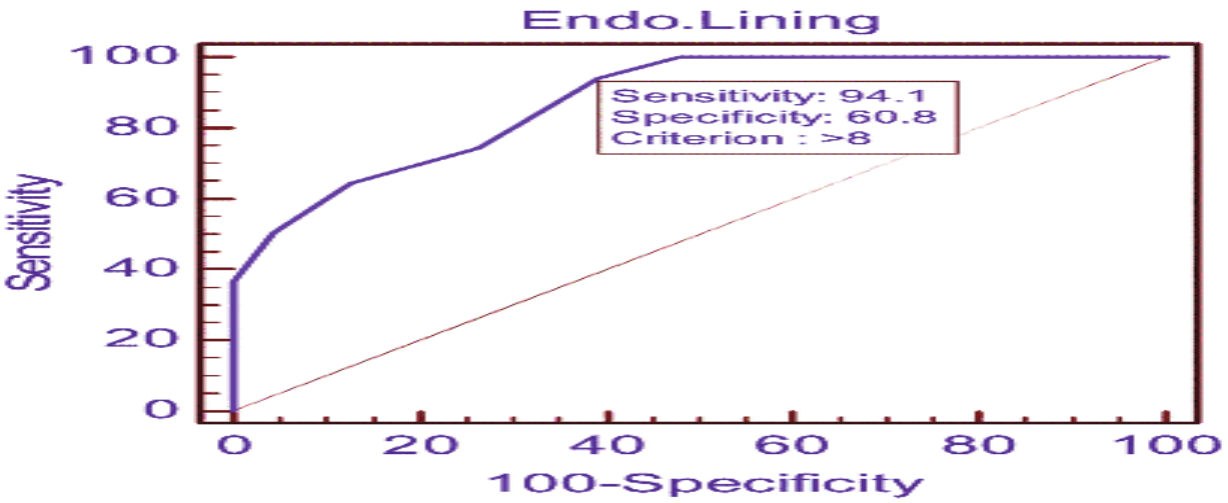

Figure 1: Receiver operating curve of endometrial thickness for clinical pregnancy measured after ovulation induction.

DISCUSSION

Infertility is described as the failure to conceive after one year of sexual intercourse without protection. Infertility can have several causes, and occasionally the exact cause is unknown. The focus has now turned to implantation and endometrial receptivity as, despite extensive diagnostic testing, the cause remains unexplained in 10–25 percent of couples [12].

Roughly 20% of infertility cases are caused by anovulation. Type 2 anovulation, which accounts for about 85% of cases of anovulatory infertility, is defined by the World Health Organization as having normal gonadotropin levels. Polycystic ovarian syndrome accounts for the majority of cases of anovulation [13].

The thickness of the endometrium is a powerful indicator of the likelihood of implantation. Patients with an endometrial thickness of more than 9 mm have a considerably higher rate of embryo implantation and clinical pregnancy, according to several studies. It is believed that the ability of the endometrium to promote implantation and pregnancy is diminished when its thickness is less than 7 mm [14].

Clomiphene citrate is a non-steroidal anti-estrogen that enhances the release of gonadotropin-releasing hormone (GnRH) by blocking estrogen receptors in the hypothalamus. Following an increase in gonadotropin secretion by the pituitary gland, follicle growth and ovulation occurred [15]. Using CC for OI increases the ovulation rate to 70–85% and the pregnancy rate to 40–70%. Only around 15% of women who are not yet pregnant experience a response to CC (CC resistance). The term "CC failure" describes the inability to conceive after CC treatment, even though ovulation has occurred [16].

It was revealed that an ultrasound showed a thin endometrium, indicating inadequate endometrial growth. Endometrial blood flow is essential for the endometrium to grow in response to estrogen. When CC failed to enhance endometrial blood flow and thickness, vasodilators were considered as a possible option for infertile women. By blocking phosphodiesterase-5 (PDE5) and cGMP-dependent protein kinases (PKGs), sildenafil citrate (SC) makes nitric oxide (NO) work more effectively, which relaxes smooth muscle cells. Increased endometrial cell proliferation and better uterine blood flow may be possible side effects of sildenafil citrate [17].

At the Zagazig University Hospital's Obstetrics and Gynecology outpatient clinic for infertility, we enrolled 98 patients in a randomized controlled clinical trial. To compare the success rate of using clomiphene citrate alone against sildenafil plus clomiphene citrate in treating infertility, the patients undergoing the study were split into two groups. The study population's mean standard deviation age was as follows: The values were 28.78 ± 3.15 in group A and 28.54 ± 2.76 in group B.

Our findings are consistent with those of Abdel Hamid et al. [18], who set out to determine whether or not polycystic ovary syndrome patients' endometrial thickness and pregnancy rates would be affected by the addition of vaginal sildenafil citrate to clomiphene citrate, an ovarian stimulant medicine. They also found no statistically significant variation in demographic information between the two studied groups.

Neither group differed significantly from the other with respect to the duration or the type of infertility. Ataalla et al. [19] revealed the same thing: there was no significant difference between the two groups with respect to the length or type of infertility (primary or secondary) ($P>0.05$).

In terms of follicular size on the ninth day, this research showed that the two groups were significantly different ($p=0.011$). Abdel Hamid et al. [18] who aimed to determine whether sildenafil citrate, when used in conjunction with clomiphene citrate (CC), may improve the efficacy of ovulation induction (OI) in PCOS patients (PCOS). In agreement with our findings, they revealed that compared to the CC group, the C/S group had significantly greater rates of follicular maturation (43.4 percent) and ovulation (41.4 percent) ($p = 0.02$), respectively. Adjuvant sildenafil did not enhance ovarian responsiveness in women who had previously had a poor response when used in conjunction with controlled ovarian hyperstimulation, according to another study [19].

In contrast to our result, significant changes in follicular number were observed between two groups after sildenafil treatment, according to Fahmy et al. [4], who aimed to evaluate the efficacy of oral sildenafil in treating female infertility.

Regarding changes in endometrial thickness, the patients who had endometrial thickness less than 7mm and who had endometrial thickness from 7 to 13 mm differed significantly between both groups (15 patients (30.6%), 30 patients (61.2%) in the clomid only group versus four patients (8.2%), and 41 patients (83.7%) in the clomid plus sildenafil citrate group with p values of 0.05 and 0.013 respectively. Also, statistically significant differences were found according to pregnancy groups in < 7 mm and 7 -13mm ($p<0.001$ and $p= 0.002$, respectively).

The present study results were in line with Abdel Hamid et al. [18] findings as they revealed that the endometrium was noticeably thicker in the Sildenafil group (13.4±1.814 mm) as compared to the control group that received only clomiphene citrate (8.52±2.081 mm) (P=0.01). group B had a statistically significant increase in endometrial receptivity when endometrial thickness was more than 7 mm (P=0.019). There have been previous reports of improved endometrial thickness when combining sildenafil with clomiphene citrate during ovulation induction. This may be due to the vasodilator effect of sildenafil citrate, which increases uterine blood flow. The study group may have had thicker endometrial tissue compared to the control group [20].

In a study conducted by Firouzabadi et al. [11], it was found that oral sildenafil can help improve endometrial thickness and receptivity in patients who have experienced past IVF failure because of low endometrial thickness. Consistent with the present study findings, a randomized clinical trial comparing the efficacy of sildenafil alone vs. sildenafil plus clomiphene citrate in inducing ovulation in patients with unexplained infertility found no significant difference in the number of mature follicles. Still, the sildenafil group did show a statistically significant increase in endometrial thickness. Nevertheless, our investigation did not find a sildenafil group with a substantially greater pregnancy rate. Contrary to our findings, this study did not include PCOS patients but rather individuals with unexplained infertility [21].

There was a strong association between endometrial thickness and the prevalence of conception, as reported by Soliman et al. [17] in their research. In the late proliferative period, a vaginal ultrasound-determined endometrial thickness of more than 9 mm is strongly associated with the chance of pregnancy. While using sildenafil from day 8 to day 13 of the cycle, Fisch et al. [22] revealed that endometrial thickness increases dramatically to >7mm. Various methods of reporting sildenafil citrate's effect on endometrial thickness have also been documented.

By reducing the endometrial spiral artery's mean resistance index (RI) values, sildenafil suppositories enhance blood flow to the endometrium (SA). When this happens, the endometrium grows and becomes more receptive, which increases the likelihood of pregnancy in women with unexplained infertility. Endometrial thickness is influenced in this way by sildenafil medication [23].

We found that the pregnancy rates in group B were 25 cases (51%); 23 patients got pregnant with endometrium thickness of 7 to 13mm, while only two patients got pregnant with endometrium thickness >13mm, and no pregnancy recorded with endometrial thickness less than 7mm. Parallel to our study, Seventy percent of the 105 individuals studied by Sher et al. [24] who were managed using vaginal sildenafil for endometrial thickness that was greater than 9 mm, almost 30% of women tested had endometrial thickness measurements below 9 mm. A statistically significant rate of implantation was seen in nearly half of the individuals with endometrial thickness more than 9 mm.

In addition, Abdel Hamid et al. [18] found that the pregnancy rate was slightly greater in the group that received both sildenafil and clomiphene citrate (8 patients = 27.6%) than in the group that received only clomiphene citrate (14 patients = 48.3%).

In addition, combining sildenafil citrate with clomiphene citrate significantly increased the likelihood of clinical pregnancy, according to a meta-analysis that examined the effects of sildenafil citrate in assisted reproductive technology. This contrasted with women who got clomiphene citrate alone. Compared to women who took estradiol valerate alone, those who took the combination with sildenafil citrate had a significantly greater rate of clinical pregnancy [25]. Consistent with these results, research conducted by Jerzek et al. [26] demonstrated a strong correlation between endometrial thickness, as assessed by vaginal ultrasonography during the late proliferative phase, and the likelihood of conception. There is a strong

correlation between the prevalence of conception and endometrial thickness larger than 9 mm.

When considering Endometrial Thickness, follicular development, pregnancy rates, and side effects, in a study including Clomiphene Citrate and ovulation induction cycles, Pranathi et al. [27] assessed the role of Sildenafil (CC). Sildenafil improves ET and enhances fertility, as they demonstrated.

Also, the findings of Zinger et al. [28] were in line with our results as they detected that concomitant administration of sildenafil citrate had a beneficial impact on uterine receptivity. Appropriate endometrial thickness and good blood supply to the endometrium are usually considered an essential requirement for implantation. Additionally, a prospective randomized study was conducted by Kim et al. [29] on twenty-one patients who were given 25 mg of sildenafil citrate daily as a luteal supplement. The researchers found that the pregnancy rate was twice as high in the study group, although this difference was not statistically significant.

Contrary to the results of Ataalla et al. [19], the rates of pregnancy were statistically not significantly higher in the sildenafil group (6 cases compared to 4 cases in the control group). Possible causes for this include similar patient demographics in both groups and a small sample size in the research. Another explanation for the significantly larger endometrium in the sildenafil group is that both groups' endometrium was within the acceptable range on the day of HCG.

Endometrial thickness was 9.8 mm in the sildenafil citrate group and 8 mm in the control group, and the chemical pregnancy rate was higher in the sildenafil citrate group as well. According to Firouzabadi et al. [11], however, the difference did not reach a statistical significance. Although there was no statistically significant difference in the pregnancy rates between the two groups, we discovered that the treatment group had a 2.5-fold greater rate of pregnancy than the placebo group, as demonstrated by Fahmy et al. [4].

This study had some limitations. First, it had a relatively small sample size, which could limit the generalizability of our findings to larger populations. Secondly, our study focused on specific aspects of medication effectiveness and side effects and did not delve into other potential factors that could influence treatment outcomes. Further research with larger and more diverse samples, longer follow-up periods, and consideration of additional variables is warranted to provide a more comprehensive understanding of whether adding sildenafil citrate to clomiphene citrate has a great efficacy as adjuvant therapy in the induction of ovulation. However, further studies are needed to evaluate its effect on fetal outcomes in pregnant women.

CONCLUSION

We revealed that Sildenafil citrate improves endometrial growth and increases the likelihood of pregnancy in women taking clomiphene citrate 50 mg twice day for ovulation induction. This may be because it causes the endometrial thickness to increase.

CONFLICTS OF INTEREST

No potential conflict of interest was reported by the authors.

REFRENCES

1. Fogarty NME, McCarthy A, Snijders KE, Powell BE, Kubikova N, Blakeley P,et al. Genome editing reveals a role for OCT4 in human embryogenesis [published correction appears in Nature. 2017 Oct 04;:]. *Nature*. 2017;550(7674):67-73.
2. Mangal S, Mehirishi S. To study and compare the effect of vaginal sildenafil and estradiol valerate on endometrial thickness, blood flow, and pregnancy rates in infertile women undergoing intrauterine insemination. *Int J Reprod Contracept Obstet Gynecol*. 2016;5(7):2274–7.
3. Mathyk B, Schwartz A, DeCherney A, Ata B. A critical appraisal of studies on endometrial thickness and embryo transfer outcome. Reprod Biomed Online. 2023;47(4):103259.
4. Fahmy A, El Sokkary M, Sayed S.T he value of oral sildenafil in the treatment of female infertility: A randomized clinical trial. Life Sci J, 2015,12, 78-82.
5. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertil Steril*. 2009;92(5):1520-4.

6. Navot D, Scott RT, Droesch K, Veeck LL, Liu HC, Rosenwaks Z. The window of embryo transfer and the efficiency of human conception in vitro. *Fertil Steril*. 1991;55(1):114-8.
7. Mercé LT, Barco MJ, Bau S, Troyano J. Are endometrial parameters by three-dimensional ultrasound and power Doppler angiography related to in vitro fertilization/embryo transfer outcome?. *Fertil Steril*. 2008;89(1):111-7.
8. Langarizadeh MA, Salary A, Tavakoli MR, Nejad BG, Fadaei S, Jahani Z, et al. An overview of the history, current strategies, and potential future treatment approaches in erectile dysfunction: a comprehensive review. Sex Med Rev. 2023;11(3):253-67.
9. Richter KS, Bugge KR, Bromer JG, Levy MJ. Relationship between endometrial thickness and embryo implantation, based on 1,294 cycles of in vitro fertilization with transfer of two blastocyst-stage embryos. *Fertil Steril*. 2007;87(1):53-9.
10. Dehghani Firouzabadi R, Davar R, Hojjat F, Mahdavi M. Effect of sildenafil citrate on endometrial preparation and outcome of frozen-thawed embryo transfer cycles: a randomized clinical trial. *Iran J Reprod Med*. 2013;11(2):151-8.
11. Khazei N, Ayati E, Movafegh A, & Azimaraghi O. Azimaraghi. Effect of vaginal sildenafil on in vitro fertilization success rates in women with previous failed in vitro fertilization attempts. *Asian J Pharm Clin Res* 2018; 11: 486–8.
12. Szamatowicz M, Szamatowicz J. Proven and unproven methods for diagnosis and treatment of infertility. Adv Med Sci. 2020;65(1):93-96.
13. Weiss NS, van Vliet MN, Limpens J, Hompes PGA, Lambalk CB, Mochtar MH, et al. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. *Hum Reprod*. 2017;32(5):1009-18.
14. Legro RS. Evaluation and Treatment of Polycystic Ovary Syndrome. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 11, 2017.
15. Balen AH. Ovulation induction in the management of anovulatory polycystic ovary syndrome. *Mol Cell Endocrinol*. 2013;373(1-2):77-82.
16. Mohammed W, Abbas M, Abdelazim I, Salman M. Sildenafil citrate as an adjuvant to clomiphene citrate for ovulation induction in polycystic ovary syndrome: crossover randomized controlled trial. Menopause Review/ Prz Menopauzalny. 2022;21(1):20-6.
17. Soliman GM, Fetih G, Abbas AM. Thermosensitive bioadhesive gels for the vaginal delivery of sildenafil citrate: in vitro characterization and clinical evaluation in women using clomiphene citrate for induction of ovulation. *Drug Dev Ind Pharm*. 2017;43(3):399-408.
18. Abdel Hamid S, Farag A, El-Husseiny A, Ahmed T. Effect of Sildenafil Citrate on Success Rate of Ovulation Induction by Clomiphene Citrate. *ejhm*,2021, 85(2), 3509-13.
19. Ataalla W, Abd Elhamid T, Elhalwagy A. Adjuvant sildenafil therapy in poor responders undergoing in vitro fertilization: A prospective, randomized, double- blind, placebo-controlled trial. Middle East Fertil. Soc. J,2016, 21: 175-9.
20. Fetih AN, Habib DM, Abdelaal II, Hussein M, Fetih GN, Othman ER. Adding sildenafil vaginal gel to clomiphene citrate in infertile women with prior clomiphene citrate failure due to thin endometrium: a prospective self-controlled clinical trial. *Facts Views Vis Obgyn*. 2017;9(1):21-7.
21. Aboelroose AA, Ibrahim ZM, Madny EH, Elmazzahy AM, Taha OT. A randomized clinical trial of sildenafil plus clomiphene citrate to improve the success rate of ovulation induction in patients with unexplained infertility. *Int J Gynaecol Obstet*. 2020;150(1):72-6.
22. Fisch P, Casper RF, Brown SE, Wrixon W, Collins JA, Reid RL, et al. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. *Fertil Steril*. 1989;51(5):828-33.
23. El-Shourbagy S, Ossman A, El-Mohamady A.The role of sildenafil citrate (viagra) suppositories on endometrial response (thickness and mean resistance index of endometrial spiral artery) in cases of unexplained infertility. MMJ,2017, 30(2): 343-46.
24. Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. *Fertil Steril*. 2002;78(5):1073-6.

25. Rouholamin S, Sepidarkish M, Razavi M, Nabati A, Marou zadeh S, Rezaeinejad M. Effect of sildenafil citrate in women undergoing assisted reproduction: a meta- analysis based on randomized controlled trials. Research Square,2020, 20: 1-20.
26. Jerzak M, Kniotek M, Mrozek J, Górski A, Baranowski W. Sildenafil citrate decreased natural killer cell activity and enhanced chance of successful pregnancy in women with a history of recurrent miscarriage. *Fertil Steril*. 2008;90(5):1848-53.
27. Pranathi Reddy L, Madhavi Y, Mohammed I. Role of Sildenafil in ovulation induction – A comparative study of outcomes with Sildenafil in ovulation induction cycles with Clomiphene Citrate. IAIM, 2016; 3(12) 26-32.
28. Zinger M, Liu JH, Thomas MA. Successful use of vaginal sildenafil citrate in two infertility patients with Asherman's syndrome. *J Womens Health (Larchmt)*. 2006;15(4):442-4.
29. KIM K. R, LEE H. S, RYU,H. E, PARK C. Y, MIN S. H, PARK C. Et al. Efficacy of luteal supplementation of vaginal sildenafil and oral estrogen on pregnancy rate following IVF-ET in women with a history of thin endometria: A pilot study. *J Wowens Med,* 2010,3, 155158.

Citation

Al-Sadek, K., Abo Elwan, Y., Abdallah, W., Mohamed, A. Efficacy of Adding Sildenafil Citrate to Clomiphene Citrate as Adjuvant Therapy in Induction of Ovulation. *Zagazig University Medical Journal*, 2024; (3830-3839): -. doi: 10.21608/zumj.2024.262762.3112