

Effect of Sildenafil Citrate on Success Rate of Ovulation Induction by Clomiphene Citrate

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ABSTRACT

Background: Disorders of ovulation are common causes of infertility, and polycystic ovary syndrome (PCOS) is by far the most frequent condition.

Objective: The aim of this work was to evaluate the effect of adding vaginal sildenafil citrate to clomiphene citrate used as ovarian stimulant drug on both endometrial thickness and pregnancy rate in patient with polycystic ovary syndrome (PCO).

Patients and Methods: This prospective Comparative study included a total of 58 patients with primary and secondary infertility aged between 18 years to 35 years, attending at Outpatient Clinics, Obstetrics and Gynecology Department, Zagazig University Hospitals. Patients were divided into two equal groups; each were 29. 1st Group was given clomiphene, and 2nd group was given Clomiphene citrate and Sildenafil. A transvaginal Scan for imaging the uterus and adnexa for any pathology and measuring the basic endometrial thickness was also done on Day 3.

Results: This study shows that there was an increase in endometrial thickness in sildenafil group (13.4±1.814 mm) comparable with clomiphene citrate group only (8.52±2.081 mm) (P=0.01). The result was statistically significant with increase threshold regard for implantation with statistically significant in group B (P=0.018).

Conclusions: It could be concluded that addition of sildenafil citrate to clomiphene citrate therapy for induction of ovulation in patients with PCOS resulted in significant increase of endometrial thickness and non-significant increase of pregnancy Rates.

Keywords: Sildenafil, Clomiphene, Polycystic ovary syndrome.

INTRODUCTION

Infertility is defined as the inability to conceive after one year of unprotected intercourse. The causative factors of infertility are diverse and at times unexplained. Despite extensive diagnostic workup, etiology in 10 – 25% of the couples remains unexplained⁽¹⁾ and this has brought implantation and endometrial receptivity into focus⁽²⁾.

One of the strongest predictors of implantation is endometrial thickness (ET)⁽³⁾. A number of studies have put forth that embryo implantation and clinical pregnancy rates are significantly higher in patients with an Endometrial Thickness more than 9 mm⁽⁴⁾. Endometrial thickness less than 7 mm is thought to be less able to support implantation and pregnancy⁽⁵⁾.

The available option for treating thin endometrium is deal up with largely empiric or experimental by the use of estrogens, hCG, piroxicam, Granulocyte Colony Stimulating Factor (G-CSF) and Acetylsalicylic acid⁽³⁾. Most of these treatments are based on the fact that an increase in blood flow to the endometrium causes endometrial development and thickening. The importance of endometrial appearance as a predictor of outcome in patients undergoing induction of ovulation is well established. However, treatment with estrogens alone does not appear to improve pregnancy rates significantly in patients with an inadequate endometrial response⁽⁶⁾.

Clomiphene citrate is the first-line treatment for anovulation⁽⁷⁾. It is an antiestrogen agonist Clomiphene citrate antagonist that interacts with hypothalamic estrogen receptors. The hypothalamus interprets this signal falsely with a rise in circulating luteinizing hormone (LH) and follicle stimulating hormone (FSH)⁽⁸⁾.

Although CC is easy to use and results in ovulation in most patients (57-91%), the pregnancy rates are disappointing (27-40%)⁽⁹⁾. It is because of the adverse effects of CC mainly on quality of the cervical mucus and the endometrial development during the stimulation⁽¹⁰⁾.

It has been reported that vaginal Sildenafil significantly reduced peripheral natural killer cell (NK-cell) activity and improved successful pregnancy rates in women with histories of recurrent miscarriages. Although the mechanism of influence by Sildenafil on natural killer cell activity is unclear, it seems that enhancement of uterine artery flow has an effective influence on the local endometrial NK-cell population⁽¹¹⁾.

The aim of the current work was to investigate whether sildenafil vaginal tablet plus clomiphene citrate would improve endometrial thickness, ovulation rates and pregnancy rates compared with clomiphene citrate alone.

PATIENTS AND METHODS



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This prospective Comparative study included a total of 58 patients with primary and secondary infertility aged between 18 years to 35 years, attending at Outpatient Clinics, Obstetrics and Gynecology Department, Zagazig University Hospitals. This study was conducted between May 2019 to September 2020.

Patients were distributed into two equal sized groups A & B, by closed envelope technique. In group A, 29 patients were prescribed Clomiphene citrate (CC) alone. In group B, 29 patients were prescribed Clomiphene citrate (CC) and Sildenafil tab.

Ethical Consideration:

An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Age less than 35 years and more than 18 years, primary or secondary infertility, with regular menstrual cycles, and normal semen parameters of the husband, BMI less than 35k/m². PCO was diagnosed according to Rotterdam, ESHR, ASRM workshop ⁽¹²⁾.

Exclusion criteria:

Pathology of uterus and ovaries, endocrine and thyroid disorders, tubal infertility as detected by Hysterosalpingogram (HSG), and cardiovascular, renal or hepatic disorders.

All the couples with infertility were initially taken up for detailed history taking and then subjected to general and local medical examination. A basic semen analysis was done and read according to WHO 2010 criteria ⁽¹³⁾, to rule out male factor infertility and limit confounding. This was then followed by investigating

the female partner by basal hormonal profile on Day 3 (Follicle Stimulating hormone, Luteinizing hormone and Prolactin). A Transvaginal Scan (TVS) for imaging the uterus and adnexa for any pathology and measuring the basic Endometrial Thickness was also one on Day 3. The patients who met the criteria were then taken for ovulation induction in the next cycle.

Ovulation induction in group A and B was done with 50 mg CC (Clomid) orally 2 times/day from Day 3 to Day 7 of the cycle. In group B additionally vaginal Sildenafil tablets 25mg/12h daily was given from Day 8 up to ovulation trigger. TVS scan as performed for Follicular study and measurement of endometrial thickness (ET). Basically, at day 3, then day 9 and thereafter daily till leading follicle reach 18-20mm in diameter. 5000 IU of Human Chorionic Gonadotrophin - hCG was administered intramuscularly as an ovulation trigger if the follicular size was 18mm – 20mm. Pregnancy was detected by testing for the β subunit hCG in urine on Day 30. Patients were closely monitored during this period for side effects as Ovarian Hyperstimulation Syndrome (OHSS). The patients were followed thereafter for a period of 8 weeks for spontaneous miscarriages, tubal ectopics and multiple gestation.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ²) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULTS

Table (1): Demographic characteristics in studied groups.

Characteristic	Group A clomiphene citrate only group (N =29)	Group B Sildenafil group (N =29)	P value
Age (years) Mean± S.D Range (20-35)	30.45±6.522	28.28±6.216	P =0.56
Parity (Mean± S.D)	0.3±0.021	0.29±0.081	P =0.61
Types of infertility • Primary • Secondary	N=18(62.1 %) N=11(37.9 %)	15(51.7) 14(48.3%)	P = 0.56
Duration of infertility(years) Mean± S.D	5.3±1.7	5.7±1.6	P =0.60
BMI (kg/m ²)- Mean ±S.D	21.7 ± 1.93	22.3 ± 1.76	P = 0.8

Both groups were comparable with non- significant differences.

Table (2): Hormonal profile of studied groups

Hormonal	Group A clomiphene citrate only (N =29) Mean± S.D	Group B Sildenafil group (N =29) Mean± S.D	P value
TSH (u IU/ml)	2.02 ±0.96	2.09±0.20	P=0.81
Day-2 serum LH (IU/ml)	9.28±2.46	8.95±2.50	P=0.80
Day-2 serum FSH (IU/ml)	6.37±0.96	6.18±0.92	P=0.54
Prolactin (ng/ml)	18.21±1.20	17.00±1.35	P=0.62

Both groups were comparable with no statistically significant differences between both groups regarding TSH, LH, FSH and prolactin serum levels.

Table (3): Endometrial thickness and number of dominant follicles (> 18 mm) in studied groups.

Ultrasound Characteristic at day of HCG administration	Group A clomiphene citrate only group (N =29) Mean± S.D	Group B Sildenafil group (N =29) Mean± S.D	P value
Endometrial Thickness (mm)	8.52±2.081	13.4±1.814	P =0.01**
Number of dominant Follicles > 18 mm	2.45±0.783	2.52±0.714	P=0.81

Endometrial Thickness was significantly high (P=0.001) in Sildenafil group (13.4±1.814 mm) compared to control group with clomiphene citrate only (8.52±2.081 mm). However, number of dominant follicles > 18 mm was comparable in both groups with no statistically significant difference.

Table (4): Stratification of studied groups according to Endometrial thickness threshold (7mm)

Endometrial thickness	Group A clomiphene citrate only group (N =29)	Group B Sildenafil group (N =29)	P value
Cases > 7mm	15(51.7%)	18(62.1%)	0.019*
Cases < 7mm	14(48.2%)	11(37.9%)	0.813

Proportion of patient with Endometrial thickness above (7mm) was significantly high in sildenafil group (P=0.019)

Pregnancy Test in both groups by serum B.HCG done 3-5 days after expected menses. Shows a non-significant higher pregnancy rate in sildenafil group (14/29- 48.3%) compared to clomiphene citrate only group (8/29- 27.6%) (Figure 1).

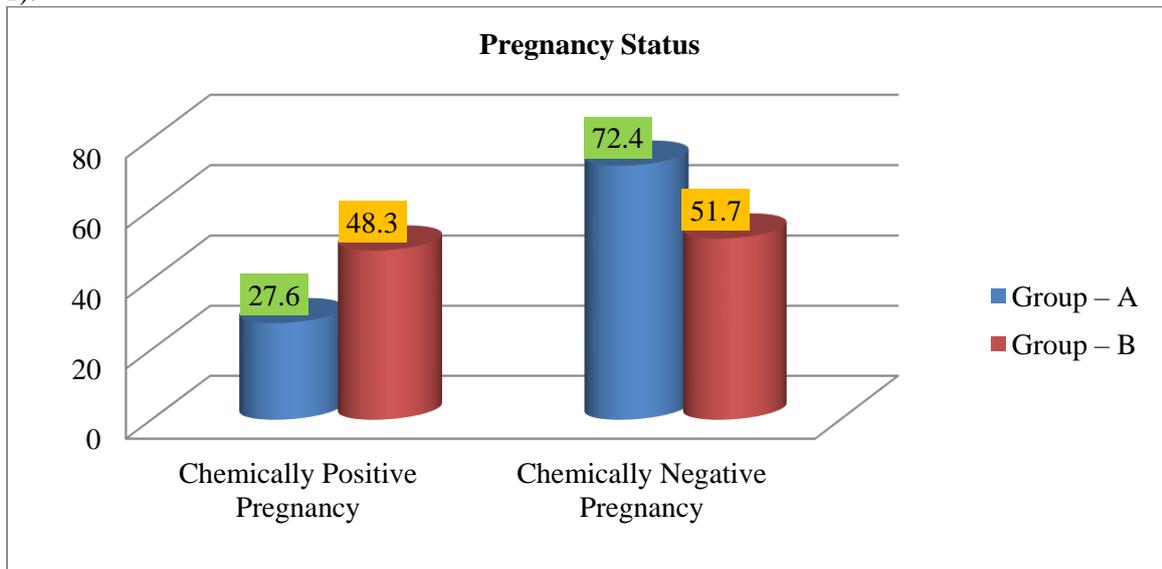


Figure (1): Pregnancy rates (by serum B.HCG) of studied groups.

DISCUSSION

The demographic data show no significant difference between two studied group regarding to age, parity, BMI, type, and duration of infertility. Regarding to hormonal profile of studied groups. Both groups were comparable with no statistically significant differences between TSH, LH, FSH and prolactin serum levels.

This study shows that endometrium was significantly thicker in Sildenafil group (13.4 ± 1.814 mm) compared to control group with clomiphene citrate only (8.52 ± 2.081 mm) (**P=0.01**). with endometrial thickness above 7 mm, a level below which receptivity of endometrium is improved was statistically significant in group B ($P=0.019$). Improved endometrial thickness in the study group compared with the control group might be attributed to the vasodilator effect of sildenafil citrate, which leads to an increase in uterine blood flow improved endometrial thickness when adding Sildenafil to Clomiphene citrate during ovulation induction has been reported in other studies⁽¹⁴⁾.

A systematic review and meta-analysis, on effect of sildenafil citrate on treatment of infertility in women with a thin endometrium, reported that Sildenafil citrate is effective in improving endometrial thickness, the clinical pregnancy rate, and the biochemical pregnancy rate in women who have a thin endometrium⁽¹⁵⁾. Some studies have reported that Sildenafil citrate improves the uterine artery blood flow and the sonographic endometrial thickening in patients with a prior assisted reproductive cycle failing due to poor endometrial response with a comparable higher pregnancy rates⁽¹⁶⁾.

On the other hand, some authors reported a non-significant increase of endometrial thickness when adding sildenafil to conventional gonadotropin-releasing hormone (GnRH) protocol during ovarian stimulation⁽¹⁷⁾.

We reported a comparable number of preovulatory dominant follicles (> 18 mm) in both groups. So, sildenafil does not appear to affect follicular growth or numbers. Similarly, which according with other studies which reported that adjuvant sildenafil does not enhance ovarian responsiveness in cases of previous low ovarian response to controlled ovarian hyperstimulation⁽¹⁸⁾.

Also, in a randomized clinical trial of sildenafil plus clomiphene citrate to improve the success rate of ovulation induction in patients with unexplained infertility, similar to result of this study, the number of mature follicles didn't differ significantly among the studied groups with a significant increase of endometrial thickness in sildenafil group. However, a significantly higher pregnancy rate was reported in sildenafil group which is not similar to our study. But this study was carried out on patients with unexplained infertility and not on patients with PCOS as in our study⁽⁶⁾.

The result of the study reported, only, a non-

significant higher pregnancy rate in sildenafil group (8 patients =27.6%) compared to clomiphene citrate only group (14 patients = 48.3%).

El-Shourbagy et al.⁽¹⁹⁾ stated that treatment with sildenafil suppositories enhances endometrial blood flow by decreasing the mean resistance index (RI) values of endometrial spiral artery (SA) and consequently improves endometrial growth and receptivity in cases of unexplained infertility, thus yielding a better conception rate. However, this study was carried out on patients with unexplained infertility and abnormal uterine perfusion may be a contributing factor to etiopathology of infertility in this category of infertility⁽²⁰⁾. Additionally, clomiphene citrate, that may adversely affect the endometrium, was not used in this study⁽¹⁹⁾.

Contrary to result of this study, a meta-analysis evaluating the effect of sildenafil citrate in women undergoing assisted reproduction reported that the probability of clinical pregnancy was significantly higher in women who received the combination of sildenafil citrate and clomiphene citrate compared with clomiphene citrate alone. Furthermore, clinical pregnancy was reported to be significantly increased in women who received combination of estradiol valerate and sildenafil citrate compared to estradiol valerate⁽²¹⁾.

Our study, compared to a meta-analysis included a small number of cases. So, non-significant pregnancy rate reported in our study could be explained on the light of this fact. Consequently, a larger study including more patients may prove significant pregnancy rates⁽²¹⁾.

CONCLUSIONS

It could be concluded that addition of sildenafil citrate to clomiphene citrate therapy for induction of ovulation in patients with PCOS resulted in significant increase of endometrial thickness and non-significant increase of pregnancy Rates.

Sildenafil citrate could be added to clomiphene citrate during induction of ovulation in patients with PCOS to increase of endometrial thickness in patient with slim endometrium. Larger studies, including large number of patients, are still required to better evaluate the effect of adding Sildenafil citrate to clomiphene citrate during induction of ovulation in patients with PCOS pregnancy rates.

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