

Original Article

Comparison of Clomiphene Citrate Alone and Clomiphene Plus Sildenafil Citrate to Improve Ovulation Induction in Patients with Unexplained Subfertility

Clomiphene Citrate Alone and Plus Sildenafil Citrate to Improve Ovulation

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ABSTRACT

Objective: To compare the efficacy of Clomiphene Citrate (CC) plus Sildenafil with Clomiphene Citrate (CC) alone when used in ovulation induction.

Study Design: A non-randomized control trial study

Place and Duration of Study: This study was conducted at the Obstetrical & Gynecology Department of Nishtar Hospital, Multan from 11th March 2022 to 20th April 2023.

Materials and Methods: The estimated sample size of 62 patients was divided into Group A (Clomiphene Citrate + Sildenafil) and Group B (Clomiphene Citrate); each group was categorized into 31 patients. The outcome was measured by abdominal ultrasonography endometrial thickness of at least 7mm for conception, TVS no development of mature ovarian follicles to at least 18 to 20 mm, and positive β -hCG screening pregnancy rates. An organized proforma collected data. The chi-square assessment controlled the post-stratification of effect modifiers and effect modifiers, and a p-value ≤ 0.05 was taken as statistically significant.

Results: Both groups were comparable with non-significant differences. The study's participants were 26.22 years old on average. ET in the sildenafil group was more incredible (9.63 ± 1.98) compared to the control group (7.38 ± 1.14) (p-value < 0.05). After 3 cycles of induction, pregnancy rates were higher in group A than in group B (74.1% vs 54.83%) (P-value < 0.05). At the same time, the no. of mature follicles development had statistically insignificant results.

Conclusion: Clomiphene citrate, along with sildenafil, has a higher pregnancy rate in sub-fertile women than clomiphene alone, with fewer side effects.

Key Words: Infertility, Endometrium Thickness, Clomiphene, Sildenafil, Pregnancy

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INTRODUCTION

Infertility occurs after a year of unprotected sexual intercourse. Per WHO, anovulation affects 82% of women with anovulatory infertility and normal gonadotropin levels. Most polycystic ovarian syndrome cases¹. After rigorous diagnostic testing, 10–25% of etiologies remain unknown. Implantation is best predicted by endometrial width. (ET), with > 9 mm endometrial thickness have higher clinical pregnancy².

Thin endometrium can facilitate implantation and pregnancy, although most therapies are empirical or experimental³.

Assisted reproductive technology (ART) in which implantation requires a receptive endometrium and embryo-endometrium synchronization⁴. Endometrial thickness predicts ART success. Poor endometrial receptivity, necessary for a successful pregnancy, is one reason embryo implantation fails⁵. The thin endometrium is < 7 mm,⁶ increases conception risk regardless of ovarian stimulation. Endometrial girth and pattern affect conception.^{7,8}

Pregnancy depends on endometrial blood flow; several studies show that implantation requires a robust blood supply. To improve endometrial receptivity, estrogens and low-dose aspirin are indicated. NO synthetase isoforms in the uterus increase vasodilation via c-GMP, which is increased by Sildenafil citrate. In our investigation, we added sildenafil to clomiphene to determine its effects on ET and vascularity.⁹ Several techniques have prompted follicular formation. Typical therapy for erectile dysfunction is clomiphene citrate. By alleviating the hypothalamus of negative

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endogenous and enhancing gonadotropins, clomiphene citrate stimulates ovulation.⁹ Clomiphene citrate, a treatment for anovulation, with Sildenafil citrate may promote the development of the endometrial lining and uterine blood flow when combined with estrogen. Sildenafil citrate increases endometrial thickness and clinical and biochemical pregnancy rates in women with thin endometrium. This treatment may be advantageous for thin endometria.¹⁰

The current study aimed at whether combining sildenafil and clomiphene citrate, compared to clomiphene citrate alone, would increase ovulation, endometrial thickness, and conception rates in individuals with unexplained infertility. It is less expensive since it is a developing social issue and is less costly when considering the financial load. There needed to be more information available.

MATERIALS AND METHODS

Using a non-probability consecutive sampling technique, it was a non-Randomized controlled trial at the Gynecology & Obstetrics Department of Nishtar Hospital, Multan, from 11th March 2022 to 20th April 2023. The institutional review board granted ethical permission (No.122; Dated 17-02-2022) and was carried out under Helsinki's Declaration. Using Openepi to sample size calculation for comparing two means, ET between the two groups as 4 ± 1.4 and 9.2 ± 1.9 ¹¹, with a confidence interval of 95% and an 80% power of the study, the sample size was 62. Sub-fertile women, 20–35 years old, primary/secondary sub-fertility, normal menstrual cycle, and $\text{BMI} < 30 \text{ kg/m}^2$. Endometrial cysts, medication hypersensitivity, and HSG-detected tubal subfertility were eliminated. The outcome was measured by abdominal ultrasonography endometrial thickness of at least 7mm for conception, TVS no development of mature ovarian follicles to at least 18 to 20 mm, and positive β -hCG screening pregnancy rates. An organized proforma collected data.

Eligible patients, after informed consent, history and local examination were undergone, baseline hormonal profiles (FSH, LH, prolactin blood level) and hysterosalpingography on day 3 of the menstrual cycle to rule out aberrant hormone levels and tubal subfertility. On an alternate basis, Group A took sildenafil citrate (25 mg) twice daily from days 8-12

and clomiphene citrate (100 mg) once daily from 3-7. Group B received the same clomiphene citrate dose as Group A on the same day, along with a starch-based placebo pill in place of sildenafil. On Day 13, abdominal ultrasound measured ET and follicular development. 5000 IU of human chorionic gonadotrophin (hCG) was given intramuscularly to stimulate ovulation in follicles between 18-20 centimetres. On Day 30, urine hCG subunits confirmed pregnancy. Patients were monitored for adverse effects. If induction failed and there was no chemical pregnancy, it was tried again on Day 3 of the next cycle. After three attempts, the patient was referred to a reproductive expert. TVS and pregnancy screening on day 30 were analysed. After collecting the required data, complete statistical analysis was completed using SPSS v26. Quantitative variables like age, BMI, duration of sub-fertility, and ET mean and standard deviation were calculated. Qualitative data were presented as frequencies and percentages like gender, follicular development, pregnancy rate, and side effects noted or not. The chi-Square test and Student's t-test were used where applicable for variables. The chi-square assessment controlled the post-stratification of effect modifiers and effect modifiers, and a p-value ≤ 0.05 was taken as statistically significant.

RESULTS

Sixty-two infertile women were treated with clomiphene citrate (Group B) and clomiphene plus sildenafil (Group A). The average age of the study participants was 28.46 years. Group B's mean age was 25.36 ± 3.75 -year, while Group A's average was 27.07 ± 4.67 . There were no statistically significant differences among the patient demographic characteristics. (Table 1).

Patients in group A had comparatively more endometrial thickness development than group B (9.63 ± 1.98 vs 7.47 ± 1.14 mm, p-value=0.001). After three induction cycles, pregnancy rates were 54.83% in group B versus 74.1% in group A (p-value <0.05). The average number of mature follicles was comparative results in both groups (Table 2). Regarding the side effects, CC plus sildenafil group had more headaches, dizziness, and flushing than the CC alone group (p-value <0.05). (Table 3).

Table No. 1: Demographic characteristics of the study population

Characteristic	Group A (N = 31)	Group B (N = 31)	P-value
Age (years)	27.071 ± 4.57 years	25.368 ± 3.74 years	0.07
Height (cm)	5.4 ± 1.83	5.2 ± 1.78	0.6
Weight (kg)	62 ± 1.95	58 ± 1.97	0.7
BMI (kg/m^2)	22.3 ± 1.76	21.7 ± 1.93	0.8
Mean Duration of sub-fertility (years)	1.9 ± 0.01	2.5 ± 0.02	0.09

Table No. 2: Outcome variables of two groups

Characteristic	Group A	Group B	P-value
Endometrial Thickness (mean)	9.63 ± 1.98mm	7.46 ± 2.3 mm	0.001
No. of mature Follicular (mean)	1.62 ± 0.72	1.62 ± 0.72	0.09
Pregnancy rate	23 (74.1%)	17 (54.83%)	0.04

Table No. 3: Comparison of side effects between two groups

Side Effect	Group A	Group B	p-value
Headache	4 (12%)	2 (5%)	0.006
Dizziness	4 (12%)	1 (2.5%)	
Flushing	5 (16.5%)	4 (10%)	
Blurred Vision	3 (9.6%)	2 (5%)	
GIT Disturbance	2 (6%)	2 (5%)	
No Side Effects	12 (38.5%)	19 (61.5%)	
Miscarriages till 8 th weeks	1 (3.5%)	1 (2.5%)	

DISCUSSION

Ovulatory disorders cause 30–40% of female infertility. Ovulation induction is cheaper and less invasive. CC starts induction. Ahmed Abdel Kader Fahmy et al. found that CC patients have high fertilization rates but low implantation rates. Implantation is assisted reproduction's weakest link.¹²

Treat the thin endometrium before trying pregnancy. First, rule out Asherman's syndrome using hysteroscopy.¹³ Another cause, like chronic endometritis, is confirmed by hysteroscopy and endometrial biopsies. The endometrium may respond to a tighter cut-off.¹⁴ Low endometrial thickness, ineffective ART, pregnancy problems such as preeclampsia, and intrauterine growth abnormalities are often linked.^{15,16} Low-dose aspirin and phosphodiesterase inhibitors can be used to treat.

Sildenafil boosted endometrial thickness and pregnancy rates compared to clomiphene citrate alone, according to current studies. Compared to the control group, the study group had higher adverse effects. Except for the main infertility duration, both groups had similar demographics. This contradicts previous research that found no significant variations in population age, infertility duration, or category.¹⁷ The research group's thicker endometrium may be due to sildenafil citrate's vasodilator action, which increases uterine blood flow.¹⁸ This was highlighted by Fetih et al.¹ and Mangal and Mehirishi (2017).¹⁹

Patients reported headache (20.0%) and flushing (12.5%) as sildenafil side effects. Berman et al. (2003)²⁰ confirmed this. Sildenafil affects circulation. Contrary to previous findings, the research group's greater pregnancy rate was statistically significant.²¹

Stimulation regimens may cause this. Anovulatory infertility patients need sildenafil studies. In thin endometrium, IVF/ICSI failures should also be evaluated. Oral preparations had more harmful effects in the current study. Thus, vaginal preparations need more research.

Group B's endometrial thickness increased somewhat after hCG injection. Oral or vaginal sildenafil citrate alone or with estradiol significantly thickened endometrium in prior versions.²² A vaginal suppository may alleviate low-blood-pressure headaches better than oral sildenafil. In another study,¹⁸ 9 mm, vaginal sildenafil decreased endometrial thickness in 70% of subjects. In the prospective study,²³ women with ET <8 mm and right artery radial vascular resistance were given vaginal sildenafil citrate, vitamin E, and L-arginine to investigate their effects.

In contrast to a meta-analysis, our research only comprised a few cases. Therefore, in the context of this fact, the non-significant rate of pregnancy found in our research could be justified. As a result, a more extensive study with more participants could demonstrate significant pregnancy rates.²⁴

CONCLUSION

Based on current research findings, we infer that increased pregnancy rates were observed in infertile women with ovulatory disorders when treated with sildenafil as an adjunct to clomiphene citrate. This could be clarified by an endometrium that has enlarged.

Author's Contribution:

Concept & Design of Study:	Saima Ashraf
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Revisiting Critically:	Saima Ashraf, Hina Ilyas
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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