

To study and compare the effect of vaginal sildenafil and estradiol valerate on endometrial thickness, blood flow and pregnancy rates in infertile women undergoing ovulation induction by letrozole

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Abstract

Objectives: To evaluate effect of vaginal sildenafil citrate and estradiol valerate on endometrial thickness, blood flow and pregnancy rates in infertile women undergoing ovulation induction by letrozole.

Study Design, Methodology & Population: It is a comparative prospective study including 50 women with primary or secondary infertility with stimulated cycles by Letrozole. Patients with thin endometrium were randomly distributed in two groups. In group A, 25 patients were included and given sildenafil citrate 25 mg vaginally every 6 hours from day 8th of the cycle. In group B, 25 patients were given tablet estradiol valerate 2 mg 8 hourly. Patients were evaluated by trans-vaginal sonography (TVS) on day 13th of the cycle for

endometrial thickness and pattern with number and size of Graafian follicle.

Results: Mean endometrial thickness at the time of hCG trigger was 9.54 mm in sildenafil group and 9.92 mm in estradiol group (p value 0.14). 72% patients in sildenafil group and 68% in estradiol valerate group developed trilaminar pattern of endometrium. (p value 0.03). Zone 3 endometrial vascularity was found in 60% patients in sildenafil group and 44% patients in estradiol valerate group. The clinical pregnancy rates were 2 (8%) in group A and 1 (4%) in group 2 after 3 cycles of ovulation induction.

Conclusion: Both vaginal sildenafil citrate and estradiol valerate can be effective in improving endometrial

thickness in infertile women undergoing ovulation induction with letrozole.

Keywords: Infertility, Sildenafil, Estradiol Valerate, Endometrial Thickness

Introduction

Infertility is a common issue affecting couples worldwide, with various underlying causes. One common cause of infertility is inadequate endometrial development, which can lead to implantation failure and unsuccessful pregnancies. In recent years, there has been growing interest in the use of pharmacological agents to enhance endometrial thickness and improve blood flow to the endometrium, thereby increasing the chances of successful implantation and pregnancy. Among the pharmacological agents used for this purpose, sildenafil and estradiol valerate have gained attention due to their potential effects on endometrial receptivity. Sildenafil citrate is an effective and selective inhibitor of phosphodiesterase-5 (PDE-5). This improves the vasodilatory effect of nitric oxide by preventing the degradation of cyclic guanosine monophosphate (cGMP), leading to vascular relaxation and improved uterine blood flow, and increasing endometrial receptivity. This results in relaxation of the vasculature and enhanced blood flow and increased endometrial thickness.¹ On the other hand, estradiol valerate, a synthetic form of estrogen, has been widely used for hormonal support in assisted reproductive technology (ART) cycles and is known to promote endometrial growth and development.²

Changes in the endometrial vascularity appear on color Doppler examination, which may reflect the histologic changes described by the pathologists.

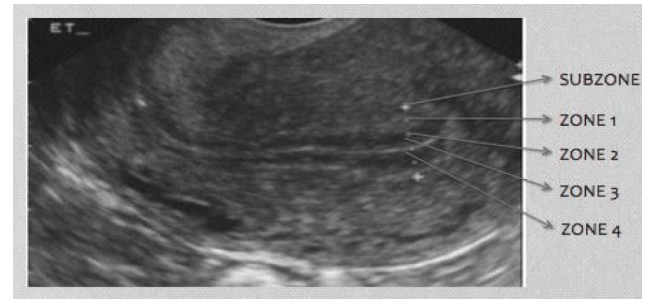
The endometrial and periendometrial areas can be divided into the following four zones³

Zone 1: A 2 mm thick area surrounding the hyperechoic outer layer of endometrium.

Zone 2: The hyperechoic outer layer of endometrium.

Zone 3: The hypoechoic inner layer of endometrium.

Zone 4: The endometrial cavity.



Several studies have individually explored the effects of sildenafil or estradiol valerate on endometrial thickness, blood flow, and pregnancy rates in infertile women undergoing ovulation induction. However, limited research has directly compared the effects of these two agents in the same study population. Therefore, a comparative analysis is warranted to evaluate the relative efficacy of vaginal sildenafil and estradiol valerate in improving endometrial parameters and pregnancy outcomes. The present study aims to investigate and compare the effects of vaginal sildenafil and estradiol valerate on endometrial thickness, blood flow, and pregnancy rates in infertile women undergoing ovulation induction with letrozole. This research will provide valuable insights into the potential benefits and differences between these two agents in improving endometrial receptivity, which may have significant implications for enhancing the success rates of fertility treatments.

Materials And Methods

It was a hospital based comparative prospective study done in department of obstetrics and gynaecology, Seth G.S. Medical College and KEM Hospital, Mumbai over a period of 10 months (September 22-May 23).

Inclusion criteria

- Women between the age of 20 and 35

- Primary and secondary infertility undergoing ovulation induction by letrozole
- Normal husband semen analysis

Exclusion criteria

- All females with hypothyroidism and hyperprolactinemia
- Uterine anomalies, ovarian pathologies and tubal factor infertility

Procedure

After obtaining informed consent from all participants, all patients underwent thorough history, examination and investigation.

Those fitting into inclusion criteria were given ovulation induction by letrozole 2.5 mg from day 3 to day 7 (5 days) of menstrual cycle. Participants were randomly assigned to one of two equal groups:

1. Group A: 50 participants in this group received vaginal sildenafil 25 mg every 6 hours from day 8 of the cycle.
2. Group B: 50 participants in this group will receive estradiol valerate 2mg 8 hourly administered orally from day 8 of the cycle.

Folliculometry was done from day 7 of menstrual cycle. Patients were re-evaluated by TVS on alternate day of cycle for endometrial thickness, distribution of blood flow with number and size of Graafian follicle. If the follicular size was 18–20 mm, 5000 IU of human chorionic gonadotropin (hCG) was injected intramuscularly. USG was performed every day until the follicular scan reached 18 mm if the follicular growth was less than that. Pregnancy outcomes were noted in next menstrual cycle. Any adverse events or side effects related to the study interventions were recorded.

Data collection and Statistical Analysis: Data on demographic characteristics, baseline parameters, treatment regimens, and outcome measures will be collected and entered into a secure database. Statistical

analysis will be performed using appropriate statistical tests, such as independent t-tests or Mann-Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. A p-value < 0.05 will be considered statistically significant.

Results

Mean age in group A and group B was 27.8 and 29.2 respectively. 21 out of 25 patients (84%) in group A had primary infertility whereas it was in 22 patients (88%) in group B. None of the patient characteristics was found to be statistically significant (Table 1).

Table 1

Patient characteristics	Group A (25)	Group B (25)
Mean Age (years)	27.8	29.2
Primary Infertility	21	22
Secondary Infertility	4	3
BMI (kg/m ²)	23.3	24.7

Mean endometrial thickness on day 7 was 5.42 mm in sildenafil group whereas it was 5.76 mm in estradiol group. The mean of number of follicles >18 mm at the time of hcg trigger was 1.44 and 1.28 in the two groups respectively. The difference is again statistically insignificant. (Table 2). None of these cycle characteristics had significant impact on the results obtained.

Table 2

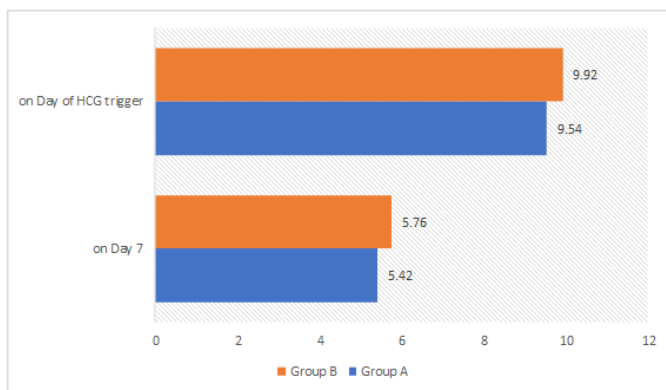
Cycle characteristics	Group A (25)	Group B (25)
Day 7 endometrial thickness	5.42	5.76
Mean Follicle Number at the time of HCG trigger	1.44	1.28

Mean endometrial thickness at the time of HCG trigger was 9.54 mm in group A whereas it was 9.92 mm in

group B. Although the endometrium was found to be thicker in estradiol group, the results were statistically insignificant (p value 0.14). 1 out of 25 cycles in group B failed to achieve ET > 7mm although there was no such case in group A. 72% (18) patients in group A and 68% (17) in group B developed trilaminar pattern of endometrium. The result was found to be statistically significant. (p value 0.03). 60% (15) patients in group A had vascularity up to zone 3 whereas 44% (11) patients in group B had zone 3 endometrial vascularity (p value 0.038). (Table 3).

Table 3

USG monitoring on day of hCG trigger	Group A (25)	Group B (25)
Endometrial thickness on day of HCG trigger	9.54	9.92
Cycle with ET < 7mm on day 13	0	1 (4%)
Trilaminar endometrial pattern	72%	68%
Zone 3 Endometrial Vascularity	60%	44%



The biochemical pregnancy rates were 2 in group A and 1 in group 2 (P>0.05) which is insignificant for comparison (Table 4).

Table 4

Pregnancy Rate	Group A (25)	Group B (25)
PR	2 (8%)	1 (4%)

None of the patients observed any side effect from administration of drug in each group (Table 5)

Table 5

Side Effect	Group A (25)	Group B (25)
SE	0	0

Discussion

The present study aimed to investigate and compare the effects of vaginal sildenafil and estradiol valerate on endometrial thickness, blood flow, and pregnancy rates in infertile women undergoing induction of ovulation by letrozole. Several previous studies have contributed to our understanding of the relationship between endometrial thickness and pattern, as well as the efficacy of different interventions in improving endometrial conditions and pregnancy outcomes. Dickey et al.⁴ conducted a study on ovulation induction cycles and found that endometrial thickness and pattern played a significant role in the success of achieving pregnancy. This supports the importance of assessing endometrial characteristics in infertility treatments. Torres et al.⁵ performed a meta-analysis that examined the use of ethinyl estradiol for the treatment of thin endometrium in patients undergoing ovulation induction with clomiphene citrate. Their findings indicated that the addition of ethinyl estradiol improved endometrial thickness compared to placebo, further emphasizing the potential benefits of interventions to enhance endometrial conditions. Mangal and Mehriishi.⁶ conducted a comparative prospective study specifically focusing on intrauterine insemination (IUI) cycles. They concluded that the pregnancy rate was significantly higher in the group of women who used vaginal sildenafil compared to

those who used estradiol valerate. This suggests that sildenafil may have a positive impact on pregnancy outcomes in IUI cycles. El-Shourbagy et al.⁷ conducted a prospective study in which sildenafil citrate suppositories were administered to women with unexplained primary infertility. They found that treatment with sildenafil citrate significantly increased endometrial thickness and led to a higher pregnancy rate compared to the control group that received no treatment. Firouzabadi et al.⁸ investigated the use of oral sildenafil in women undergoing embryo transfer. They observed that sildenafil led to significantly higher endometrial thickness and a more favorable triple-line pattern. These previous studies support the findings of the present study, indicating that interventions such as estradiol valerate and sildenafil can have positive effects on endometrial thickness, blood flow, and pregnancy rates. However, larger-scale studies may be necessary to further validate these results. Overall, the collective evidence suggests that optimizing endometrial conditions through the use of specific interventions may improve pregnancy outcomes in infertile women undergoing fertility treatments.

Conclusion

Both vaginal sildenafil citrate and estradiol valerate can be effective in improving endometrial thickness in infertile women undergoing ovulation induction with letrozole.

References

1. Abdel Kader Fahmy A, El Sokkary M, Sayed S. The value of oral sildenafil in the treatment of female infertility: a randomized clinical trial. *Life Sci J.* 2015;12(4):78-82.
2. Gerli S, Gholami H, Manna A, Scotto Di Frega A, Vitiello C, Unfer V. Use of ethinyl estradiol to reverse the antiestrogenic effects of clomiphene citrate in patients undergoing intrauterine

insemination: a comparative, randomized study.

Middle East Fertil Soc J. 2018;23(2):131-136.

3. Michael A. The uterine biophysical profile (UBP). *Endosonography in obstetrics and gynaecology.* Gautam Allahabadia (Ed). Rotunda Medical Technologies (P) Ltd. Mumbai, India; 1997:343-52.
4. Dickey RP, Olar TT, Taylor SN, Curole DN, Rye PH, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: Effect of clomiphene citrate alone and with human menopausal gonadotropin. *Fertil Steril.* 1993;59:756-760.
5. Torres RF, Habana AE, Tansengco LG. The Effect of estrogen supplementation on the endometrium and pregnancy rate among infertile women treated with clomifene citrate: a meta-analysis. *Fertil Steril.* 2005;84:S162-S3.
6. 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): 2274-2277.
7. El-Shourbagy S, Ossman AM, 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. *Menoufia Medical Journal.* 2017 Apr 1;30(2):343-394.
8. Firouzabadi DR, 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.