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## Research Article

# 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

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## ABSTRACT

**Background:** The objective of this study was to study and compare the effect of vaginal sildenafil citrate and estradiol valerate on endometrial thickness, blood flow and pregnancy rates in infertile women undergoing intrauterine insemination (IUI).

**Methods:** It is a comparative prospective study including 100 women with primary or secondary infertility with stimulated cycles undergoing IUI. Patients with thin endometrium were randomly distributed in two groups. In group A, 50 patients were included and given sildenafil citrate 25 mg vaginally every 6 hours from day 8<sup>th</sup> of the cycle. In group B, 50 patients were given tablet estradiol valerate 2 mg 6-8 hourly. Patients were evaluated by trans-vaginal sonography (TVS) on day 13<sup>th</sup> of cycle for endometrial thickness and pattern with number and size of Graffian follicle.

**Results:** Mean endometrial thickness at the time of hCG trigger was 9.42 mm in sildenafil group and 9.94 mm in estradiol group (p value 0.14). 64% patients given sildenafil vaginally had vascularity up to zone 3 whereas 48% patients given estradiol valerate orally had zone 3 endometrial vascularity (p value = 0.038). The clinical pregnancy rates were 10 (20%) in group 1 and 7 (14%) in group 2 after 3 cycles of IUI. (p value = 0.042).

**Conclusions:** Both estradiol valerate and Sildenafil citrate can be used for improving the endometrium. Sildenafil when compared to estradiol valerate has better results as far as endometrial vascularity is concerned and marginally increased pregnancy outcome in patients undergoing IUI.

**Keywords:** Infertility, Sildenafil, Estradiol valerate, Endometrial thickness

## INTRODUCTION

Infertility is defined as the inability to conceive after one year of unprotected intercourse. Although endometrial factor and implantation failure are known causes of female infertility, the impact of interventions improving it has not been widely studied in an unexplained infertile population of patients undergoing IUI. New clinical treatments, such as therapeutic endometrial biopsy/injury, have gained recent attention to correct the so-called

endometrial factor infertility.<sup>1,2</sup> However, endometrial development during IUI cycles has been less studied.

One of the strongest predictors of implantation is endometrial thickness. A number of reports have shown that embryo implantation and clinical pregnancy rates (PRs) are significantly higher in patients with an endometrial thickness >9 mm.<sup>3,4</sup> Thin endometrium, generally measuring <7 mm, are thought to be less able to support implantation and pregnancy.<sup>5</sup>

The thickness of the endometrium is dependent on several influences including reproductive age, phase of menstrual cycle, ovarian hormone (estrogen and progesterone) concentration, and endometrial hormone receptor density.<sup>6,7</sup> Available treatments for thin, unresponsive endometrium are limited and largely empiric or experimental including high doses of estrogens, HCG, piroxicam and granulocyte colony stimulating factor.<sup>8</sup> Treatments, such as acetylsalicylic acid, have also been proposed. The results of this intervention are mixed.<sup>9,10</sup> Most of these methods are proposed to function in a similar manner, by increasing blood flow to the endometrium and allowing for its thickening and development. Vaginal sildenafil citrate is another treatment that has been suggested for its ability to relax vascular smooth muscle through a cyclic guanosine monophosphate-mediated pathway, and improve uterine artery blood flow. 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 zones<sup>11</sup>

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.

## METHODS

It was a hospital based comparative prospective study done in IVF centre, SMS Medical College, Jaipur, India over a period of ten months (July 14-April 15) including 100 women with primary or secondary infertility. Women <40 years of age requiring IUI with either husband or donor semen were included. Exclusion criteria were bilateral tubal factor, women age >40, husband total sperm count <15 million to limit confounding. Patients were either stimulated with clomiphene citrate or gonadotropin's depending on the age, hormonal status and previous cycle response. Patients with thin endometrium (Day 8 ET <7mm) were randomly distributed in two groups. In group A, 50 patients were included and given sildenafil citrate 25 mg vaginally every 6 hours for 5 days from day 8th of the cycle. In

group B, 50 patients were given tablet estradiol valerate 2 mg 6-8 hourly. Patients were re-evaluated by TVS on day 13th of cycle for endometrial thickness, pattern, zone wise distribution of blood flow with number and size of Graffian follicle.

Data was then obtained regarding the difference in endometrial thickness, pattern, vascularity and pregnancy rates after 3 cycles of stimulated cycles plus IUI and analyzed to find out the statistical importance of the data obtained.

## RESULTS

Mean age in group A and group B was 26.8 and 28.2 respectively. 42 out of 50 patients (84%) in group A had primary infertility whereas it was in 44 patients (88%) in group B. None of the patient characteristics was found to be statistically significant (Table 1). 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 1.52 and 1.68 in the two groups respectively. The difference is again statistically insignificant. 43 out of 50 patients in group a (86%) and 41 out of 50 (82%) were stimulated using clomiphene citrate (50/100 mg) whereas rest were given gonadotrophins (HMG/FSH). 16 out of 50 couples (32%) in group A and 20 out of 50 couples (40%) in group B had male factor infertility also and were offered IUI with donor semen (Table 2). None of these cycle characteristics had significant impact on the results obtained.

**Table 1: Patient characteristics.**

	Sildenafil group ( A-50 patients)	Estradiol valerate group (B-50 patients)
Mean age (years)	26.8	28.2
Primary infertility	42	44
Secondary infertility	8	6
BMI (kg/m <sup>2</sup> )	23.3	22.7

Mean age: group A = 26.8+/- 4.6; mean age: group B = 28.2+/- 5.4.

**Table 2: Cycle characteristics.**

	Sildenafil group ( A-50 patients)	Estradiol valerate group (B-50 patients)
Day 7 endometrial thickness (mm)	5.42	5.76
Stimulation	Clomiphene citrate	43
	Gonadotrophins	7
Type of IUI husband (H)/donor (D)	34(H), 16(D)	30(H), 20(D)

Mean endometrial thickness at the time of HCG trigger was 9.42 mm in sildenafil group whereas it was 9.94 mm in estradiol group. Although the endometrium was found to be thicker in estradiol group, the results were statistically insignificant (p value 0.14). Two out of 50 cycles in estradiol group were cancelled as patients failed to achieve ET > 7mm although there was no cancellation in sildenafil group. 74% patients in group A and 68% in group B developed trilaminar pattern of endometrium. 64% patients given sildenafil vaginally had vascularity up to zone 3 whereas 48% patients given estradiol valerate orally had zone 3 endometrial vascularity (p value 0.038). The result was found to be statistically significant and helpful in the treatment of other patients at our institute. The clinical pregnancy rates after 1 IUI were 6 in group 1 (12%) and 4 in group 2 (8%) which further rose to 10 (20%) and 7 (14%) respectively after 3 cycles of IUI (p value 0.042). thus a significant increase in clinical pregnancy rates was also observed when sildenafil was used in patients with poor endometrium as compared to estradiol valerate group (Table 3).

**Table 3: USG monitoring on day of hCG trigger.**

	Sildenafil group (A-50 patients)	Estradiol valerate group (B-50 patients)
Endometrial thickness (mm)	9.42	9.94
Endometrial pattern (trilaminar)	37	34
Endometrial blood flow (zone 3)	32	24
Follicles >18 mm (day of trigger)	1.52	1.68
Cycle cancellation (ET<7 mm/>14 mm)	0	2

p value (endometrial vascularity) = 0.038(Statistically significant).

**Table 4: Clinical pregnancy rates.**

	Sildenafil group (A-50 patients)	Estradiol valerate group (B-50 patients)
After 1 IUI	6 (12%)	4 (8%)
After 3 IUI	10 (20%)	7 (14%)

p value (after 3 IUI) = 0.042 (statistically significant).

## DISCUSSION

The results of the present study were compared to previous studies. In a prospective study by Takasaki et al of 61 patients with a thin endometrium (8 mm), there was a significant improvement in endometrial thickness in 11 patients.<sup>12</sup> In a meta-analysis done by Torres RF et al use of pure ethinyl estradiol for treatment of thin endometrium was examined, the observations made were: addition of ethinyl estradiol (EE) does improve the

endometrial thickness in comparison to patients where only placebo was used.<sup>13</sup> Cetinkaya K et al used vaginally administered local oestrogen 25 mcgms from 4<sup>th</sup> day for 15 days in clomiphene citrate induced cycle. They reported significant increase in endometrial thickness on the day of ovulation (7.6+/- 1.4 mm versus 8.3+/-2.1 mm) than the group where only clomiphene citrate was used, but there was no change in pregnancy rate. Dose schedule is different from fresh cycle.<sup>14</sup> Jimenez PT et al used oral estradiol 2 mg thrice daily from day one for 12 days. They reported appropriate development of endometrium in 67% patients.<sup>15</sup> Takasaki et al used 100 mg sildenafil intravaginal starting first day of cycle till day of ovulation and 92% patients showed improvement in endometrial thickness.<sup>12</sup> Firouzbadi et al used 50 mg orally Sildenafil starting 1st day till 45-72 hours prior to embryo transfer. Endometrial thickness and triple line pattern was found significantly higher with sildenafil and estradiol valerate as compared to estradiol alone. Clinical pregnancy rate was higher but not significant.<sup>16</sup> Jerzak M et al used 25 mg Sildenafil four times a day for 3 to 6 days as intra-vaginal suppository. Endometrial thickness was significantly increased.<sup>17</sup> All these studies further support the present study. Although most of the studies have compared estradiol or sildenafil alone with patient's previous cycle taken as control. Some studies have been published comparing estradiol alone to a combination of estradiol plus Sildenafil also. Present study is one of its own kinds and would need further large randomized control trials to further support the results. To summarize, adequately thick, trilaminar pattern endometrial milieu is important for implantation of the embryo and continuation of pregnancy. Both estradiol and Sildenafil can be used for improving the endometrium (thickness and vascularity) and to support embryo growth. Sildenafil when compared to estradiol valerate has better results as far as endometrial vascularity is concerned and marginally increased pregnancy outcome in patients undergoing IUI. Improving the endometrial blood flow to enable an estrogenic milieu for proliferation remains the cornerstone of achieving adequate endometrial growth and receptivity thus achieving a better pregnancy rate and outcome.

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