SULL FOR RESERACE	Original Research Paper	Obstetrics & Gynaecology		
Armong Mernational	ROLE OF SILDENAFIL CITRATE AND ESTRADIOL VALERATE COMPARED WITH ONLY ESTRADIOL VALERATE IN THE TREATMENT OF THIN ENDOMETRIUM IN CASES OF CONTROLLED OVARIAN HYPERSTIMULATION WITH INTRAUTERINE INSEMINATION.			
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ABSTRACT Backgro manage	pund: Improving endometrial thickness(ET) is ement of infertility requiring precision in the drug dos	one of the cornerstone treatment in the ages and routes. Estradiol valerate has been		

improvise the ET.

Materials: A randomized controlled study of 50 pts in the estradiol only group and 50 pts in the estradiol + sildenafil group were studied in pts undergoing Controlled Ovarian Hyperstimulation with Intrauterine IUI.

Results: Sildenafil citrate with Estradiol valerate group showed a significant increase in ET, sub-endometrial blood flows, and endometrial pattern, thus increasing the clinical pregnancy rates.

Conclusion: Sildenafil citrate should be included as a routine to improve ET along with Estradiol valerate in the treatment of pts with thin endometrium

KEYWORDS:

INTRODUCTION:

One of the major components of infertility management is to prevent Implantation failure. Implantation is a process of attachment of developing embryo to the maternal decidua. Implantation consists of 2 components: thick endometrium (9mm) and Blastocyst rupture. Adequate growth of the endometrium is required to support the ovum implantation during menstrual cycle. Endometrial thickness (ET) is one of the strongest predictors of implantation. The pregnancy rates are higher when the endometrium thickness is >9 mm(1) and endometrial lining <7 mm had low pregnancy rates because of poor support for implantation(2). The endometrium is the special epithelial lining of the uterine cavity having two layers: A superficial functional layer and a deeper basal layer. The endometrial growth is dependent on the uterine blood flow and angiogenesis (2). Basal one-third layer is supplied by small, straight, and short arteries and superficial two-third of endometrium is supplied by coiled arteries, branch of uterine artery(3). The average EM is about 8-10 mm in the secretory phase. Angiogenesis plays a significant role in the development of a dominant follicle, formation of a corpus luteum, and growth of endometrium(4). Angiogenesis is essential to support endometrial growth after menstruation and to provide a vascularized receptive endometrium for implantation(5). Improved blood supply increases the delivery of hormones-estrogen which increases the ET in the proliferative phase and also induces progesterone receptors on it to facilitate implantation. Sildenafil Citrate, a type 5 specific phosphodiesterase inhibitor has been increasingly used for improving endometrial thickness by improving endometrial blood supply. This study has been mainly focused on the addition of sildenafil citrate to estradiol valerate to increase ET in patients undergoing COH with IUI.

MATERIALS AND METHODS:

A randomized controlled study was conducted in a tertiary care institute in Mumbai, India for a period of 3 yrs after complying to institutional Ethics norms and written informed consent from the patients.

The main aim of the study was to compare the improvement in ET in 2 groups of patients, each consisting of 50 pts:

- Ovulation induction with clomiphene citrate 50mg OD(D2-D6) + Tab Estradiol valerate 2mg TDS (D2 -D16) with IUI after follicle of 18mm diameter has ruptured.
- 2) Ovulation induction with clomiphene citrate 50mg OD(D2-

D6) + Tab Estradiol valerate 2mg TDS (D2 -D16) + Tab Sildenafil citrate 25mcg BD per vaginal (D7-D16) with IUI after follicle of 18mm diameter has ruptured.

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Primary outcomes measured were:

- 1) Endometrial thickness on day 8, 10, 12 and 14
- 2) Endometrial pattern
- 3) Sub-endometrial blood flows

Secondary outcomes measured were:

- 1) Clinical pregnancy rates
- 2) Ongoing pregnancy rates

Endometrial pattern has been graded into Grade A-Receptive or triple line endometrium, Grade B-homogenous character near junctional zone and central echogenic line, Grade Cnon receptive homogenous endometrium (6). Applebaum Scoring system has been used to assess the sub-endometrial blood flows and endometrial receptivity (7). According to this system the endometrial receptivity has been categorized into 4 zones:

Zonel- Blood flow reaching upto the Myometrium surrounding the endometrium

- Zone 2-Hyperechoic endometrial edge
- Zone 3-Internal endometrial hypoechoic zone
- Zone 4-Endometrial cavity

Clinical Pregnancy rate : Defined as presence of intrauterine G-sac on the transvaginal ultrasound with fetal pole and fetal cardiac activity by 7weeks since IUI (8).

Ongoing Pregnancy rate : defined as pregnancy continuing beyond the period of viability (28weeks).

Patients were standardized according to their demographics – age, socioeconomic status, education and on the type of infertility. All the basic infertility work -up was done including hormonal profile(FBS/PLBS, TSH, Sr prolactin, FSH/LH, AMH), and tubal patency.

Inclusion Criteria:

- 1) Age group -18-35 yrs
- 2) Endometrial thickness <7mm till Day 14 in the previous cycle

VOLUME-8, ISSUE-7, JULY-2019 • PRINT ISSN No. 2277 - 8160 STATISTICS: The continuous data was analyzed using Exclusion criteria: unpaired or paired T test, while the qualitative data $>35\,\mathrm{yrs}$ 1) was analyzed using Fischer's exact test or chi square 2) Asherman's syndrome test. Statistical significance was set at Pvalue < 0.05. 3) Genital kochs 4) Endometriosis **RESULTS:** All patients included in the study were Contraindications to IUI 5) standardized on the basis of age, period of infertility, BMI, type 6) Not giving consent of infertility and socioeconomic status.

	SILDENAFIL GROUP	SILDENAFIL + ESTRADIOL	Tests of significance	P value
	(n=50)	VALERATE GROUP ($n=50$)		
Age	29.4 ± 4.8	30.2 ± 3.6	Unpaired t test	Not significant ($p = 1.01$)
BMI	23.4 ± 3.5	24.2 ± 34.1	Unpaired t test	Not significant (p=1.5)
Period of infertility	3.5 ± 1.2	4.2 ± 2.1	Unpaired t test	Not significant ($p = 2.3$)

8% of patients belonged to age group of 20-25 yrs, 17% in 25-30 yrs and 75% in 30-35 yrs.

Endometrial thickness showed a significant improvement at day12 and day14, the endometrium completely prepared by day 16-18 for implantation in the patients who received sildenafil citrate with estradiol.



The endometrial pattern improved to grade A upto 75% in the cases group whereas only 35% in the control group. The subendometrial blood flow and endometrial receptivity increased to zone 4 in 78% of the cases but only reached 34% in the control group, however estradiol only group had a majority of patients with blood flow reaching only upto zone 3. Clinical pregnancy rates after a maximum of 3 IUI cycles were 23% in the cases group whereas only 12% in the control group. The ongoing pregnancy rates were 21% in the cases group and only 8% in the control group. All these results were highly statistically significant.

	Sildenafil + estradiol group (n=50)	Estradiol group (n=50)	Tests of significance	P value
Endometrial	10.4mm ±	8.8mm ±	Unpaired	P<0.03*
thickness	2.111111	1.011111	i lesi	
Sub- endometrial blood flow (zone 4)	36	23	Chi square test	P<0.021*
Endometrial pattern (GRADE A)	42	26	Chi square test	P<0.04*
Clinical pregnancy rate (after 3 IUI)	23%	12%	Chi square test	P<0.013*
Ongoing pregnancy rate	21%	8%	Chi square test	P<0.001*

DISCUSSION:

Infertility management requires subtle corrections which can make a tremendous impact. The results in this study confirm the superiority of using Sildenafil citrate with estradiol valerate for improving the endometrial thickness and hence

the pregnancy rates. These results also corroborate with the results from other 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 (9). In a study of 61 pts done by Mangal et al, there was significant difference in endometrial thickness, endometrial pattern, sub-endometrial blood flows in patients using sildenafil citrate with estradiol valerate (10). Firouzabadi 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 estadiol valerate as compared to estradiol alone. Clinical pregnancy rate was higher but not significant (11). Jerzak M et al used 25 mg Sildenafil four times a day for 3 to 6 days as intravaginal suppository. Endometrial thickness was significantly increased (12). Although most of the studies have compared estradiol or sildenafil alone with patient's previous cycle taken as control, this study focusses to compare the addition of sildenafil on an already established benefit of using estradiol valerate.

CONCLUSION:

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. Newer therapies have been propagated like using Granulocyte colony stimulating factor, Platelet rich plasma, BAP-C, but all of them continue to be deterred by the cost factor.

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