

## Comparative Evaluation of Clomiphene Citrate Alone and Clomiphene Citrate and Sildenafil Citrate for Treatment of Infertility and its Outcome

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### ABSTRACT

**OBJECTIVE:** To compare the effect of clomiphene citrate alone and clomiphene and sildenafil citrate for infertility treatment and its outcome.

**MATERIAL AND METHODS:** This study was carried out in the Department of Obstetrics and Gynecology of GSVM MEDICAL COLLEGE, KANPUR from JANUARY 2016 to SEPTEMBER 2017. Total 80 infertile women were included in this study and randomly divided into 2 groups, study and control groups. Control group were given oral CLOMIPHENE CITRATE tablets (50 mg daily for 5 days) for ovulation induction. Women in study group were advised to take Sildenafil Citrate capsule, 25 mg qid, starting from day 1-14 of the cycle in addition to clomiphene citrate. Assessment of endometrial thickness, pattern and vascularity was done on day 1, 8 and 14 of the cycle. **RESULTS:** In our study, none of the demographic characteristics of the patients showed statistically significant difference. Both the groups were comparable in terms of demographic profile. On adding sildenafil citrate to clomiphene cycles, post-treatment, percentage of patients with  $ET \geq 8$  mm was increased from 45.2% to 76.2%. On comparing Mean ET before and after treatment with clomiphene and sildenafil citrate, mean ET in sildenafil treated patients was significantly increased from  $7.15 \pm 1.34$  mm to  $9.16 \pm 1.98$  mm ( $p < 0.0001$ ). Using unpaired t test, we found significant difference between the two groups, RA-RI and PI values decreased after treatment with sildenafil citrate ( $p < 0.0001$ ). After 3 cycles of induction, pregnancy rates were 18.4% in control group and 38.1% in study group. 3 months follow up after conception showed 15 single IU pregnancy in study group while 6 single IU pregnancy in control group. **CONCLUSION:** As our study shows, use of Sildenafil Citrate is a good way to improve endometrial thickness and receptivity and thus pregnancy rates. Thus, we recommend its use in infertile patients.

**Key words:** Sildenafil Citrate, Endometrial growth, Clomiphene citrate, ovarian stimulation.

### INTRODUCTION

WHO defines Infertility as the inability to conceive after one year of unprotected intercourse. Infertility affects about 10 percent of the reproductive age population. Twenty-five percent of infertile couples have more than one factor that contributes to their infertility. The female factors contribute almost half in the aetiologies of infertility followed by male factors (30-40%), and the rest are attributed to a mixture of both or by problems unknown. **One of the strongest predictors of implantation is Endometrial Thickness (ET).** Successful pregnancy requires adequate growth of the endometrium to support the ovum implantation during menstrual cycle. Clomiphene citrate (CC) is the first line treatment for ovulation induction in women with anovulatory infertility. An important cause of clomiphene citrate failure is its anti-estrogenic effect on the endometrium i.e. it causes endometrial thinning. Poor endometrial development is

associated with a decreased probability of pregnancy. If the embryo does implant and pregnancy occurs, the thin endometrium may not be able to supply an adequate amount of nutrients to maintain pregnancy. The pregnancy rates are higher when the endometrium thickness is  $>9$  mm and endometrial lining  $<7$  mm had low pregnancy rates because of poor support for implantation. Therefore, 8- 13 mm is the ideal endometrial thickness for successful pregnancy. Sildenafil Citrate is a selective inhibitor of the type V cGMP-specific phosphodiesterase. Sildenafil Citrate enhances the vasodilatory effect of NO by inhibiting phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP. Sildenafil citrate, by its vasodilatory effect on uterine endometrium, improves the uterine blood flow and hence increases endometrial thickness. In our study, we have added sildenafil citrate to clomiphene induced cycles in infertile patients. Our aim was to counteract the antiestrogenic side-effect of clomiphene citrate on uterine endometrium, as clomiphene causes endometrial thinning. Hence, here is an attempt to review the effect of Sildenafil Citrate on the uterine endometrium, which increases the pregnancy outcome, i.e. its utility in the management of female infertility.

**MATERIAL AND METHODS :** The study was conducted on 140 patients attending the outpatient clinics with complain of primary or secondary infertility in the department of obstetrics and gynecology of **UPPER INDIA SUGAR EXCHANGE MATERNITY HOSPITAL, GSVM MEDICAL COLLEGE, KANPUR** during the period from January 2016 to september 2017. Of these patients those with anovulatory and unexplained infertility were taken into this study ( $n = 80$ ). A total of 80 patients were recruited in this study and divided into Control group (clomiphene citrate only) and Study group (Sildenafil Citrate and clomiphene citrate both).

### **INCLUSION CRITERION**

- ✓ Patients with infertility in reproductive age group.
- ✓ Patent fallopian tubes on hysterosalpingography.
- ✓ Mature one or more graffian follicles either spontaneously or by ovulation induction.
- ✓ Normal uterus by ultrasound examination.
- ✓ Normal hormonal profile (serum FSH, LH, prolactin, estrogen, free testosterone)

### **EXCLUSION CRITERIA**

- ✓ Significant cardiovascular disease
- ✓ Severe liver disease and renal failure
- ✓ Previous history of stroke or MI
- ✓ Patients on nitrates
- ✓ Hypotension (bp  $<90/60$ )
- ✓ Multiple uterine fibroid
- ✓ Uterine congenital anomalies
- ✓ Acute or chronic attack of PID
- ✓ Presence of any Organic lesion of uterus, tubes or ovaries such as endometrial polyps, ovarian cysts, leiomyomas.
- ✓ Endocrine abnormalities such as hyperprolactinemia or abnormal thyroid functions.
- ✓ Male factor infertility
- ✓ Clinical and ultrasonic suspicion of endometriosis and adenomyosis.

- ✓ Those with ovarian hyperstimulation at present cycle.

All couples with infertility were assessed initially by full history and then general clinical and gynecological examination. Basic semen analysis was done to rule out male factor infertility. Female partner was investigated by basal hormonal profile, hysterosalpingogram. TRANSVAGINAL SCAN (TVS) for imaging uterus and adnexa for any pathology, baseline TVS was done to assess the endometrial thickness, character and echogenicity and to assess graffian follicle growth on day 2. The patients, who accepted to participate in the study, Ovulation induction regimen was started in next cycle. The patients were randomly distributed into 2 groups:

- **CONTROL GROUP** – patients were prescribed only clomiphene citrate.
- **STUDY GROUP** - patients were prescribed both clomiphene and sildenafil citrate.

In control group, Clomiphene citrate was given from next cycle, 50 mg od from day 1 to day 5. While in study group, Sildenafil citrate was given to the patients in a dose of 25 mg administered 4 times per day for 14 days from day 1 to day 14 of cycle along with Clomiphene citrate was given, 50 mg od from day 1 to day 5. Endometrial thickness and uterine PI and endometrial RA-RI were measured in the late follicular phase on day 14. Post treatment, these patients were re-evaluated by TVS on day 2, 8 and day 14 of the cycle for endometrial thickness and character and the number and size of graffian follicle using T.V.S. with doppler. Day 14 endometrial thickness, RA-RI and uterine PI were compared in both control group and study groups in the treatment cycle.

**RESULTS:** On comparing ET on day 14 after treatment in both groups, it clearly shows increased ET in sildenafil group ( $9.16 \pm 1.98$ ), as compared to control group ( $7.38 \pm 1.14$ ), this study has p value  $< 0.0001$ , which shows study is highly significant. On comparing RA-RI values between two groups, we found significant difference between the two groups (0.84 in control group and 0.74 in study group), (RA-RI values decreased after treatment with sildenafil). P value in our study was  $< 0.0001$ , it shows study is highly significant. On comparing PI values between two groups, using unpaired t test, we found significant difference (2.68 in control group and 2.16 in study group) between the two groups (PI values decreased after treatment with sildenafil thus increasing endometrial blood flow). P value  $< 0.0001$ . After 3 cycles of induction, Pregnancy rates were 18.4% in control group as compared to 38.1% in study group. 3 months follow up after conception showed 15 single IU pregnancy in study group while 6 single IU pregnancy in control group. Out of those Pregnant, there was 1 miscarriage in clomiphene group while 2 miscarriages in study group. No ectopic pregnancy reported. 1 patient was diagnosed with twin gestation in each control and study group. Side-effects were found significantly higher in study group when compared to clomiphene group. Headache (10%) and dizziness (7%) were found to be the most common complaints in study group.

**CONCLUSION:** Based on the findings of the study we conclude that sildenafil citrate as an adjunct to clomiphene citrate increases pregnancy rates in infertile women with ovulatory disorders and unexplained infertility. Clomiphene citrate (CC) is the first line treatment for ovulation induction in women with anovulatory infertility. An important cause of clomiphene citrate failure is its anti-estrogenic side-effect on the endometrium i.e. it causes endometrial thinning resulting into low implantation rates. On adding sildenafil citrate we counteracted this undesirable side-effect of clomiphene citrate. Our results have shown that sildenafil citrate when

added to CC, increases ET significantly, and improved uterine blood flow. Based on the findings of the study we conclude that sildenafil as an adjunct to clomiphene citrate increases pregnancy rates in infertile women with ovulatory disorders and unexplained infertility.

Since our sample size is very small, further studies are required to assess the long-term effects of Sildenafil on infertility and pregnancy outcomes.

	<b>Control group n = 38)</b>	<b>Study group (n = 42)</b>	<b>p-value</b>
<b>RA-RI</b>	0.84 ± 0.07	0.74 ± 0.1	<0.0001
<b>PI</b>	2.68 ± 0.35	2.16 ± 0.51	0.0001

**Table 1:** Comparison of endometrial thickness on day 14 between control (clomiphene citrate) and study group (clomiphene citrate + sildenafil citrate)

<b>Endometrial thickness on day 14 (treatment cycle)</b>		
	<b>Control group (n = 38)</b>	<b>Study group (after treatment) (n = 42)</b>
<b>Mean ET (mm)</b>	7.38 ± 1.14	9.16 ± 1.98
<b>p value</b>	<0.0001	

**Table 2:** Comparative study between study and control group according to RA-RI (Radial Artery Resistance Index) and PI (Pulsatility Index) on day 14

**Table 3:** Distribution of patient according to pregnancy rates in both groups (after 3 cycles of induction).

<b>Pregnancy status</b>	<b>Control group (n = 38)</b>	<b>Study group (n = 42)</b>	<b>P value</b>
<b>Positive pregnancy test</b>	7 (18.4%)	16 (38.1%)	<0.05
<b>1<sup>st</sup> cycle</b>	2	5	
<b>2<sup>nd</sup> cycle</b>	2	7	
<b>3<sup>rd</sup> cycle</b>	3	4	
<b>Negative pregnancy test</b>	31 (81.6%)	26 (61.9%)	

**Table 4:** Distribution of patient according to pregnancy outcome (3 month follow up)

	<b>Control Group (n= 38)</b>	<b>Study Group (n= 42)</b>
<b>Single intrauterine pregnancy</b>	6	15
<b>Ectopic Pregnancy</b>	Nil	Nil
<b>Twin pregnancy</b>	1	1
<b>Miscarriage</b>	1	2



**Fig.1:** Doppler view of rt uterine artery showing RA-RI and PI