Original Research Article

Role of Sildenafil in ovulation induction – A comparative study of outcomes with Sildenafil in ovulation induction cycles with Clomiphene Citrate

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Abstract

Background: Sildenafil causes vasodilatation by relaxing the smooth muscles of blood vessels. This enhances endometrial development, the health of which is indispensable for implantation and embryonic and fetal development.

Aim: To assess the role of Sildenafil when used in ovulation induction cycles with Clomiphene Citrate (CC) with reference to Endometrial Thickness (ET), follicular development, Pregnancy rates and Side Effects.

Materials and methods: In this prospective comparative study on 80 infertile women, we randomly divided them into two groups. In group A with 40 patients, ovulation induction with CC was given and in group B with 40 patients oral Sildenafil Citrate 25mg – BD, was added from Day 8 up to hCG trigger, in the CC induced cycle. A transvaginal ultrasound was done on Day 13 to assess follicular growth and ET. A urine β-hCG on Day 30 was done to detect pregnancy. Patients were followed up for 8 weeks to monitor miscarriages, ectopics and multi foetal gestation.

Results: Mean ET at the time of hCG trigger was 9.64 in the Sildenafil group compared to 8.47 in group A without Sildenafil (p value 0.01). 65% of the patients in group B conceived with 3 cycles of ovulation induction compared to 42.5% who conceived in group A (p value 0.04). The mean of total number of follicles greater than 18 mm at hCG trigger was 1.62 and 1.91 in group A and B respectively (p – 0.09). Side Effects were significantly higher in group B with sildenafil compared to group A with CC alone (p – 0.006).

Conclusions: As our study shows that use of Sildenafil improves ET and rates of conception, we recommend the routine use of Sildenafil in ovulation induction protocols.

Key words

Sildenafil, Clomiphene Citrate, Ovulation induction cycle.

Introduction

Infertility is defined as the inability to conceive after one year of unprotected intercourse. The causative factors of infertility are diverse and at times unexplained. Despite extensive diagnostic workup, etiology in 10 – 25% of the couples remains unexplained [1] and this has bought implantation and endometrial receptivity into focus [2].

One of the strongest predictors of implantation is Endometrial Thickness (ET) [3]. A number of studies have put forth that embryo implantation and clinical pregnancy rates are significantly higher in patients with an ET more than 9 mm [4]. Endometrial thickness less than 7 mm is thought to be less able to support implantation and pregnancy [5]. The available option for thin endometrium are limited and largely empiric or experimental by the use of estrogens, hCG, piroxican, Granulocyte Colony Stimulating Factor (G-CSF)and Acetylsalicylic acid [3]. Most of these treatments are based on the fact that an increase in blood flow to the endometrium causes endometrial development and thickening.

Sildenafil citrate is a specific, 5 – Phospho Diesterase (5- PDE) inhibitor, the first of this group to be approved by United States – Food & Drug Administration (US - FDA). Nitrous oxide (NO) which is endogenously produced activates cyclic Guanosine Monophosphate (cGMP) which cases smooth muscle relaxation via the Protein Kinase G (PKG) pathway. Inherently cGMP is broken down to GMP by 5 – PDE leading to termination of its physiological action. Sildenafil inhibits the action of 5-PDE thereby leading to an increase in cGMP levels. Thus Sildenafil causes vasodilatation by potentiating the action of NO on smooth muscles of blood vessels.

Nitroglycerin (NTG) has already been reported to have successfully improved uterine artery blood flow and ET in patients on in-vitro fertilization in its capacity as a NO producer / donator, but its use is limited due to higher incidence of side effects like headache and hypotension [6].

The current study aims at evaluating the effect of 50 mg Sildenafil on ET, Follicular development, Pregnancy rate and Side Effects in patients who were prescribed the drug for ovulation induction cycles with CC.

Materials and methods

This study was conducted as a Prospective Comparative Study at ESIC Medical College, Hyderabad, India which is a tertiary referral centre with 35 referring dispensaries and hospitals. The study was conducted over a period of four months from May 2016 to September 2016. The study included 80 patients with primary and secondary infertility aged between 18 years to 40 years, attending the outpatient wing of the department.

Inclusion criteria

Age less than 40 years and more than 18 years, Primary or Secondary infertility, with regular menstrual cycles, and normal semen parameters of the husband

Exclusion criteria

Pathology of uterus and ovaries, endocrine disorders except thyroid disorders, tubal infertility as detected by Hysterosalpingogram (HSG), hypotension (Blood Pressure less than 100/60 mmHg) and cardiovascular, renal or hepatic disorders

All the couples with infertility were initially taken up for detailed history taking and then subjected to general and local medical examination. A basic semen analysis was done and read with WHO 2010 criteria, to rule out male factor infertility and limit confounding. This was then followed by investigating the female partner by basal hormonal profile on Day 3 (Follicle Stimulating hormone, Luteinizing hormone and Prolactin). A Transvaginal Scan (TVS) for imaging the uterus and adnexa for any pathology and measuring the basic Endometrial Thickness was also one on Day 3. The patients who met the criteria were then taken for ovulation induction in the next cycle.

The patients were included in the study after obtaining an informed consent in written from the couple. They were distributed into two groups randomly. In group A, 40 patients were prescribed CC alone. In group B, 40 patients were prescribed CC and Sildenafil.

Ovulation induction in group A and B was done with 100mg CC (Siphene, Serum Institute of India) from Day 3 to Day 7 of the cycle. In group B additionally Sildenafil (Viagra, Pfizer) 25mg twice daily was given from Day 8 up to ovulation trigger. Follicular study and Ultrasonography (USG) based measurement of endometrial thickness (ET) was done by a TVS (5 – 7.5 MHz transducer) on the Day 13. 5000 IU of Human Chorionic Gonadotrophin - hCG (Fertigyn, Sun Rise International Labs Ltd.) was administered intramuscularly as an ovulation trigger if the follicular size was 18mm – 20mm (Fig 1). If follicular size noted was less than 18mm, USG was repeated daily till follicular scan reaches 18 – 20mm. Pregnancy was detected by testing for the β subunit of hCG in urine on Day 30. Patients were closely monitored during this period for side effects and Ovarian Hyperstimulation Syndrome (OHSS). The patients were followed thereafter for a period of 8 weeks for spontaneous miscarriages, tubal ectopics and multiple gestation.

In case of induction failure with no chemically detectable pregnancy, another cycle of induction was started on Day 3 of next cycle. A maximum of 3 cycles were continued even after which if the patient doesn't conceive the patient was prescribed Oral Contraceptive pills for 2 cycles.

The data was tabulated and introduced into a computer on social science statistics online tool on http://www.socscistatistics.com/Default.aspx. Paired data was statistically evaluated using Chi Square test and unpaired independent data was analyzed using unpaired t Test.

Results

Age wise distribution of patients was as per **Table – 1**. Patients, methods and outcomes were as per **Figure – 1**. Mean age of patients in the study was 26.22 years. Mean age in group A was 25.36 years with a standard deviation of 3.75 years whereas in group B was 27.08 years with a standard deviation of 4.67 years (P – 0.07). 33 out of 40 patients (82.5%) in group A had primary infertility whereas 35 out of 40 patients (87.5%) had primary infertility in group B (P – 0.5). None of the demographic characteristics of the patients showed statistically significant differences (**Table - 2**).

Table – 1: Age wise distribution of patients in the study (N = 80).

Age frequency	No of patients	%
< 20 years	4	5%
21-25 years	32	40%
26 –30 years	28	35%
31 – 35 years	14	17.5%
36 – 40 years	2	2.5%
Average age – 26.225 years		

The mean of ET measured on day 13 in group A was found to be 8.47 mm and in group B was found to be 9.64 mm. This shows a statistically significant improvement in ET upon Sildenafil administration with P value 0.01 (**Table - 3**). The mean number of follicles measuring equal to or greater than 18 mm on day 13 TVS were found

to be 1.62 and 1.91 in group A and group B respectively. Though a slight increase in the number of follicles is observed with the use of Sildenafil, it is statistically insignificant with a P value of 0.09 (**Table - 3**).

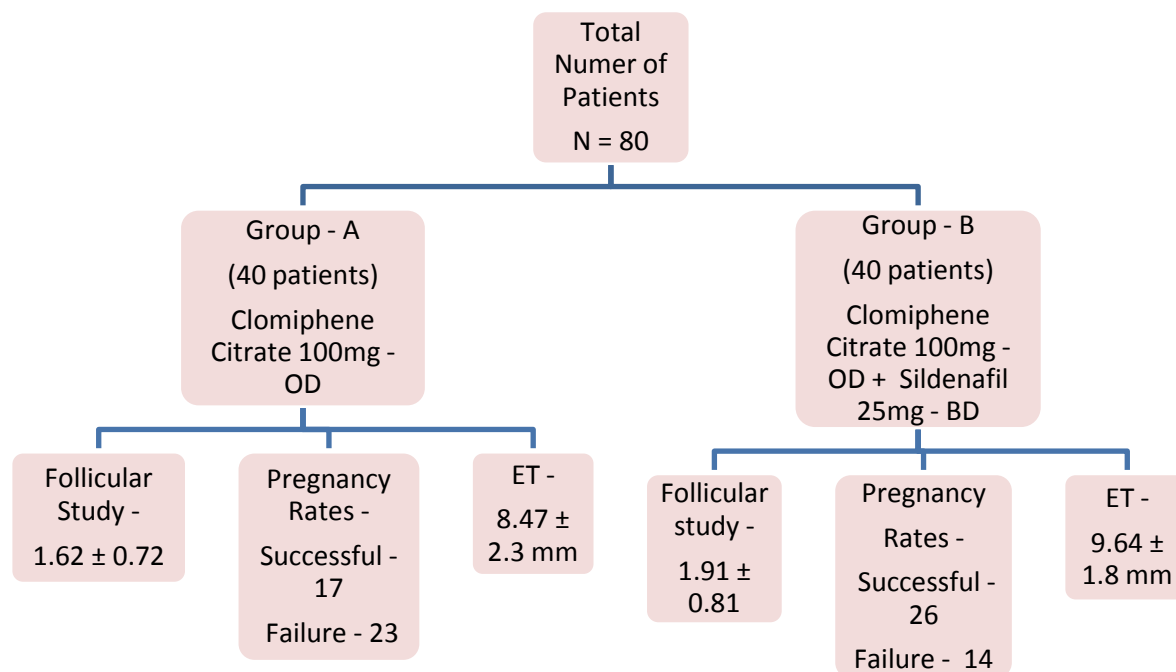**Figure - 1:** Patients and Methods and outcomes.

Table – 2: Demographic characteristics in Groups.

Characteristic	Group – A (N = 40)	Group – B (N = 40)	P	Significance
Primary Infertility	33 (82.5%)	35 (87.5%)	$P* = 0.5$	Not Statistically significant
Secondary infertility	7 (17.5%)	5 (12.5%)		
Mean Age (years)	25.369 ± 3.75 years	27.081 ± 4.67 years	$P** = 0.07$	Not Statistically significant
BMI (kg/m^2)	21.7 ± 1.93	22.3 ± 1.76	$P** = 0.8$	Not Statistically significant

P* - value of statistical significance calculated by Chi Square Test
P** - value of statistical significance calculated by unpaired t test

Table – 3: Comparison of ET and Follicular development in Group A and Group B.

Characteristic	Group – A (N = 40)	Group – B (N = 40)	$P**$	Significance
Endometrial Thickness (mean)	8.47 ± 2.3 mm	9.64 ± 1.8 mm	0.01	Statistically significant
Number of Follicles > 18 mm (mean)	1.62 ± 0.72	1.91 ± 0.81	0.09	Not Statistically significant

$P**$ - value of statistical significance calculated by unpaired t test

Pregnancy rates measured over three ovulation induction cycles were significantly higher in group B which was prescribed Sildenafil when compared to group A without Sildenafil. 17

patients in group A (42.5%) conceived compared to 26 patients in group B (65%). β hCG was not detected even after three consecutive cycles in 23 patients (57.5%) in group A compared to 14 patients (35%) in group B. Analysis of the data by Chi square test revealed a statistically significant (P – 0.04) improvement in rates of conception detected chemically(Table - 4). 29.41% of the patients(5 patients) who conceived in group A achieved pregnancy in the first cycle of induction compared to 26.9% in group B(7 patients). 7 of the 17 patients who conceived (41.17%) in group A and 10 of the 26 patients (38.46%) who conceived in group B were chemically positive for pregnancy in second cycle. 5 out of 17 patients(29.41%) and 9 out of 26 patients(34.61%) were detected positive for pregnancy after the third cycle (**Table - 4**).

Table – 4: Distribution of patients with reference to pregnancy rates in Groups.

Pregnancy Status	Group – A (N = 40)	Group – B (N = 40)	P*	Significance
Chemically Positive Pregnancy	17 (42.5%)	26 (65%)		
1st Cycle	5 (29.41%)	7 (26.9%)		
2nd Cycle	7 (41.17%)	10 (38.46%)	0.04	Statistically Significant
3rd Cycle	5 (29.41%)	9 (34.61%)		
Chemically Negative Pregnancy	23 (57.5%)	14 (35%)		

P* - value of statistical significance calculated by Chi Square Test

Side effects were found significantly higher in group B when compared to group A with a statistical significance (P – 0.006) calculated by Chi Square Test (**Table - 5**). Headache in 6 patients (15%) and dizziness in 6 patients (15%) were found to be the most common complaints in group B compared to group A with 2 patients (5%) complaining of headache and 1 patient (2.5%) complaining of dizziness. 5 patients (12.5%) complained of flushing, 4 patients(10%) complained of blurring of vision and 2 patients (5%) complained of GIT disorders in group B compared to 10% (4 patients) complaining of flushing, 5% (2 patients) complaining of blurring of vision and 5% (2 patients) complaining of GIT disorders in group A. 29 patients (72.5%) didn't report any side effects in group A whereas only 17 patients (42.5%) in group B didn't report any side effects.

Eight weeks follow up after conception showed miscarriage in 1 patient (2.5%) of group A, compared to 2 patients (5%) in group B. No ectopic pregnancies were detected. No tubal ectopics were reported. 2 patients in group A and 2 in group B were diagnosed with twin gestation (**Table - 6**).

Discussion

Ovulatory disorders account for approximately 30 – 40 % of all the cases of female infertility and are the commonest and easiest cause of infertility to diagnose and treat [7]. Ovulation induction in such cases is a less expensive and less invasive method. CC is usually the first line drug to be used for induction. Ahmed AbdelKader Fahmy, et al. reported that despite good rates of ovulation with CC many patients still don't achieve pregnancy due to implantation failure [1]. Mishra V.V. et al also reported that implantation is the weakest link for the success of any assisted reproductive technique with endometrial receptivity as the crucial necessity for implantation [2].

Steroid hormones, Growth factors and cytokines regulate endometrial development. Some of the regulatory factors are produced locally and others have to be transferred to the endometrium, for which sufficient blood supply is required [1].

Senturk, et al. reported that women with ET less than 6mm are less likely to conceive and ET should be at least 7mm for considering the possibility of implantation [8]. A thin endometrium is characterized by high blood flow impedance of radial artery, poor epithelial growth, decreased expression of vascular endothelial growth factor and poor vascular development as proposed by Miwa, et al. [9].

Table – 5: Group wise distribution of side effects.

Side Effect	Group – A (N = 40)	Group – B (N = 40)	P*	*Significance*
Headache	2 (5%)	6 (15%)		
Dizziness	1 (2.5%)	6 (15%)		
Flushing	4 (10%)	5 (12.5%)	0.006	Statistically Significant
Blurring of Vision	2 (5%)	4 (10%)		
GIT Disorders	2 (5%)	2 (5%)		
No Side Effects	29 (72.5%)	17 (42.5%)		
Miscarriages up to 8 weeks	1 (2.5%)	3 (7.5%)		

Table - 6: Eight weeks follow up characteristics.

Characteristic	Group – A (N = 40)	Group – B (N = 40)
Miscarriages	1 (2.5%)	2 (5%)
Tubal Ectopic	0	0
Twin gestation	2 (5%)	2 (5%)

Owing to its vasodilatory effect Sildenafil citrate causes vascular smooth muscle relaxation and improves ET by augmenting the physiological action of NO produced endogenously. The current study aimed at evaluating the value of oral Sildenafil 50mg on the pregnancy rate in women undergoing ovulation induction by CC. The study shows statistically significant increase in ET, pregnancy rates in the group which was prescribed Sildenafil. Also a statistically higher rate of complications like headache and dizziness were reported in this group.

The results of our study are in accordance with Fisch, et al. who reported an increase in ET when used from day 8 to day 13 [10]. Jerzak, et al. reported that there is a good correlation between endometrial thickness and prevalence of conception and that ET greater than 9 mm as determined by vaginal ultrasound correlates well with pregnancy rate [11].

The study is also in agreement with Dehgahani, et al. who recommended the routine use of oral sildenafil in women with a previous failure of assisted reproductive techniques [12]. In an Indian study on 55 patients, Mishra et al reported a statistically significant improvement in endometrial vascularity reflecting positively at conceptional rates in patients undergoing IVF [2].

We report a statistically insignificant increase in the mean number of follicles greater than 18 mm on day 13 TVS. Ahmed et al reported a mean increase in number of follicles with the use of sildenafil which was again insignificant.

Berman et al. reported that the main side effects of sildenafil are headache, flushing, blurring of vision, nausea and dyspepsia [13]. Basson, et al. reported that side effects of Sildenafil are usually mild to moderate in nature and are dose related [14] which is again in agreement with the findings of our study.

Conclusions

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. This could be explained by an increased endometrial thickness. Also a higher rate of side effects with oral Sildenafil is noted but none of them were severe and intolerable. Further studies are required to assess the long term effect/s of Sildenafil on fertility and fetal outcomes.

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