



PROSPECTIVE STUDY OF EFFECT OF VAGINAL SILDENAFIL CITRATE IN IMPROVING ENDOMETRIUM IN INDUCTION OF OVULATION

Obstetrics & Gynaecology

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ABSTRACT

Endometrial thickness is a prognostic factor for successful pregnancy. This Prospective study is aimed to examine the role of sildenafil citrate in improving endometrial lining in women with a thin endometrium in ovulation induction.

KEYWORDS

OI-Ovulation induction; Sc- Sildenafil Citrate; HCG- Human Chorionic gonadotrophin

INTRODUCTION

Subfertility generally describes any form of reduced fertility with prolonged time of unwanted non-conception(1) Infertility is defined as the inability to conceive after 1 year of unprotected intercourse of reasonable frequency. It can be subdivided into primary infertility, that is, no prior pregnancies, and secondary infertility, referring to infertility following at least one prior conception(2)

Endometrium is the dynamic epithelial lining of uterine cavity, lying above the internal os which is influenced by the cyclical hormonal changes, A successful pregnancy requires adequate growth of endometrium to support the implantation during menstrual cycle. Embryo implantation depends on the quality of the ovum and endometrial receptivity. Successful embryo implantation can take place only in a receptive uterus.(3)

Endometrial thickness is one of the strongest predictors of implantation. The pregnancy rates are higher when the endometrial thickness is greater than 9mm, implantation and pregnancy rates are lower when the endometrial thickness is less than 7 mm.(4) Endometrial growth and receptivity is dependent on uterine blood flow. Uterine artery high resistance flow may cause poor endometrial growth. In several studies, it was proved that uterine artery doppler indices mean was higher in subfertile and infertile women than the fertile women(5)

Thin endometrium may be due to high blood flow impedance in uterine radial artery which remains high throughout the menstrual cycle, impairs the growth of glandular epithelium and results in a decrease in vascular endothelial growth factor expression. VEGF regulates angiogenesis in the human endometrium. low VEGF levels cause poor vascular development, thereby decreasing the blood flow to the endometrium leading to thin endometrium. (6) The other potential causes for thin endometrium might be Asherman syndrome, deficient estrogen, prior dilatation and curettage, infections and radiation, improper usage of clomiphene.(8)

Endometrial patterns are classified as pattern A: triple-line pattern which comprises of a central hyperechoic line surrounded by two hypoechoic layers; pattern B: an intermediate isoechoic pattern which has same reflectivity as the surrounding myometrium and poorly defined central echogenic line; and pattern C: homogenous, hyperechogenic endometrium. Studies show that implantation rates and clinical pregnancy rates are higher in women with triple line pattern.(7)

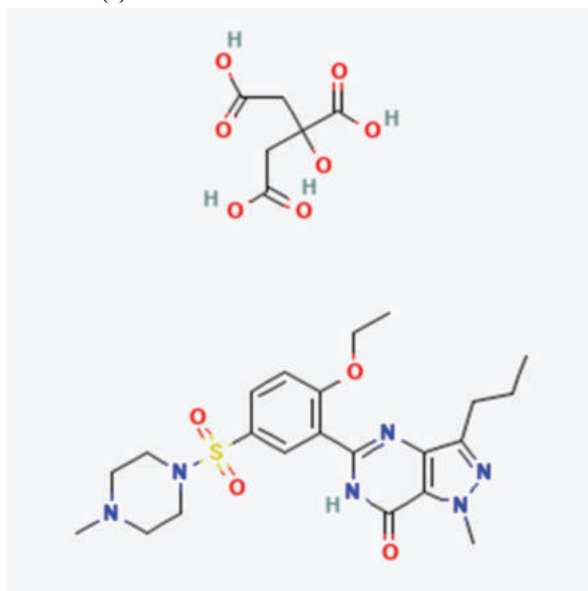
The available treatment options for thin endometrium are limited and are based on the fact that an increase in blood flow to the endometrium causes endometrial development and thickening. They are largely empirical or experimental, such as Estrogens, hCG, G-CSF, Acetyl salicylic acid, vitamin E and L-arginine and Sildenafil citrate. (6)

Sildenafil citrate is a 5-phosphodiesterase inhibitor. It enhances the effect of nitric oxide (NO) by inhibiting 5-PDE, which causes cGMP degradation. NO relaxes smooth muscle by generating cGMP which promotes dephosphorylation of myosin light chain kinase, thereby interfering with myosin interaction with actin, leading to smooth muscle relaxation and increase in blood flow. Thus, with the use of

sildenafil, cGMP remains raised, which leads to vasodilatation and increased blood flow to the endometrium.(8).

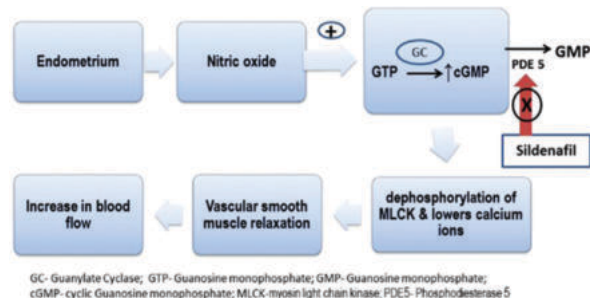
Sildenafil was first synthesized by Pfizer scientists Andrew Bell, David Brown, and Nicholas Terrett. It was initially studied for use in hypertension and angina pectoris. It was found to be not so useful in angina, but causing penile erections. Hence it was marketed for erectile dysfunction. Currently Sildenafil citrate is being studied for its vasodilatory properties.(8)

Structure:(8)



IUPAC name: 1-[4-ethoxy-3- (6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d] pyrimidin-5-yl) phenylsulfonamido]-4-methylpiperazine citrate. [18]

Chemical formula - C₂₂H₃₀N₆O₄S.



An illustration of mechanism of action of sildenafil citrate(8)

Oral usage of sildenafil citrate might have several side effects such as

headache, flushing, indigestion, sensitivity to light, nasal congestion, back pain, muscle pain, nausea, dizziness, rash. (9) All these can be avoided by vaginal route of administration and also for better local absorption.

CASE STUDY:

AIM:

- To evaluate the effect of sildenafil citrate on endometrial thickness in ovulation induction cycles given to women attending our OPD in view of subfertility
- To evaluate the effect of sildenafil citrate on uterine artery doppler studies in subfertile women
- To evaluate the effect of sildenafil citrate in the improvement of fertility and pregnancy rates.

MATERIALS AND METHODS

Source Of Data:

Study Site : Obstetrics and Gynecology Department at Krishna Institute Of Medical Sciences, Secunderabad, Telangana. Krishna Institute Of Medical Sciences, is a 1000 bedded tertiary care corporate hospital.

Study Population: Women attending to Obstetrics and Gynecology OPD with subfertility satisfying all the inclusion and exclusion criteria

Study Period : 1 Year

Study Design: Prospective interventional study

Study Sample Size : 50

The mean Endometrial Thickness in use of Sildenafil group (9.64 ± 1.8) was higher as compared to the not used group (8.47 ± 2.3) has been observed from the previous published study .

$Z_{\alpha/2} = 1.96$ is the critical value of the Normal distribution at $\alpha/2$ (with confidence level of 95%, α is 0.05).

$Z_{\beta} = 0.842$ is the critical value of the Normal distribution at β (power of the test is 80%, $\beta = 0.20$).

$\sigma^2 = 4.265$ is the estimated population variance based on the previous study.

$d = 1.17$ is the expected difference between the means.

$n = Z_{\alpha/2}^2 + Z_{\beta}^2 \times 2 \times \sigma^2 / d^2$

- $n = 1.96^2 + 0.842^2 \times 2 \times 4.265 / (1.17)^2 = 48.92 \approx 49$
- The minimum required sample is 49.

Statistical Analysis Plan:

All the qualitative factors like Diagnosis, Menstrual History, Obstetric History, Family History, etc. will be represented with the frequencies and percentages.

All the quantitative parameters like Age, BMI, and Endometrial Thickness, Uterine artery doppler parameters will be represented with means and standard deviation.

To compare the mean difference of ET before and after the treatment we will use paired t-test. To find the association between qualitative factors we will use Chi-Square test for measure of association.

All the data will be entered and maintained in MS. Excel and analyzed by using SPSS19.0v.

p value less than 0.05 will be considered as significant.

Inclusion Criteria :

- Age : Reproductive age group
- Primary and secondary infertility
- Prior ovulation induction failures (<6cycles)
- h/o thin endometrium

Exclusion Criteria :

- Structural anomalies of uterus
- Tubal factors
- Major medical illnesses
- Smokers and alcoholics
- Male factor subfertility

METHODOLOGY:

This was a prospective interventional study , all women with subfertility fulfilling the inclusion and exclusion criteria were enrolled in the study and informed consent was taken . all the enrolled women were evaluated by detailed history taking which includes age, occupation, socioeconomic status, menstrual history, obstetric history, past medical and surgical history, personal and family history .

Detailed examination was done and routine investigations were done along with which AMH, FSH, LH, Prolactin and TSH were done.

All the participating woman with subfertility were given ovulation induction either with Tab.clomiphene citrate 50mg OD or Tab. Letrozole 2.5mg BD from Day 2 to Day 6 or Day3 to Day 7 of cycle . A transvaginal ultrasound was done on Day 2 or Day 3 to measure the uterine artery doppler indices and endometrial thickness as baseline . Tab. Sildenafil citrate 25mg BD was administered vaginally from day 7 till day of ovulation or hCG trigger . Serial transvaginal ultrasound was done from day 10 till ovulation to see the development of follicle , to measure endometrial thickness and to measure uterine artery doppler indices , i.e PI, RI

Those who needed triggering , inj. HCG 5000 or 10,000 IU was given with the appropriate follicular size

Those who failed to develop a dominant follicle or conceive in one cycle, another cycle with increased dose of clomiphene or letrozole was given.

RESULTS:

Age Distribution: A total of 50 subfertile women were included in this study. The mean age was 29.02 yrs with standard deviation of 3.279. the minimum age included was 24 and the maximum age included was 38, all according to the inclusion criteria.

Table 1: Age distribution of study subject

Age (Years)	No. of Subjects	Percentage
<= 30	34	68.0%
31 - 35	13	26.0%
36 & Above	3	6.0%
Total	50	

Diagnosis:

Women with both primary and secondary subfertility were included. Of which 32 women i.e 64% of the study population had primary subfertility and rest of them secondary.

Table 2: Diagnosis of the subjects

Diagnosis	No. of Subjects	Percentage
Primary Subfertility	32	64.0%
Secondary Subfertility	18	36.0%
Total	50	

BMI:

The mean BMI was 26.306 with standard deviation of 2.5905. The minimum was 19.0 and the maximum was 30.6

Table 3: BMI

BMI	No. of Subjects	Percentage
Healthy Weight	14	28.0%
Overweight	34	68.0%
Obesity	2	4.0%
Total	50	

PAST HISTORY:

In the study group , 50% of women had h/o PCOS, 12% had hypothyroidism, 2% had both, while 36 % Of them had nil significant past history

Table 4: Past history

Past History	No. of Subjects	Percentage
Nil	18	36.0%
PCOS	25	50.0%
Hypothyroidism	6	12.0%
PCOS & Hypothyroidism	1	2.0%
Total	50	

ENDOMETRIAL THICKNESS ON DAY OF OVULATION/ hCG TRIGGER:

For all the 50 women in the study, the mean endometrial thickness on the day of ovulation/ hCG trigger was 9.722mm with standard deviation of 1.247 , the minimum being 7.6 and the maximum being 12.2 mm. 30% of the subjects had ET less than 9 and 70% had ET more than 9mm

Table 5 : ET on the day of ovulation

ET(mm) Day of Ovulation	No. of Subjects	Percentage
< 9	15	30.0%

9-14	35	70.0%
Total	50	

UTERINE ARTERY PI ON DAY 2 AND DAY OF OVULATION:

The mean uterine artery PI for the 50 women under study on day2 of cycle was 2.829 with standard deviation of 0.344 and on the day of ovulation, it was 1.971 with standard deviation of 0.414 with a p value of <0.001, which is statistically significant

Table 6: comparison between uterine PI on day 2 and day of ovulation

Uterine Artery PI	Mean	Std. Deviation	P Value(t-test)
Day2	2.83	0.344	<0.001
Day of Ovulation	1.97	0.410	

ENDOMETRIAL THICKNESS AND PREGNANCY:

Out of 11 pregnancies achieved, one had an ET less than 9mm, rest all had ET more than 9 mm.

which is considerably significant .

Table 7: Endometrial thickness & pregnancy

ET(mm) Day of Ovulation	Pregnancy		Total
	Positive	Negative	
< 9	1	14	15
9-14	10	25	35
Total	11	39	50

CONCLUSION:

1. Sildenafil citrate is effective in improving endometrial characteristics
2. The mean endometrial thickness after the usage of sildenafil was 9.7, which is considered as favorable for implantation.
3. The uterine artery PI and RI on day 2 were considerably reduced when measured after usage of Sildenafil on day of ovulation (approximately 1 week). The results were statistically significant (p value <0.001)
4. Sildenafil citrate as an adjunct along with clomiphene or letrozole may improve the clinical pregnancy rate, especially in the event of prior failed ovulation induction cycles whose cause might be thin endometrium.
5. In our study, there was considerable correlation between endometrial pattern and pregnancy.
6. In our study, there was no correlation between the number of dominant follicles and pregnancy.
7. There were no reported side effects with vaginal sildenafil.

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