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STUDY OF THE EFFECT OF SILDENAFIL CITRATE AND LETROZOLE ON ENDOMETRIAL THICKNESS IN INFERTILITY PATIENTS IN A TERTIARY CARE HOSPITAL IN EASTERN INDIA

Obstetrics & Gynaecology

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ABSTRACT

Background: Sildenafil is responsible for vascular smooth muscle relaxation and increased blood flow to the endometrium. This results in better endometrial thickness and receptivity and improvement in implantation of the embryos. **Objective:** Evaluation of the efficacy of vaginal sildenafil on the endometrial thickness and pregnancy outcomes in letrozole induced ovulation induction cycles. **Materials And Methods:** 102 infertile women were included in this prospective study. The women were allocated to two groups – Group A and Group B. Letrozole was used to induce ovulation in all these 102 women. Vaginal sildenafil twice daily was added to women of Group B from Day-8 of menstrual cycle till the day of hCG trigger. All women underwent follicular monitoring on Day-12 of menstrual cycle. If the follicle size was not adequate, then a repeat follicle scan was done after 2 days. Injection urinary hCG 5,000 IU IM was given as trigger. A timed intercourse was advised. On Day-30, a urine β-hCG was done to identify a positive pregnancy. **Result:** The mean endometrial thickness on the day of hCG trigger in women of Group B, i.e women who received sildenafil was 9.8 mm compared to 8.4 mm in Group A , i.e women without sildenafil. Pregnancy rate in women who received sildenafil was 62.7% , compared to 49.01% in women who did not receive sildenafil. **Conclusion:** Use of vaginal sildenafil in women undergoing letrozole induced ovulation induction cycles helps in improving endometrial thickness and pregnancy rates .

KEYWORDS

Sildenafil, infertility, letrozole, endometrial thickness, pregnancy.

INTRODUCTION

Infertility refers to inability to conceive after one or more years of regular unprotected sexual intercourse. Patients who have never been pregnant are said to have primary infertility, while secondary infertility refers to patients who have had a prior pregnancy unrelated to the outcome of the pregnancy. Male factors are responsible for 40% of infertility cases while female factors are responsible for 40% of cases, rest 20% are due to unknown causes.

In case of female infertility, main causes are ovulatory disorders (30-40%), endometriosis, PID (pelvic inflammatory diseases), tubal factors (25-30%), congenital developmental abnormalities and hyperprolactinemia.

Ovulatory dysfunction consists 30-40% of female infertility. There is no international consensus on comprehensive system for classification of these disorders.

The WHO classification of anovulation includes:
Type 1 – Hypo-gonadotropic Hypogonadism
Type 2 – Normo-gonadotropic Normogonadism
Type 3 – Hyper-gonadotropic Hypogonadism

The WHO classification later had extended additions of classifications till Type 7. (1) WHO classification had certain limitations with diagnostic and treatment modalities .

A new, more efficient and internationally accepted classification of ovulatory disorders was developed by the International Federation of Gynecology and Obstetrics (FIGO) and conducted using a rigorously applied Delphi process. (2,3) The type 1, 2, 3 is based on an anatomic categorization and the type 4 is specific diagnostic entity.
Type 1 – Hypothalamic
Type 2 – Pituitary
Type 3 – Ovarian
Type 4 – PCOS

One of the main factors responsible for infertility are endometrial factors and implantation failure and there is a positive correlation between endometrial thickness and the rate of conception. For optimal implantation endometrial thickness must be >7 mm.Various drugs like aspirin, heparin, l-arginine, vitamin E, nitrates, estrogen, pentoxiphylline, tocopherol, and intrauterine infusion of growth factors such as G-CSF and stem cell therapy have been used in improving thickness of thin endometrium. Recently, sildenafil citrate has been used in the treatment of thin endometrium.

Letrozole is a highly selective oral aromatase inhibitor (AI), which binds reversibly to the rate-limiting enzyme P450 aromatase which facilitates in the synthesis of estrogen and inhibits the conversion of testosterone to estradiol and androstenedione to estrone (6). The decreased level of estrogen increases the secretion of pituitary follicle-stimulating hormone (FSH) as positive feedback to stimulate ovulation. Letrozole induces ovulation in anovulatory infertility. It has no peripheral antiestrogenic effects on endometrium and cervical mucous like clomiphene. Better pregnancy outcomes and a significantly lower risk of multiple pregnancies is seen with letrozole than with clomiphene.

Sildenafil citrate is a vasoactive agent. It selectively inhibits phosphodiesterase type 5 enzyme and is able to augment the effects of nitric oxide (NO) on smooth muscle relaxation and vasodilation by stimulating the cyclic guanosine monophosphate (cGMP) pathway (4,5) .Sildenafil citrate enhances uterine blood flow and leads to estrogen-induced proliferation of the endometrium. Sildenafil citrate has utility in patients with thin endometrium, and it improves endometrial growth and pregnancy rates. Endometrial thickness (EM) is one of the most important predictors for implantation rate and ongoing pregnancy outcome. The endometrial growth depends upon the uterine blood flow and angiogenesis.

The Aim Of The Study:
To evaluate the efficacy of vaginal sildenafil on endometrial thickness in letrozole-induced ovulation .

Objectives Of The Study:

[A] Primary Objective:
- Endometrial thickness
- Follicular development

[B] Secondary Objective :

- Pregnancy outcomes

MATERIAL AND METHODS :

Study Population : Female patients who presented with infertility to the OPD of Obstetrics and Gynaecology Department at Hi-Tech Medical College and Hospital , Bhubaneswar, Odisha.

Duration Of Study : February 2024 to November 2024

Inclusion Criteria :

- Women between the age of 20 and 40 years
- Primary and secondary infertility
- Infertility in group 2 (according to WHO)
- Normal sperm parameters of the husband

Exclusion Criteria:

- > 40 years old
- Uterine, tubal and ovarian pathologies
- Sensitivity to sildenafil citrate
- Male factor infertility

Procedure:

A total of 400 patients attending the OPD for infertility were screened and 150 patients were found with ovulatory dysfunction . Of these, 102 patients were selected for the study after fulfilling the inclusion criteria and all these 102 patients gave consent for the study and underwent day 2 basal scan. They were randomly divided into 2 groups.

Group A (51) – Prescribed Letrozole 5mg orally once daily dosing from D3 to D7
Group B (51) – Prescribed Letrozole 5mg orally once daily dosing from D3 to D7 along with Sildenafil 25mg vaginally twice daily dosing from D8 till the day of hCG trigger.

A Transvaginal sonography (TVS) was done on Day 12 to measure the endometrial thickness and follicular development. If the follicle size reached 18-20 mm , then 5000 IU of urinary human chorionic gonadotropin (hCG) was injected intramuscularly. If the follicle size was < 18 mm, then the patient was again called after two days to reassess the follicle size till it reaches at least 18-20 mm, when 5000 IU IM was given. On Day 30 urine beta hCG was tested to confirm a pregnancy. Following that, the patient was observed for 8 weeks to look for ectopic pregnancies, multiple pregnancies, and spontaneous miscarriages.

If the first cycle failed to achieve a pregnancy, then a new cycle of ovulation induction was started on Day 3 of the subsequent cycle. A maximum of 3 cycles were attempted. If the patient did not become pregnant even after 3 cycles, this was considered a failure case.

RESULTS:

Table 1: Age-wise Distribution Of Patients

Age Frequency	No of patients
21-25 Years	32
26-30 Years	40
31-35 Years	26
36-40 Years	4

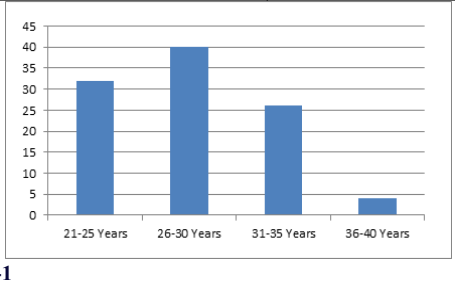

Figure-1

Table 2: Demographic Variables

Characteristic	Group-A (N=51)	Group-B (N=51)
Primary Infertility	**44 (86.2%)**	**46 (90.2%)**
Secondary Infertility	**7 (13.7%)**	**5 (9.8%)**
Mean Age (years)	**26.78**	**28.64**
Mean BMI (kg/m^2)	**21.2%**	**23.4%**

Table 3: Endometrium & Follicles on TVS on Day -12

Characteristic	Group-A (N=51)	Group-B (N=51)
Endometrial Thickness (mean)	**8.4 mm**	**9.8 mm**
Number of Follicles ≥ 18 mm (mean)	**1.5**	**2.2**

Table 4: Pregnancy status

	Group-A (N=51)	Group-B (N=51)
A. Clinically Positive	**25 (49.01%)**	**32 (62.7%)**
1st cycle	**7**	**11**
2nd cycle	**12**	**14**
3rd cycle	**6**	**7**
B. Clinically Negative	**26 (50.98%)**	**19 (37.25%)**

Table 5: Status at 8 weeks

Characteristic	Group-A (N=51)	Group-B (N=51)
Miscarriages	**3 (5.8%)**	**4 (7.8%)**
Tubal Ectopic	**0**	**1 (1.9%)**
Twin gestation	**2 (3.9%)**	**3 (5.8%)**

Patient age distribution was as shown in Table 1. The mean age in Group A was 26.78 years, whereas it was 28.64 years in Group B. Among the 51 patients in group A, 44 (86.2%) had primary infertility, and 7 (13.7%) had secondary infertility. Primary and secondary infertility affect 46 (90.2%) and 5 (9.8%) patients in Group B, respectively. Table 2 shows that the mean BMI in group A was 21.2, while it was 23.4 in Group B. The mean endometrial thickness was 8.4 mm in Group A and 9.8 mm in Group B, with Group B having a thicker endometrium. When compared to Group A, Group B has more number of follicles > 18 mm (Average follicle number in Group A/Group B of 1.5/2.2) . (Table 3)

Pregnancy rates were significantly higher in Group B, which was prescribed Sildenafil,when compared to Group A, which did not receive Sildenafil. (Table-4). In comparison to 32 patients in Group B (62.7%), only 25 patients in Group A (49.01%) had a clinically positive pregnancy.

Analysis of the number of cycles which the patients took to achieve a pregnancy was also carried out . In the first cycle, 11 (21.5%) of the group B patients and 7 (13.5%) of the group A patients got pregnant. Patients in groups A and B who conceived in their second cycles were 12 (23.5%) and 14 (27.4%) respectively. Subsequently, the third cycle resulted in conception of 6 (11.7%) patients in group A and 7 (13.7%) patients in group B.

Only 19 (37.25%) of the patients in group B failed to become pregnant after three cycles, compared to 26 (50.98%) of the patients in group A. These cases were regarded as failures. Miscarriages occurred in 3 patients (5.8% of the total) in group A at the 8-week follow-up period following conception, compared to 4 patients (7.8%) in group B. There were no ectopic pregnancies found in Group A, while 1 patient (1.9%) in Group B had an ectopic pregnancy. 2 patients in Group A and 3 patients in Group B had twin gestation. (Table-5)

DISCUSSION:

Endometrial factor is very pivotal in the successful implantation of an embryo and a positive pregnancy outcome . Growth factors, cytokines, and steroid hormones are some of the key players which steer the endometrial development, which thereby depend on autocrine, paracrine and endocrine signalling. These signallings with the regulatory elements necessitate an adequate blood supply.

Endometrial thickness (ET) shows variations according to a woman's age and menstrual cycle. A healthy endometrium is a must for a positive pregnancy outcome. An endometrial thickness between 8-15 mm is favorable for a positive pregnancy and an endometrium less than 7 mm is usually considered a thin endometrium which is not very favourable for implantation. Thin endometrium may occur due to uterine abnormalities, infections like endometritis, chemotherapy/ radiotherapy, any history of endometrial surgery or injury, long-time use of birth control pills, poor nutrition.

The "Malinova effect" in relation to vaginal sildenafil refers to the research finding, primarily associated with studies by Dr. Malinova (Malinova et al , 2013), (12) that vaginal administration of sildenafil can significantly increase endometrial thickness and improve uterine

blood flow, potentially leading to higher pregnancy rates in women struggling with infertility due to a thin endometrium.

A N Fetih et al (2017) (11) showed that sildenafil vaginal gel had a positive impact on endometrial thickness, uterine blood flow and pregnancy rate.

Sher G et al (2002) (5) showed that vaginal sildenafil improves endometrial development, thereby causing high implantation and ongoing pregnancy rates.

Mohamed TY at al (2019) (7) showed that oral sildenafil has significant effect in improving endometrial thickness and pregnancy rate when added to letrozole for treatment of anovulatory infertility among PCO women with mild side effects.

Abd El-ghany et al (2022) (8) , also conclude that highest clinical pregnancy rate is derived from letrozole with sildenafil citrate in comparison with clomiphene citrate with sildenafil citrate.

Dehghani et al. (2013) (20) suggested regular oral sildenafil use in women who have previously experienced failure with assisted reproductive technologies to increase the endometrial thickness and pregnancy rates.

Baradwan et al (2023) (21) , in his systematic review and meta-analysis revealed that sildenafil either alone or as an adjuvant to other drugs in the luteal phase, improves endometrial thickness and clinical pregnancy rate in women undergoing ART.

CONCLUSION :

Sildenafil, when used in conjunction with Letrozole, enhances the likelihood of conception in infertile women with ovulatory problems. Sildenafil therapy appears to improve the endometrial thickness and pregnancy rates in women undergoing ovulation induction with oral ovulogens. Endometrial angiogenesis mechanisms and the roles of angiogenic factors during treatments are vital for implantation of embryos. Further RCTs are still mandatory in order to finally confirm the clinical effectiveness as well as to establish the best timing, dose and duration of Sildenafil administration.

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