

The Synergistic Effect of Sildenafil with Letrozole in Ovulation Induction and Conception Rate

Harshdeep K Jadeja¹, Bindraba Rana², Bhavesh B Airao³

¹Assistant Professor, Department of Obstetrics and Gynaecology, CU Shah Medical College and Hospital Surendranagar

²Resident, Department of Obstetrics and Gynaecology, CU Shah Medical College and Hospital Surendranagar

³HOD & Professor, Department of Obstetrics and Gynaecology, CU Shah Medical College and Hospital Surendranagar

Received: 29-12-2022 / Revised: 09-01-2023 / Accepted: 11-02-2023

Corresponding author: Dr

Conflict of interest: Nil

Abstract

Background: Sildenafil relaxes the smooth muscles of blood vessels, which results in vasodilation. This promotes endometrial development, which is essential for implantation and the growth of the embryo and foetus.

Aim: To evaluate the impact of sildenafil on endometrial thickness (ET), follicular development, and pregnancy rates when used in ovulation induction cycles with letrozole.

Materials and Methods: We allocated the 80 infertile women in this prospective comparative study at random into two groups. Letrozole was used to induce ovulation in group A's 40 patients, and oral Sildenafil Citrate 25 mg BD was added in group B's 40 patients from day 8 until the hCG trigger in the Letrozole-induced cycle. On Day 13, a transvaginal ultrasound was performed to evaluate follicular development and ET. On Day 30, a urine B-hCG test was performed to identify pregnancy. Ectopic pregnancies, multiple foetal gestations, and miscarriages were all tracked for 8 weeks.

Results: After the hCG trigger was activated, the mean ET in the Sildenafil group was 10.57mm as opposed to 8.50mm in group A without Sildenafil. Compared to 21 (52.5% of the patients in group A), 30 (75%) of the 40 patients in group B became pregnant after 3 cycles of ovulation induction. The average number of follicles larger than 18 mm at hCG trigger was 1.7 for group A and 2.1 for group B, respectively.

Conclusion: We advise the regular use of Sildenafil in ovulation induction procedures because our research demonstrates that its use increases ET and conception rates.

Keywords: Infertility, Sildenafil, Letrozole, Endometrial thickness, Follicular growth, Pregnancy.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Failure to conceive after one or more years of regular sexual contact is known as infertility (unprotected). Patients with primary infertility are those who have never given birth. Those

with past successful pregnancies but a later inability to conceive are said to have secondary infertility. Male variables account for 30–40% of the causal factors, while female ones account for 40–45%. Moreover, up to 10–25% of aetiologies remain unsolved after significant diagnostic work.

Infertility in women is linked to ovulatory variables in 30–40% of cases, tubal illness in 25–30%, uterine and cervical causes in 10–15%, and pelvic endometriosis in 1–10% of cases.

According to the WHO, ovulatory variables include:

- 1) Hypogonadism caused by hypothalamic-pituitary failure.
- 2) Hypothalamic-pituitary dysfunction results in normogonadism for gonadotropin.
- 3) Hypogonadism due to hypergonatropin-induced ovarian failure

It is possible to defeat Groups A and B.

Letrozole

Letrozole lessens estrogen-induced negative feedback and suppresses ovarian estradiol secretion.

FSH levels increase as a result. FSH sensitivity rises as intraovarian androgen levels rise. It has no peripheral antiestrogenic effects on endometrium and cervical mucus, in contrast to clomiphene. Better pregnancy rates and a substantially lower chance of multiple pregnancies than with clomiphene. On the other hand, letrozole's risk of foetal congenital abnormalities needs to be confirmed through randomized prospective trials.

Sildenafil

Sildenafil functions as a specific PDE-5 inhibitor, enhancing the vasodilatory effects of nitric oxide by blocking the degradation of cGMP, which results in increased uterine blood flow and thicker endometrium. In contrast, a different study hypothesized that sildenafil might influence the vasoactive cytokines that control endometrial growth or

implantation. By encouraging the growth of spiral arteries and raising uterine arterial blood flow, they discovered that sildenafil promotes uterine receptivity. They advised individuals who have previously experienced assisted reproductive technology cycle failure because of subpar EM to regularly take oral sildenafil citrate.

The Aim of the Study:

To learn more about sildenafil's function in Letrozole-induced ovulation.

Objectives of the study:

In relation to

[A] Main Objective

- Endometrial thickness
- Follicular development

[B] Secondary Objective

- Conceive rate

Material and Methods

We looked at every patient who presented with infertility to the obstetrics and gynecology department at the CU Shah Medical College and hospital.

Duration of study: January 2022 to December 2022

Inclusion criteria:

- Women between the age of 20 and 40
- Primary and secondary infertility
- Infertility in groups 1 and 2 (according to WHO)
- Normal sperm parameters of the husband

Exclusion criteria:

- >40 years old
- Except for thyroid disorders all endocrine pathologies.
- Uterine and ovarian pathologies.

Procedures

All patients after taking through history investigation (fitting the inclusion criteria) were divided randomly in 2 group:

Group A – Prescribed Letrozole D3 to D7 alone

Group B – Prescribed Letrozole D3 to D7 along with Sildenafil 50mg for ovulation trigger.

A TVS (Trans vaginal sonography) was done on Day 13 to measure the endometrial thickness and follicular development. If the follicular size was 18–20 mm, 5000 IU of human chorionic gonadotropin (hCG) was injected intramuscularly. USG was performed every day until the follicular scan reached 18 mm if the follicular growth was less than that. Testing the beta component of hCG in urine on

day 30 allowed for the pregnancy to be identified. Following that, the patient was observed for 8 weeks to look for ectopic pregnancies, multiple pregnancies, and spontaneous miscarriages.

A new cycle of induction was started on day 3 of the subsequent cycle in the event that the induction failed and there was no detectable pregnancy. A maximum of 3 cycles were attempted; if the patient did not become pregnant, this was considered a failure case, and oral contraceptives were prescribed for a period of three months

Result

Table 1: Age-wise distribution of patients

Age Frequency	No of Patients
21-25 Years	32
26-30 Years	28
31-35 Years	18
36-40 Years	2

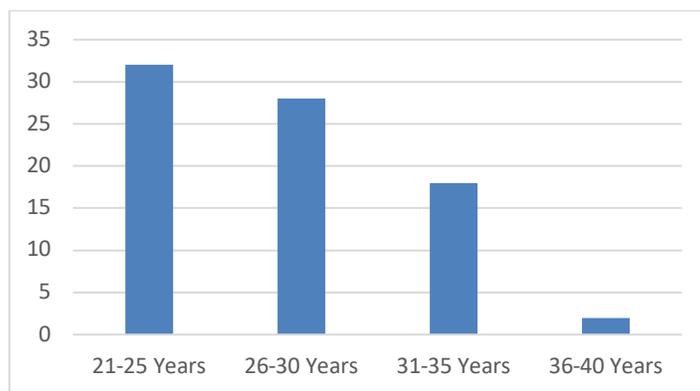


Figure 1

Table 2: Demographic variables

Characteristic	Group – A (N = 40)	Group – B (N - 40)
Primary Infertility	33 (82.5%)	35 (87.5%)
Secondary infertility	7 (17.5%)	5 (12.5%)
Mean Age (years)	25.369	27.08
BMI (kg/m ²)	21.7	22.3

Table 3: Time of approach (TVS on Day -13)

Characteristic	Group-A (N=40)	Group-B (N= 40)
Endometrial Thickness (mean)	8.5 mm	10.57 mm
Number of Follicles > 18 mm (mean)	1.7	2.1

Table 4: Pregnancy status

	Group A	Group B
A. Clinically Positive	21(52.5%)	30(75%)
1st cycle	5	10
2nd cycle	8	11
3rd cycle	8	9
B. Clinically Negative	19(47.5)	10(25%)

Table 5: Status at 8 weeks

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%)

Patient age distribution was as shown in Table 1. The mean age in group A was 25.36, whereas it was 27.08 in group B. Among the 40 patients in group A, 33 (82.5%) had primary infertility, and 7 (17.5%) had secondary infertility. Primary and secondary infertility affect 35 (87.5%) and 5 (12.5%) patients in group B, respectively. Table 2 shows that the mean BMI in group A was 21.7, while it was 22.3 in group B. Endometrial thickness was 8.5 mm in group A and 10.57 mm in group B, with group B having a thicker endometrium. When compared to group A, group B has larger follicular size, with a mean value of 2.1 mm. (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 30 individuals in group B (75%), only 21 patients in group A (52.5%) became pregnant. In comparison to 11 patients (25%) in group B, pregnancy was not achieved in 19 patients (47.5%) in group A even after three consecutive cycles.

Cycle-wise data analysis was carried out: In the first cycle, 10 (25%) of the group B patients and 5 (12.5%) of the group A patients both got pregnant. Patients in groups A and B who conceived in their second cycles were each 8 (20%) and 11 (27.5%). Accordingly, the third

cycle resulted in the conception of 8 (20%) patients in group A and 9 (22.5%) patients in group B.

Only 10 (25%) of the patients in group B failed to become pregnant after three cycles, compared to 19 (47.5%) of the patients in group A. These cases were regarded as failures. A miscarriage occurred in 1 patient (2.5% of the total) in group A at the 8-week mark following conception, compared to 2 patients (5%) in group B. There were no ectopic pregnancies found. Two patients in Group A and two patients in Group B both had twin gestation diagnoses. (Table-5)

Discussion

Endometrial development is governed by growth factors, cytokines, and steroid hormones. While some of the regulatory elements can be created locally, others must be transported to the endometrium, which necessitates an adequate blood supply.

According to Senturk *et al.*, women with an ET of less than 6 mm have a lower chance of getting pregnant, and the ET needs to be at least 7 mm to account for radial artery impedance. Poor epithelial growth impairs vascular development and vascular endothelial growth factor expression, claim Miwa *et al* [1,2].

The result concurs with Dehghani, *et al.* who suggested habitual oral sildenafil use in women who have previously experienced failure with assisted reproductive technologies. Mishra *et al.* reported a statistically significant improvement in endometrial vascularity reflecting favorably at conception rates in patients undergoing IVF in an Indian study on 55 patients[3].

Because Sildenafil citrate has a vasodilatory effect, it relaxes vascular smooth muscle and enhances ET by enhancing the physiological effects of endogenous NO. The objective of the current study was to assess the effect of oral Sildenafil 50mg on the likelihood of pregnancy in women undergoing sildenafil-induced ovulation. The study demonstrates an increase in ET that is statistically significant and results in pregnancy. We document an increase in the mean number of follicles larger than 18 mm on day 13 TVS that is statistically significant. Ahmed *et al.* found a negligible mean increase in follicle count when sildenafil was used [4,5].

Conclusion

The results of the study lead us to the conclusion that sildenafil, when used in conjunction with Letrozole, enhances the likelihood of conception in infertile women with ovulatory problems. An increased endometrial thickness and follicular development may be responsible for this. In comparison to group A, group B also experienced greater headaches, dizziness,

and vision blurring; however, none of these side effects were severe or unbearable. More research is necessary to determine the long-term impact of sildenafil on foetal health and fertility.

Reference

1. Amed Abdel Kader Fahmy, Mohamed El Sökkary, Shrihan Sayed. The value of oral Sildenafil in the treatment of female infertility: A Randomised controlled trial. *Life Sci. J.*, 2015; 12 (4): 78-82.
2. Dr. BN Chakravorty, Inflatility and Hormones in Gyanecology in: DC Cutta's Textbook of Gynecology; Ith edition. Jaypee Brothers Medical Publishers (P) Ltd, 2016; CH17: C432: 199, 209, 441.
3. Mishra V.V., Choudhary S. Bandwal P., *et al.* Vaginal Sildenafil: Role in Improving Endometrial blood flow in women undergoing IVF with frozen thawed embryo cycles. *IJSR*, 2015; 4(8): 292
4. Mangal S, *et al.* To study and compare the effect of vaginal Sildenafil and Estradiol Valerate pregnancy on Endometrial rates in infertile women. Thickness, blood flow and undergoing intrauterine insemination *Int. J Reprod contracept obstet Gynecol.*, 2016; 5(7): 2274-22 77.
5. Paulus WE, Strehler E, Zhang M, Jelinkova L, El-Danasouri I, Sterzik k. Benefit of vaged sildenafil citrate in assisted reproduction therapy. *Fertil Steril.* 2002; 77(4): 846-7