



ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

EFFECT OF SILDENAFIL CITRATE AND ESTRADIOL VALERATE ON ENDOMETRIAL THICKNESS IN OVULATION INDUCTION WITH CLOMIPHENE CITRATE

KEY WORDS:

Dr. Tejal
Madhukar
Monika Patil*

*Corresponding Author

Dr. Ashutosh
Vinay Bahulekar

ABSTRACT **Background:** Clomiphene citrate (CC) is the most commonly used oral agent for ovulation induction in anovulatory infertility. Despite its efficacy, CC has anti-estrogenic effects on the endometrium and cervical mucus, which may impair implantation. Strategies to overcome this drawback include adjuvant therapies such as estradiol valerate, which promotes endometrial proliferation, and sildenafil citrate, which enhances uterine blood flow and vascularity. Comparative data between these two adjuvants remain limited.

INTRODUCTION:

Infertility is a big global health concern, which is characterized by the inability to attain a clinical pregnancy after at least twelve months of consistent, unprotected intercourse [1]. Globally, infertility affects 8 to 12% of the population [2]. In India alone, between 13 to 19 million couples are estimated to be infertile at any given time [3].

Clomiphene citrate (CC) continues to be the primary pharmacologic agent employed to induce ovulation.

The anti-estrogenic action of clomiphene on the endometrium and cervical mucus is believed to contribute to discrepancies between ovulation and conception rates. Optimal endometrial receptivity is vital for successful implantation. Sildenafil citrate, a selective phosphodiesterase-5 inhibitor, enhances nitric oxide-mediated vasodilatation thereby improving uterine perfusion and potentially aiding endometrial development [4,5] and remodeling of the endometrial matrix [6].

Estradiol valerate promote endometrial proliferation, likely due to enhanced perfusion of the basal layer.

Based on these considerations, the current hospital-based comparative study was conducted to evaluate endometrial thickness following ovulation induction by using clomiphene citrate in isolation versus combination along with adjuvant agents-estradiol valerate and sildenafil citrate.

MATERIALS AND METHODS

Study Design And Participants:

A prospective observational and comparative study was conducted at Krishna Vishwa Vidyapeeth, including 96 subjects suffering from primary or secondary infertility patients on whom ovulation induction is done with clomiphene citrate. Exclusions include ovulation inductions done other than clomiphene citrate and any contraindication of Clomiphene Citrate, Sildenafil citrate and Estradiol valerate. Participants were randomized into two groups: Group A: Clomiphene Citrate Alone

Group B: Clomiphene citrate + estradiol valerate

Group C: Clomiphene citrate + sildenafil citrate

Endometrial thickness was measured using transvaginal sonography on the day of hCG trigger. Endometrial pattern, ovulation rate, and clinical pregnancy rate were also assessed. Statistical analysis was performed using appropriate tests, with $p < 0.05$ considered significant.

RESULTS:

Results of the present study substantiate the use of sildenafil and estradiol valerate as effective adjuvants to clomiphene citrate. Both agents improved endometrial thickness more than clomiphene citrate in isolation. Given the importance of adequate endometrial growth and perfusion in achieving successful implantation, especially in patients with suboptimal endometrial response, the findings have important implications for enhancing outcomes in ovulation induction protocols.

Endometrial Thickness (mm)	Group	N	Mean	SD	p-value
Day 2	A	32	3.07	0.43	0.74
	B	32	3.00	0.33	
	C	32	3.03	0.35	
Day 5	A	32	3.46	0.53	0.586
	B	32	3.76	0.46	
	C	32	3.88	0.40	
Day 7	A	32	4.76	0.60	0.361
	B	32	4.62	0.57	
	C	32	5.01	0.52	
Day 9	A	32	5.51	0.71	0.429
	B	32	5.60	0.72	
	C	32	5.89	0.77	
Day 14	A	32	7.19	1.44	<0.01 (all groups)
	B	32	8.21	1.19	
	C	32	8.78	1.11	

Study Group	Mean Endometrial Thickness (Day 14)	Statistical Significance
Group A (CC only)	7.19 mm	Reference group
Group B (Sildenafil + CC)	8.21 mm	$p < 0.01$
Group C (Estradiol + CC)	8.78 mm	$p < 0.01$ vs Group A

DISCUSSION:

The present study was undertaken to evaluate and compare the efficacy of estradiol valerate and sildenafil citrate as adjuvants to clomiphene citrate (CC) in improving endometrial receptivity, assessed in terms of endometrial thickness, among women undergoing ovulation induction. A total of 96 women were recruited and equally divided into three groups: Group A received CC alone, Group B received CC with sildenafil, and Group C received CC with estradiol valerate. The findings were interpreted in the context of baseline demographic comparability, serial follicular ultrasound evaluations, and supporting evidence from prior clinical studies.

CONCLUSION:

This study demonstrates that the addition of either sildenafil citrate or estradiol valerate to clomiphene citrate significantly enhances endometrial thickness in women undergoing ovulation induction. By Day 14 of the treatment cycle, both adjuvant groups-sildenafil (Group B) and estradiol (Group C)-showed significantly greater endometrial thickness compared to clomiphene citrate alone (Group A), with the estradiol group achieving the highest mean thickness. These findings support the use of either sildenafil or estradiol as effective adjuvants to clomiphene citrate for improving endometrial receptivity, which may translate into better clinical outcomes in ovulation induction protocols. Further studies with larger samples and pregnancy outcome measures are warranted to substantiate these findings.

REFERENCES:

1. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. *Human Repro Update*. 2011;17(5):575-88.
2. Singh K, Kumari R, Ranjan R, Bharti G. Analysis of causes and clinical pattern of infertility in couples coming to a tertiary care centre in Bihar, India. *Int J Reprod Contracept Obstet Gynecol*. 2017;6(6):2279- 83.
3. Mittal S. Investigating infertility. In: Gutgutia R Infertility management series. 1st edition. Jaypee Brothers Med Publishers (P) Ltd; 2018:356-357.
4. Li X, Luan T, Zhao C et al. Effect of sildenafil citrate on treatment of infertility in women with a thin endometrium: a systematic review and meta-analysis. *Journal of International Medical Research*. 2021;48(11):0300060520969584.
5. Li X, Su Y, Xie Q et al. The effect of sildenafil citrate on poor endometrium in patients undergoing frozenthawed embryo transfer following resection of intrauterine adhesions: A retrospective study. *Gynecologic and Obstetric*
6. Mohammed W, Abbas M, Abdelazim I et al. Sildenafil citrate as an adjuvant to clomiphene citrate for ovulation induction in polycystic ovary syndrome: crossover randomized controlled trial. *Menopause Review*. 2022;21(1):20-26.