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EFFECT OF SILDENAFIL ON ENDOMETRIUM IN CLOMIPHENE CITRATE INDUCED CYCLES

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ABSTRACT: About 30% of cases of infertility are caused by disorders of ovulation. These disorders are often accompanied by irregular periods (oligo menorrhoea) or the absence of periods (amenorrhoea). A veritable avalanche of drugs, methods, and modalities for effective treatment of infertility, particularly anovulation, came at the same time from multiple directions during the 1960s and 1970s. Clomiphene citrate (MRL-41) was first applied in 1961 by Greenblatt et al. This simple, cheap, and relatively safe treatment has enabled thousands of an ovulatory woman to become mothers. A prospective observational study is done on 60 women for a duration of 18 months at the Department of Obstetrics and Gynaecology, Vinayaka Mission Medical College Karaikal, Women less than 35 years of age having primary or secondary infertility, Patient with patent fallopian tubes were included in the study. The results of our study revealed that Sildenafil added to conventional gonadotropin-releasing hormone (GnRH) protocol during ovarian stimulation has, however, been reported to increase endometrial thickness by a non-significant amount.

1. INTRODUCTION

For approximately 35–40 years, menstruation cycles affect female health, mood, and daily living quality from the beginning of adolescence to menopause. This sophisticated, naturally designed mechanism serves the primary purpose of providing gametes and a well-prepared environment for embryo implantation. The pituitary gland secretes follicular stimulating hormone (FSH) that stimulates the growth of multiple follicles inside the ovary. Growth of these follicles releases estrogen, which inhibits FSH secretion in a negative feedback loop involving the pituitary gland, the hypothalamus, and inhibin B. A dominant follicle is naturally selected and allowed to grow as a result of becoming more sensitive to lowered FSH levels while adjacent follicles experience atresia. Estrogen continues to be secreted by this dominant follicle. When estrogen levels remain high, the pituitary gland releases luteinizing hormone

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abruptly, triggering ovulation. In the aftermath of ovulation, the dominant follicle transforms into a corpus luteum, which secretes estrogen and progesterone and collapses, initiating menstruation. The fertility window begins approximately 3–5 days (sperm lifespan) before ovulation and lasts approximately 1–2 days (oocyte lifespan) after ovulation. Contraception can be encouraged or discouraged by identifying this window rather than simply detecting ovulation. About 30% of cases of infertility are caused by disorders of ovulation. These disorders are often accompanied by irregular periods (oligo menorrhoea) or the absence of periods (amenorrhoea). Several of them are simple and effective. Prior to the early 1960s, there was no effective treatment for this disorder. A veritable avalanche of drugs, methods, and modalities for effective treatment of infertility, particularly anovulation, came at the same time from multiple directions during the 1960s and 1970s. Clomiphene citrate (MRL-41) was first applied in 1961 by Greenblatt et al. This simple, cheap, and relatively safe treatment has enabled thousands of an ovulatory woman to become mothers.

AIMS AND OBJECTIVES:

AIM:

The efficacy of Sildenafil citrate in improving the endometrial thickness in clomiphene citrate induced cycles in infertile women

OBJECTIVE:

To study the role of sildenafil citrate on endometrial characters in ovulation induction cycle

MATERIALS AND METHODS: A prospective observational study is done on 60 women for a duration of 18 months at the Department of Obstetrics and Gynaecology, Vinayaka Mission Medical College Karaikal, Women less than 35 years of age having primary or secondary infertility, Patient with patent fallopian tubes were included in the study. Women with any organic lesions of uterus, tubes, or ovaries, Presence of congenital and acquired uterine anomalies, Tubal factors of infertility, known cases of cardiac diseases, and those who has sensitivity to sildenafil citrate were excluded from the study. After approval by ethical committee, detailed history, general & local examination was done. Basic investigations, thyroid profile and hormonal profile on D2 of cycle, Semen analysis was done in partner to rule out male factors were performed. After applying inclusion and exclusion criteria and after taking proper written and informed consent patients given the following treatment.

IN FIRST CYCLE:

-Ovulation induction with tab. clomiphene citrate 50mg daily d2 –d6

-USG was done on alternate days from D 8 onwards (till HCG trigger) and ovulation to check endometrial thickness, follicular growth

IN SECOND CYCLE:

-Ovulation induction with Tab.Clomiphene citrate 50mg daily D2 –D6+Tab. Sildenafil citrate 25mg from D7 till HCG trigger

-USG was done on alternate days from D 8 onwards (till HCG trigger) and ovulation to check endometrial thickness, follicular growth.

STATISTICAL ANALYSIS: All the data collected were coded and entered in Microsoft Excel sheet which was re-checked and analysed using SPSS statistical software version 22. Quantitative variables were summarised using mean and standard deviation (SD). Categorical variables were represented using frequency and percentage. The data were represented using the tables, figures, bar diagram and pie chart. Independent sample t-test was used to test statistical significance of difference between means of variables among two independent groups. Pearson Chi-square test and Fisher's exact test were used for comparing categorical variables between groups. A p value of <0.05 was considered statistically significant.

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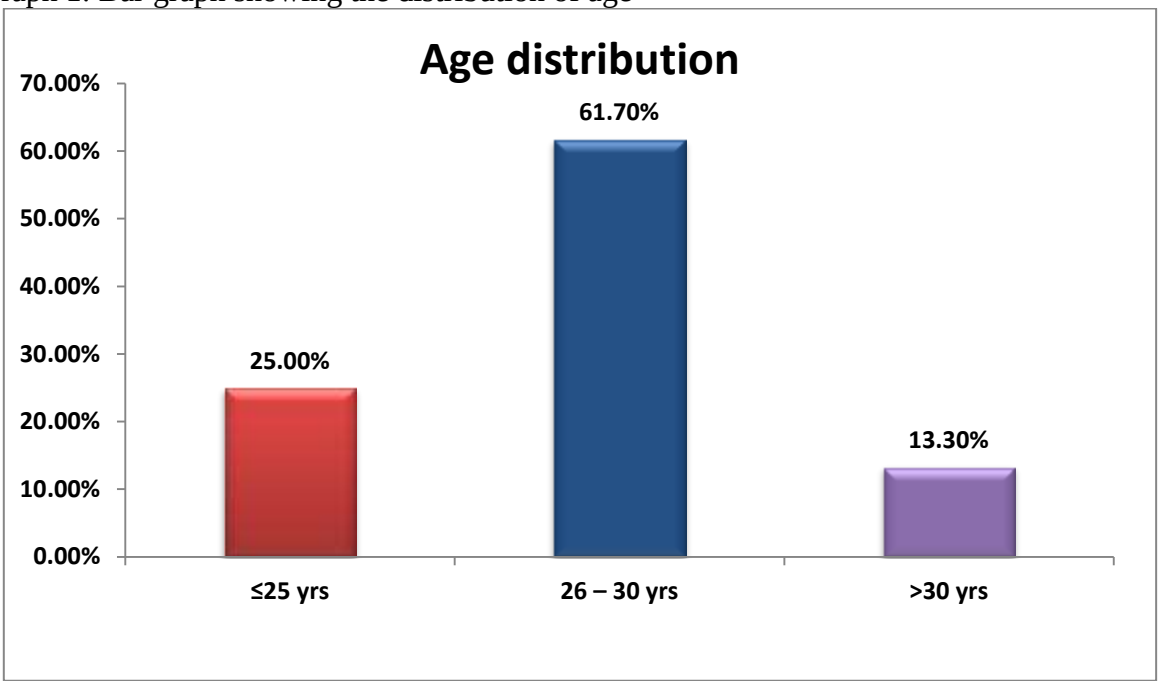
2. OBSERVATIONS AND RESULTS

Graph 1: Bar graph showing the distribution of age



Graph 2: Bar graph showing the Parity

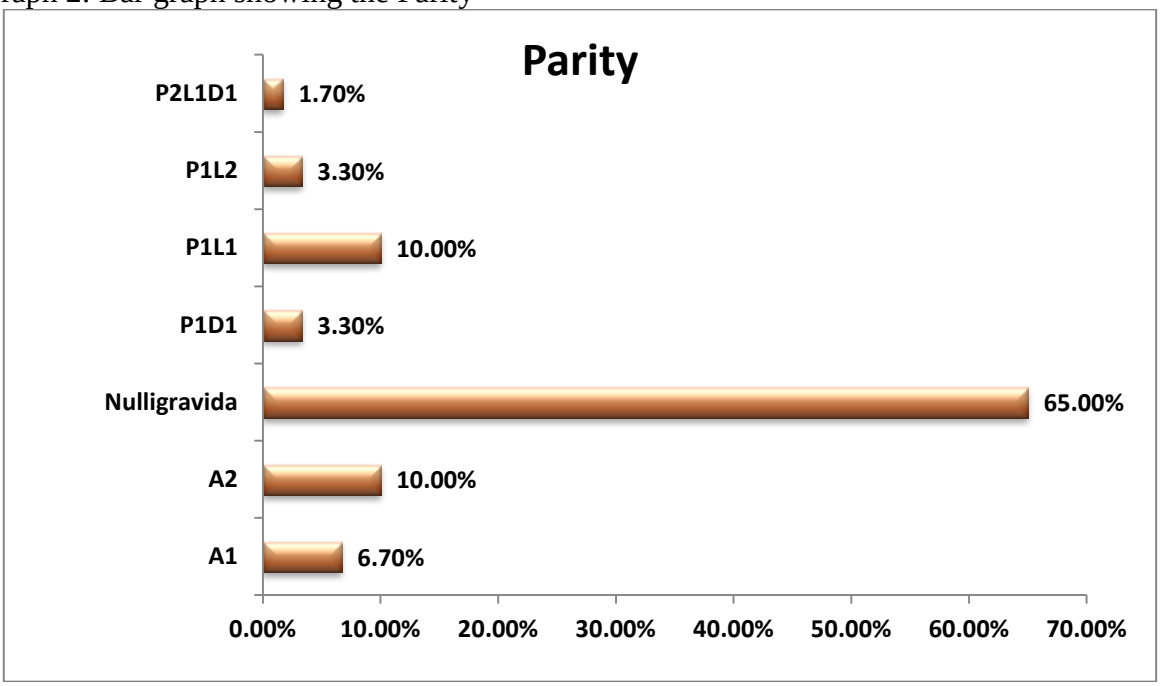


Table 1: Table showing the Duration of Infertility

Duration of Infertility	F	Percentage
≤3 yrs	42	70.0%

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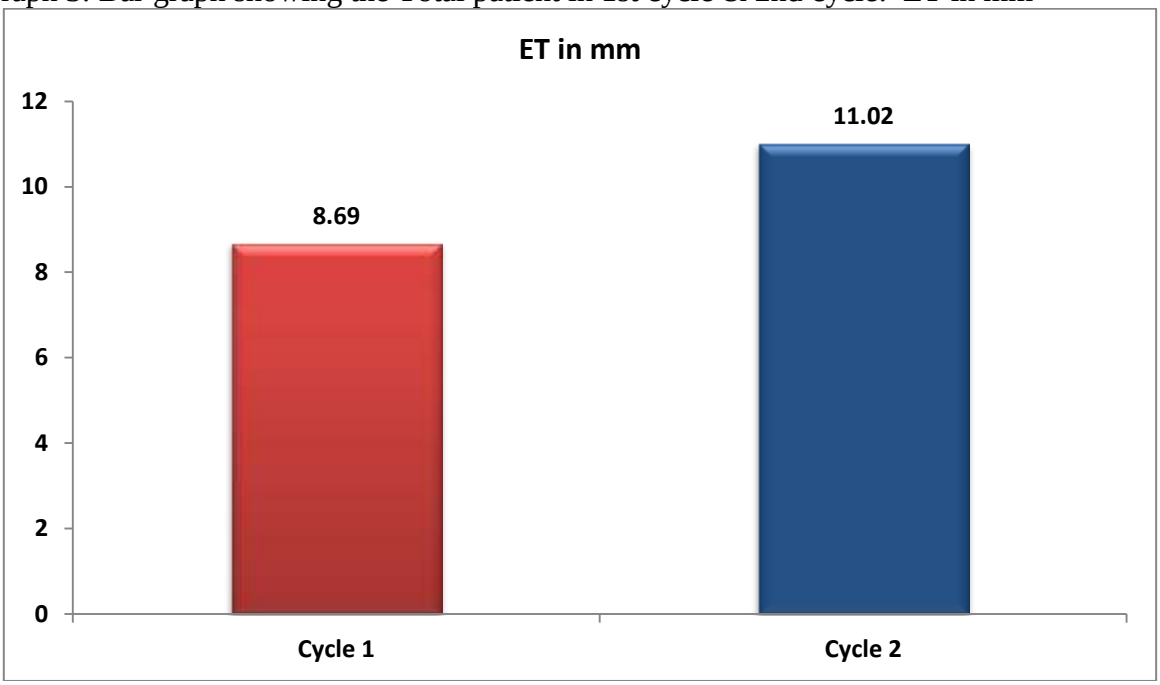
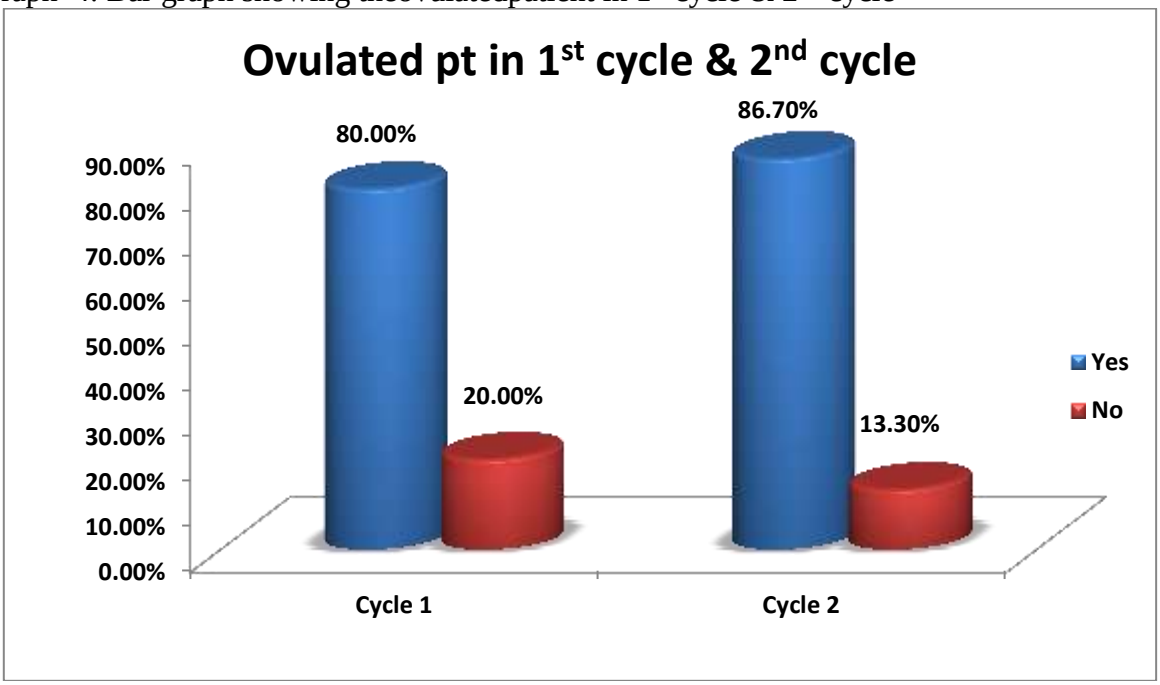
4 – 6 yrs	15	25.0%
>6 yrs	3	5.0%
Total	60	100%

Graph 3: Bar graph showing the Total patient in 1st cycle & 2nd cycle: ET in mm



Graph 4: Bar graph showing theovulatedpatient in 1st cycle & 2nd cycle



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Graph 5: Bar graph showing the Non Ovulated pt in 1st cycle & 2nd cycle

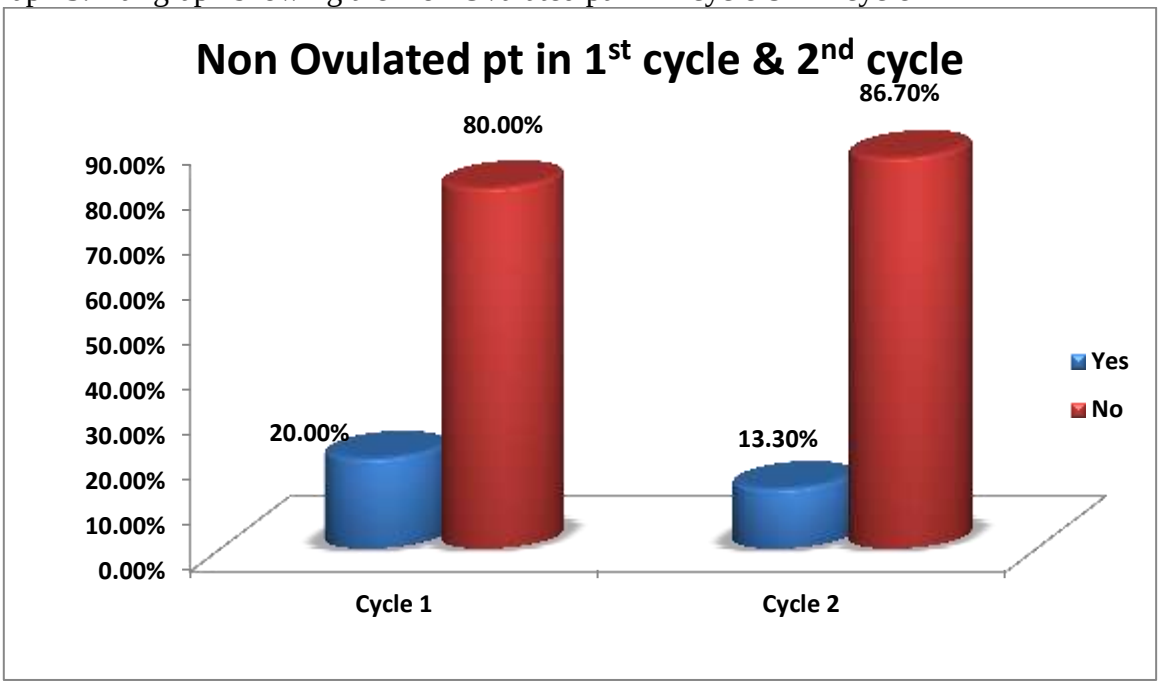

Table 2: Table showing the Cycle 1 ET in mm with Ovulation+

ET in mm	Ovulation +	N	Mean ± SD	T value	P value
Cycle 1	Yes	48	8.98 ± 1.14	4.365	0.0001
	No	12	7.51 ± 0.51		

Table 3: Table showing the Cycle 2 ET in mm with Ovulation+

ET in mm	Ovulation +	N	Mean ± SD	T value	P value
Cycle 2	Yes	52	11.12 ± 1.57	1.417	0.162
	No	8	10.32 ± 0.55		

Table 4: Table showing the Cycle 1 ET in mm with Non Ovulation

ET in mm	Non Ovulation	N	Mean ± SD	T value	P value
Cycle 1	Yes	12	7.51 ± 0.51	4.365	0.0001
	No	48	8.98 ± 1.14		

Table 5: Table showing the Cycle 2 ET in mm with Non Ovulation

ET in mm	Non Ovulation	N	Mean ± SD	T value	P value
Cycle 2	Yes	8	10.32 ± 0.55	1.417	0.162

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	No	52	11.12 ± 1.57		

Table 6: Table showing the ET in mm with Non Ovulation mean comparison for study cycles

ET in mm	Non Ovulation	N	Mean ± SD	T value	P value
ET in mm	Cycle 1	12	7.51 ± 0.47	-12.309	0.0001
	Cycle 2	8	10.32 ± 0.55		

Table 7: Table showing the Non Ovulation Cycle 1 involved Ovulation+ Cycle 2 mean comparison

ET in mm with Non Ovulation Cycle 1 involved Ovulation+ Cycle 2	Variable	N	Mean ± SD	T value	P value
	Non Ovulation Cycle 1	12	7.51 ± 0.47	-8.373	0.0001
	Ovulation+ Cycle 2	7	10.07 ± 0.88		

Table 8: Table showing the ET in mm with Non Ovulation followed both cycle mean comparison

ET in mm	Non Ovulation	N	Mean ± SD	T value	P value
ET in mm	Cycle 1	12	7.51 ± 0.47	-2.947	0.009
	Cycle 2	7	9.00 ± 1.67		

3. DISCUSSION

The use of clomiphene citrate in ovulation induction has been associated with a discrepancy between high ovulation rates (70-80%) and low pregnancy rates (10-20%) (Badawy et al., 2007; Badawy et al., 2008). During clomiphene citrate induction cycles, poor endometrial growth is attributed to its anti-estrogenic effect on the endometrium (Mitwally and Casper, 2006). The effectiveness of various strategies to minimize estrogenic antagonist effects of clomiphene citrate has been limited (Reynolds et al., 2010).

In the present study, we tested if Sildenafil citrate could improve endometrial thickness in clomiphene citrate-induced cycles in infertile women for the first time. Adding sildenafil to clomiphene citrate significantly increased endometrial thickness, and improved uterine blood flow. Furthermore, we have shown a statistically significant increase in pregnancy rates.

In our study, 61.7% of the patients were between 26 and 30 years old. Twenty-five percent of the patients were over the age of 25. Over 30% of the patients were over 30 years old. In a prospective comparative study, Taha Abdel Fattah Ahmed and colleagues included 58 patients between 18 and 35 years of age with primary and secondary infertility.65.0% of the patients in our study were nulligravida. The percentage of A2 participants was 10.0%. The percentage of P1L1 participants was 10.0%. The percentage of A1 participants was 6.7%. The percentage of P2L1D1 participants was 1.7%. 70.0% of the participants in our study had an infertility issue for the period of three years. Our study found that 25.0% of patients were between the ages of 4 and 6 years old. According to Shailza Vardhan, the mean duration of

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infertility in groups I and II was 3.6 years and 4.2 years, respectively. Y. Srilaxmi et al., reported median duration of infertility was 4.26 years.

Thin endometrium remains a challenge for gynaecologists despite various treatment options for infertility. A study was conducted to evaluate the effect of sildenafil citrate and clomiphene citrate in females with a thin endometrium as a cause of implantation failure in patients with dysovulatory infertility. As a result of cycle 1, the mean endometrial thickness was 8.69 x 1.19 mm. Cycle 2 ended with a mean endometrial thickness of 11.02 ± 1.49. Shailza Vardhan et al., the mean endometrial thickness pre-treatment in group I was 5.20 ± 0.80 mm and in group II was 5.56 ± 0.58 mm, which significantly improves to 9.0175 ± 2.58 mm and 9.375 ± 1.989 mm in group I and group II, respectively (p value < 0.05). A vasodilator effect of sildenafil citrate may explain the improved endometrial thickness in cycle 2, which increases uterine blood flow. Other studies have shown that adding Sildenafil to Clomiphene citrate during ovulation induction improves endometrial thickness. In cycle 1 to cycle 2 the ovulation % was increased from 80% to 86.7%. A randomized clinical trial of sildenafil plus clomiphene citrate improved ovulation induction rates in patients with unexplained infertility. Cycle 1 had 22.5% ovulation and cycle 2 had 42.5% ovulation. In non-ovulated patients, cycle 1 to cycle 2 the ovulation rate was 20% and 13.3%. In our study, we compared non-ovulated patients in the first cycle with ovulated patients in the second cycle. According to this comparison, 80.7% of women were non-ovulated in cycle 1 and 86.7% were ovulated in cycle 2. In our study we found significant increase in the endometrial thickness to mean of 10.32 ± 0.55 in cycle 2 compared to 7.51 ± 0.47 in cycle 1 which is in accordance with Takasaki et al., (a prospective study of 61 patients with thin endometrium there was a significant improvement in endometrial thickness) which was also observed with Jerzal et al., Dalia Ibrahim et al., studies. The ovulation rates with CC range from 70-85% per cycle, whereas the cumulative pregnancy rates in a 6-month period are between 40- 70% (Eijkemans et al., 2003; Van Santbrink and Fauser, 2006). In Firouzabadi et al., (a study of endometrium thickness and triple line pattern with significantly higher with sildenafil), the endometrial triple line [trilaminar pattern] in Group B was 93.54% compared to 40.29% in Group A.A systematic review and meta-analysis of sildenafil citrate's effectiveness in treating infertility in women with thin endometrium has been conducted by Li X, et al. Sildenafil citrate has been shown to improve clinical pregnancy rates, biochemical pregnancy rates, and endometrial thickness in women with thin endometrium .Among patients with previous assisted reproductive cycles that failed due to poor endometrial response, Moini A has reported that Sildenafil citrate improves blood flow to the uterine arteries and causes thickening of the uterine endometrium on sonography. Sildenafil added to conventional gonadotropin-releasing hormone (GnRH) protocol during ovarian stimulation has, however, been reported to increase endometrial thickness by a non-significant amount.

4. CONCLUSION

Sildenafil citrate is easy to use and inexpensive, and is easily accepted by patients. Therefore, sildenafil citrate is more useful for clinical applications. The use of sildenafil as an enhancer of endometrial vascularity helps in improving pregnancy rates in patients with unexplained infertility treated with clomiphene, and counteracts the poor effect of clomiphene on endometrial receptivity. We consider that our results are reliable as shown by sensitivity analysis. In conclusion, sildenafil citrate plays a beneficial role in treatment of a thin endometrium. Sildenafil citrate is easy to use and inexpensive, and is easily accepted by patients. Therefore, sildenafil citrate is more useful for clinical applications. The use of

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sildenafil as an enhancer of endometrial vascularity helps in improving pregnancy rates in patients with unexplained infertility treated with clomiphene, and counteracts the poor effect of clomiphene on endometrial receptivity.

We consider that our results are reliable as shown by sensitivity analysis. In conclusion, sildenafil citrate plays a beneficial role in treatment of a thin endometrium.

5. REFERENCES

1. Pengo MF, Won CH, Bourjeily G. Sleep in women across the life span. Chest. 2018 Jul 1;154(1):196-206.
2. Hillier SG. Current concepts of the roles of follicle stimulating hormone and luteinizing hormone in folliculogenesis. Human reproduction. 1994 Feb 1;9(2):188-91.
3. Bouchard T, Fehring RJ, Schneider M. Efficacy of a new postpartum transition protocol for avoiding pregnancy. The Journal of the American Board of Family Medicine. 2013 Jan 1;26(1):35-44.
4. Ledger WL, Skull J. Amenorrhoea: investigation and treatment. Current Obstetrics & Gynaecology. 2004 Aug 1;14(4):254-60.
5. Katsikis I, Kita M, Karkanaki A, Prapas N, Panidis D. Anovulation and ovulation induction. Hippokratia. 2006 Jul;10(3):120.
6. GEMZELL C. Induction of ovulation using human pituitary or urinary FSH. Clinical Obstetrics and Gynecology. 1967 Jun 1;10(2):401-17.
7. Homburg R. Oral agents for ovulation induction–clomiphene citrate versus aromatase inhibitors. Human fertility. 2008 Jan 1;11(1):17-22.
8. Tanbo T, Mellembakken J, Bjercke S, Ring E, Åbyholm T, Fedorcsak P. Ovulation induction in polycystic ovary syndrome. Acta obstetricia et gynecologica Scandinavica. 2018 Oct;97(10):1162-7.
9. Tanbo T, Mellembakken J, Bjercke S, Ring E, Åbyholm T, Fedorcsak P. Ovulation induction in polycystic ovary syndrome. Acta obstetricia et gynecologica Scandinavica. 2018 Oct;97(10):1162-7.
10. Hashim HA. Management of Women with Clomifene Citrate Resistant Polycystic Ovary Syndrome–An Evidence Based Approach. Polycystic Ovary Syndrome. 2012 Feb 24;7(10):1-22.
11. Kuang H, Li Y, Wu X, Hou L, Wu T, Liu J, Ng EH, Stener-Victorin E, Legro RS, Zhang H. Acupuncture and clomiphene citrate for live birth in polycystic ovary syndrome: study design of a randomized controlled trial. Evidence-Based Complementary and Alternative Medicine. 2013 Jan 1;2013.
12. D Ly K, Aziz N, Safi J, Agarwal A. Evidence-based management of infertile couples with repeated implantation failure following IVF. Current Women's Health Reviews. 2010 Aug 1;6(3):200-18.
13. Ahmed ZS, Golovoy M, Abdullah Y, Ahmed RS, Dou QP. Repurposing of metformin for cancer therapy: updated patent and literature review. Recent Patents on Anti-Cancer Drug Discovery. 2021 May 1;16(2):161-86.