Section: Reproductive Medicine and Surgery

Original Research Article

THE EFFECT OF ESTRADIOL VALERATE ON ENDOMETRIUM IN OVULATION INDUCTION CYCLES

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ABSTRACT

Background: The implantation of a human embryo requires a subtle dialogue between the endometrium and the embryo.The aim is to study the effect of the addition of estradiol valerateto ovulation induction drugs on endometrial thickness and to study the pregnancy rate after the addition of estradiol valerate to ovulation induction drugs in PCOS & Non PCOS women.

Material and Methods: This study is a prospective observational study. The study spanned over a period of 9 months. The study included all infertile patients who visited the Outpatient Department and underwent ovulation induction during the specified period.The inclusion criteria for participants encompassed individuals aged between 21 and 35 years, with a body mass index (BMI) ranging from 18 to 34.9 kg/m². Primary or secondary infertility cases undergoing ovulation induction with natural conception or intrauterine insemination (IUI) were considered.Participants with Mullerian malformations, primary amenorrhea, hypogonadotropic hypogonadism, premature ovarian failure, and those who had previously undergone unsuccessful IUI/IVF were excluded from the study.

Results: The mean age was 28.82 ± 4.43 years. Around 67% of women were infertile for a duration upto 5 years. The mean duration of fertility was 4.72 ± 3.34 years. Majority of patients (64.5%) were in primary infertility group. About 58.1 % women had regular cycles and 41.9 % had irregular cycles. The cause of infertility was female factor in 41.5 % patients and male factor in 25.3 % patients.In PCOS group, irrespective of the endometrial thickness, estradiol valerate supplementation with oral ovulogens showed a comparable pregnancy rate. In the Non-PCOS group, irrespective of the endometrial thickness, estradiol valerate supplementation with oral ovulogens showed a comparable pregnancy rate.

Conclusion: The administration of estradiol valerate along with ovulogens showed improvement in endometrial thickness but did not improve the pregnancy rate.

Keywords: Endometrial thickness, Estradiol valerate, Letrozole, Ovulation induction.

INTRODUCTION

The implantation of a human embryo requires a subtle dialogue between the endometrium and the embryo. The endometrium undergoes morphological changes until it becomes receptive and this is under the control of sex steroid hormones, estrogen, and progesterone.[1] Estrogen acts in the proliferative phase of the menstrual cycle and helps in increasing endometrial thickness. To induce ovulation, oral administration of antiestrogens (clomiphene citrate) or aromatase inhibitors (letrozole) with or without gonadotrophins can be used.[2,3]

Many studies were done about affecting factors on endometrial thickness in infertile women, over the years, but the results are still unclear. Studies suggest the effect of age, etiology of infertility, and factors such as dominant follicle number on

endometrial thickness, and some of the studies suggest a strong effect of endometrial thickness on the pregnancy rate.[4] The parameters used to evaluate endometrial receptivity with a traditional two-dimensional ultrasound are an assessment of endometrial thickness and endometrial pattern. The correlation between endometrial thickness and pattern with pregnancy rate and predisposing factors for the growth of endometrium is unclear. Some studies suggest with endometrial thickness of at least 8 mm, with a high number of follicles (up to three) with an average of 15 mm, these parameters are correlated with a higher rate of conception.[5]The aim is to study the effect of the addition of estradiol valerate to ovulation induction drugs on endometrial thickness and to study the pregnancy rate after the addition of estradiol valerate to ovulation induction drugs in PCOS & Non PCOS women.

MATERIALS AND METHODS

This study is a prospective observational study.The study was conducted at the Department of Reproductive Medicine & Surgery, Sri Ramachandra Medical College and Research Institute, Chennai. The study spanned over a period of 9 months, from September 2021 to May 2022.The study included all infertile patients who visited the Outpatient Department and underwent ovulation induction at the Department of Reproductive Medicine & Surgery, Sri Ramachandra Institute of Higher Education & Research, Chennai, during the specified period.The inclusion criteria for participants encompassed individuals aged between 21 and 35 years, with a body mass index (BMI) ranging from 18 to 34.9 kg/m². Primary or secondary infertility cases undergoing ovulation induction with natural conception or intrauterine insemination (IUI) were considered.Participants with Mullerian malformations, primary amenorrhea, hypogonadotropic hypogonadism, premature ovarian failure, and those who had previously undergone unsuccessful IUI/IVF were excluded from the study.

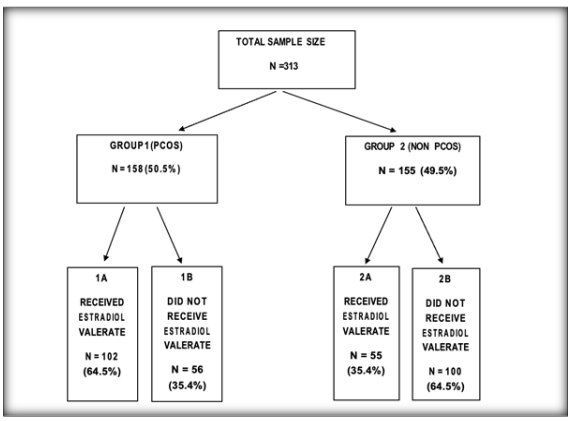

Figure 1: Graph depicting division of groups

The study analyzed two groups with different standard deviations (3 and 2.3), a mean difference of 1.2, an effect size of 0.45283, and an alpha error rate of 5%. The study aimed for 80% power, a two-sided approach, and required a sample size of 78 per group, totaling 313 participants after exclusions.The study received approval from the institutional ethical committee with the reference number CSP-MED/21/SEP/71/130.Ethical clearance was obtained, and eligible participants provided written informed consent. Transvaginal ultrasounds were conducted on day 2/3. Ovulation induction started with medications like clomiphene citrate or letrozole, with or without human menopausal gonadotropin. Estradiol valerate was administered from day 8 to 12. Serial monitoring through ultrasound assessed follicular growth and endometrial thickness. Human chorionic gonadotropin trigger was administered, and follow-up included monitoring for follicle rupture, natural conception, or intrauterine insemination.

Data were analyzed using IBM SPSS statistics software version 23. Descriptive statistics, frequency analysis, and percentage analysis described the data. Unpaired sample t-test or Mann-Whitney U test assessed differences between independent groups, while Chi-Square or Fisher's exact test explored associations. A significance level of 0.05 was employed for all statistical tests.

RESULTS

Majority (50.2%) of patients were in the age group between 26 – 30 years. The mean age was 28.82 ± 4.43 years.Around 67% of women were infertile for a duration upto 5 years.The mean duration of fertility was 4.72 ± 3.34 years.Majority of patients (64.5%) were in primary infertility group.About 58.1 % women had regular cycles and 41.9 % had irregular cycles.The cause of infertility was female factor in 41.5 % patients and male factor in 25.3 % patients.Majority of patients (77.3%) had antral follicle count of more than 15 follicles.There was equal distribution of PCOS and Non PCOS women in the study population.Majority of women (82.4 %) underwent ovulation induction and intrauterine insemination, 17.6% women underwent ovulation induction and natural relationship.The mean endometrial thickness on day 8 was 6.44 ± 1.48 mm and on the day of trigger was 9.02 ± 1.72 mm. The mean increase in thickness was 2.68 ± 1.35 mm.Majority of women (40.9 %) received letrozole for induction of ovulation followed by oral ovulogens with gonadotropins (32.2 %). [Figure 2]

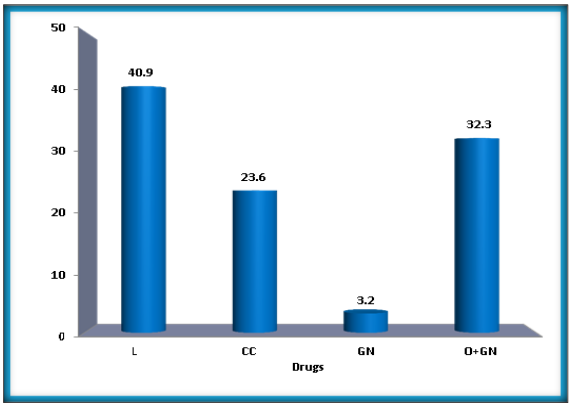

Figure 2: Ovulation induction drugs distribution (N=313)

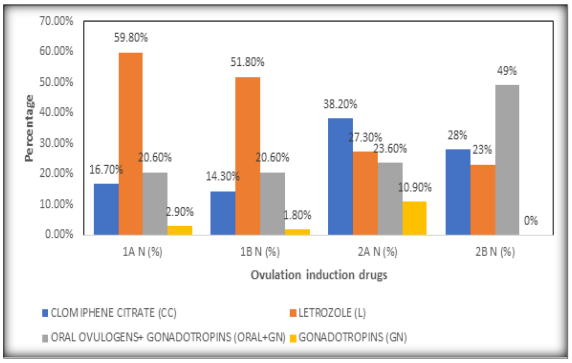

Figure 3: Comparison of ovulation induction drugs (N=313)

The majority of women received letrozole in both groups of PCOS, 59.8 % and 51.8 % with estradiol valerate (EV) and without EV group respectively. In Non PCOS group, 21.5 % women received clomiphene citrate and majority (49%) received oral ovulogens and gonadotropins in non EV group. [Figure 3]

In the PCOS group, there was significantly better ET in group 1B on D8 with clomiphene citrate, letrozole and in oral ovulogens plus gonadotropin group whereas on the trigger day, group 1B had significantly better ET in clomiphene citrate and oral ovulogens plus gonadotropin. But the increase in ET with all drugs in all groups were comparable. Pregnancy rate was comparable. [Table 1]

In Non PCOS group, ET on Day 8 was significantly better in Letrozole group which did not receive estradiol valerate but all groups were comparable with ET on trigger day and increase in ET. Pregnancy rate was comparable in all the groups (Table 2).

In PCOS group, irrespective of the endometrial thickness, estradiol valerate supplementation with oral ovulogens showed a comparable pregnancy rate. [Table 3]

In the Non-PCOS group, irrespective of the endometrial thickness, estradiol valerate supplementation with oral ovulogens showed a comparable pregnancy rate. [Table 4]

Table 1: Outcome – comparison in PCOS group between drugs and endometrial thickness (n=158)

	Clomiphene Citrate		P value	Letrozole		P value	Oral ovulogens + Gonadotropins		P value	Gonadotropins		P value
	1A	1B		1A	1B		1A	1B		1A	1B	
ET ON D8	6.07 ± 1.25	7.83 ± 1.56	**0.006**	5.74 ± 1.21	6.70 ± 1.58	**0.002**	6.02 ± 1.37	7.20 ± 1.71	**0.038**	5.63 ± 0.78	0	
ET ON TRIGGER DAY	8.95 ± 1.56	11.39± 2.55	**0.007**	8.79 ± 1.37	9.30 ± 2.18	**0.177**	8.32 ± 1.51	9.79 ± 1.97	**0.012**	7.57 ± 0.31	0	**0.17**
INCREASE IN ET	2.81 ± 1.23	3.81 ± 1.67	**0.103**	3.04 ± 1.38	2.64 ± 1.01	**0.168**	2.38 ± 1.18	2.73 ± 1.38	**0.396**	1.93 ± 0.98	0	
PREGNANCY RATE	1	0		11	7		2	2		1	0	
	1 (4%)			18 (20.8%)			4 (10.3%)			1 (25%)		

*ET-endometrial thickness

Table 2: Outcome - comparison in non pcos group between drugs and endometrial thickness (n=155)

	Clomiphene Citrate		P value	Letrozole		P value	Oral ovulogens + Gonadotropins		P value	Gonadotropins		P-value
	1A	1B		1A	1B		1A	1B		1A	1B	
ET ON D8	6.33±0.74	6.82±1.22	**0.301**	5.94±1.54	6.94±1.66	**0.008**	6.18±1.35	6.89±1.35	**0.129**	5.63±0.78	0	
ET ON TRIGGER DAY	8.80±1.33	8.96±1.6	**0.344**	9.32±1.31	9.04±1.8	**0.669**	8.38±1.11	9.10±1.71	**0.159**	7.57±0.31	0	
INCREASE IN ET	2.54±1.24	2.38±1.25	**0.111**	3.54±2.06	2.41±1.2	**0.065**	2.81±1.18	2.57±1.19	**0.691**	1.93±0.98	0	
PREGNANCY	2	2		1	1		2	1		1	0	**0.65**

RATE	4 (8.2%)		2 (5.3%)		3 (4.8%)		1 (16.7%)	

*ET-endometrial thickness

Table 3: Comparison between endometrial thickness on day 8 and supplemented with estradiol valerate and pregnancy rate in PCOS group (n=158)

ENDOMETRIAL THICKNESS		PREGNANCY RATE			P VALUE
	CC +EV	L+EV	ORAL+GN+EV	GN+EV	
<7 MM	1(7.7%)	11(20.8%)	1(5.9%)	1 (33.3%)	0.33
>= 7 MM	0	1(12.5%)	1(25%)	0	0.57

*CC-Clomiphene Citrate, EV- estradiol valerate, L-Letrozole, ORAL - Oral ovulogens, GN-Gonadotropins

Table 4: Comparison between endometrial thickness on day 8 and supplemented with estradiol valerate and pregnancy rate in non PCOS group (n=155)

ENDOMETRIAL THICKNESS		PREGNANCY RATE			P VALUE
	CC+ EV	L+EV	ORAL+GN+EV	GN+EV	
<7 MM	2 (12.5%)	1(10%)	2(20%)	1(16.7%)	0.92
>=7 MM	0	0	0	0	<0.0001

*CC- Clomiphene Citrate, EV- estradiol valerate, L- Letrozole, ORAL - Oral ovulogens, GN-Gonadotropins

DISCUSSION

This prospective observational study was primarily designed to see the improvement of endometrial thickness after administartion of estradiol valerate and its impact on pregnancy rate. We included 313 infertile couples over 9 months (September 2021 to May 2022).In our study, the mean age was 28.82 +/- 4.43 years. The majority (50.2%) were in the age group of 26-30 years.In a study done by Satirapod et al, the average age was 32 ± 4.6 years and older than our patients.[78] This could be due to the cultural difference and social trends as in our country, men and women marry at a younger age and seek help for fertility issues earlier.

The mean BMI was 26.75 ± 4. Kg/m2 for our study group. This was similar to a study done by Almner et al1, in which the mean BMI was 27.14± 2.78 Kg/m2.On the contrary, Satirapod et al2 study noted that BMI was lesser (20.4 ± 2.3 kg/m2) in their population. Carbohydrate-rich diet and sedentary lifestyle may be a few reasons for the obesity in our study population.The mean duration of infertility was 4.72 +/- 3.34 years in our study. In Seyedoshohohadaei et al study, the duration of infertility (3.37 ± 2.77 years) was similar. However, study done by Roy et al showed prolonged marital life (6.4 ± 3.8 years). As the study was done in a tertiary center, many couples had already undergone some amount of infertility evaluation and follicular monitoring and then sent to us which explains the duration of infertility. The baseline characteristics of the patients such as age, BMI, duration of infertility, and type of infertility were comparable in our study.There was an equal distribution of PCOS and Non-PCOS women in our study population. About 50.5 % of the study group were diagnosed with PCOS according to Rotterdam criteria. This is supported by the observation made by Gani et al3 on Indian women with PCOS which showed a grossly increased prevalence of metabolic syndrome (47.1% by IDF and 50% by WHO criteria) as opposed to 20–30% in non-PCOS Indians data by Joshi et al.[4]PCOS being a lifestyle disorder and the majority of patients being sedentary innately or due to Covid restrictions in the past 2 years explains the percentage in our study patients.Most of the patients (82.4%) underwent ovulation induction and intrauterine insemination in our study population.Many couples had already undergone multiple cycles of ovulation induction and natural relationship. This might be due to tertiary care center where women are referred after taking preliminary treatment.The drugs used for ovulation induction were clomiphene citrate (CC), letrozole (L), Oral ovulogens along with gonadotropins (GN).The majority of women (40.9 %) of the study population received letrozole followed by oral ovulogens with gonadotropins (32.2%). In group 1A and group 2B, 59.8 % and51.8 % received letrozole respectively and 20.[6] % patients received oral ovulogens and gonadotropins in both groups. In group 2A, 38.2% received clomiphene citrate followed by letrozole (27.3%) and in group 2B, 49% received oral plus gonadotropins followed by letrozole (28%).This difference in medication can be explained as group 1 included only PCOS women.

The mean endometrial thickness on the day of trigger with clomiphene citrate in group 1A was 8.95 ± 1.56 mm and when compared with group 1B and it was significant (p-value < 0.007). Similar results were observed in astudy by Satirapod et al,[2] where the administration of EV, an oral form of estradiol relieved the endometrial thinning effect of CC. For many years, CC has been used as the first treatment of choice for patients with PCOS. It is known that CC reduces uterine receptivity and thus reduces the chances of conception. It is associated with endometrial thinning in 15-50% of patients, probably due to prolonged estrogen receptor depletion which causes an antiestrogenic effect on target tissues especially endometrium.[5,6,7] In addition, CC may block estrogen receptors in the cervix, producing a negative effect on the quality

and quantity of cervical mucus8. Inappropriate development of endometrium is associated with low implantation rate and early pregnancy loss due to luteal phase defect.[9] Adding estradiol to clomiphene citrate starting from the 8th day of the cycle may prevent the possible detrimental effects of CC on the endometrium.[2]

Similarly, group 2A with CC had a mean ET on day 8 was 6.33 ± 0.74 mm and on the day of the trigger was 8.80 ± 1.33 mm.The mean increase in ET was 2.54 ± 1.24 mm and pregnancy in this group was 8.2 % which was statistically not significant. This correlated with a study done by Gupta et al10 they did not find any statistically significant difference in endometrial thickness and pregnancy rate after adding estradiol valerate to clomiphene citrate in the stimulated cycle. In their study,151 patients underwent IUI (intrauterine insemination) cycle, they were furtherly divided into three groups. One group received clomiphene citrate alone, the second received clomiphene citrate and estradiol valerate from day 3 till the next menstruation or till pregnancy is confirmed while the third group received clomiphene citrate with Human Menopausal Gonadotrophins (HMG) from day 7 to 9. These results were explained by a steady decline in the antiestrogenic effect of clomiphene citrate by the end of the proliferative phase, while the maximum significant difference in endometrial thickness was on day 8 of the cycle.[10]

In group 1A with letrozole, women with thin ET on day 8 (5.74 ± 1.21 mm) responded better after adding EV (8.79 ± 1.37 mm on the day of the trigger) and the increase in ET was the maximum in this group but not statistically significant. The pregnancy rate in this group was 20.8 %, the highest when compared with all the groups. This highlights the role of endometrial factors in achieving pregnancy. Groothuis et al. studied the effect of exogenous estradiol on the endometrium.[11] They observed nuclear translocation in endometrial cells occur one to three hours after administration of a low dose of estradiol. In turn, it has increased endometrial thickness and even the uterine size and weight after 72 h of estradiol administration in mice. In humans, similar changes have occurred but it was accompanied by stromal proliferation and needed a longer duration of estradiol exposure. They concluded that five days duration of estradiol exposure is an ideal period to build up thick endometrium sufficient for implantation 12. Roy et alconcluded that letrozole had a better endometrial response and pregnancy rate compared with clomiphene citrate in PCOS infertile patients.[12] Letrozole as an aromatase inhibitor does not have the antiestrogenic effect like other estrogen receptor modulator compounds, therefore it does not negatively affect endometrial thickness during ovulation induction in PCOS patients1. However, in our study increase in pregnancy rate (11 out of 18 in the letrozole group in group 1A) was found in the group who received estradiol valerate with letrozole which may be due to the positive effects of estradiol valerate on endometrial receptivity and the quality of mucus in the cervix.Similarly, group 2A with letrozole had a mean ET on day 8 was 5.94 ± 1.54 mm and on the day of the trigger was 9.32 ± 1.31 mm.The mean increase in ET was 3.54 ±2.06 mm and pregnancy in this group was 5.3% which was statistically not significant.

In comparing the mean increase in ET between CC + EV group and Letrozole + EV group in group 1, the endometrium was thicker in the Letrozole+ EV group (2.81 ± 1vs 3.04 ± 1.38 mm) and the pregnancy rate was higher in Letrozole + EV group (5.3% vs 20.8%). This correlated with the study done by Seyedoshohadaei et al, which showed that endometrial thickness increased after administration of Clomiphene plus Estradiol Valerate and Letrozole in PCOS patients, but there was significantly different in the two groups. In the Letrozole group, endometrial thickness was higher than Clomiphene plus Estradiol Valerate.[13]In group 1A with oral ovulogens plus gonadotropins, the mean endometrial thickness was 6.02 ± 1.37 mm on day 8 and 8.32 ± 1.51 mm on the day of triggerand itwas statistically significant. But increase in ET(2.38 ±1.18 mm) was not significant. In group 2A with oral ovulogens plus gonadotropins, the mean endometrial thickness was 6.18 ± 1.35 mm on day 8 and 8.38 ± 1.11 mm on the day of trigger and the mean increase in ET (2.81 ±1.18 mm) was not statistically significant. This data could not be compared due to a lack of studies of similar interest.In the PCOS group, when the endometrium was thin (<7 mm), the pregnancy rate was the highest in Letrozole + EV group (20.8%) across all the groups that received estradiol valerate. This correlated with a study done by Almner et al where they concluded that Letrozole + EV had better endometrial thickness and higher pregnancy rate.In a prospective study by Takasaki et al of 61 patients with a thin endometrium (8 mm), there was a significant improvement in endometrial thickness in 11 patients (18%) with vitamin E, L-arginine, or sildenafil through improving endometrial blood flow rather than stimulating follicular growth or increasing serum E2 levels.[14]

The outcome of our study suggest that pregnancy may not be dependent on only endometrial thickness. Wang et al,[15] found that endometrial vascularity and pattern of blood flow is positively related to implantation rate in patients going for IVF and embryo transfer. Endometrial thickness was greater in cycles resulting in pregnancy than in cycles not resulting in pregnancy (11.9 vs. 11.3 mm, respectively). Clinical pregnancy rates increased gradually from 53% among patients with a lining of <9 mm, to 77% among patients with a lining of ≥16 mm16. Endometrial thickness in conjugation with other ultrasonologic characteristics like shape,pattern and vascularity of endometrium play an important role in predicting pregnancy. Therefore, endometrial thickness should be

considered along with other endometrial factors such as pattern and blood flow to achieve pregnancy.

The study possesses several strengths. It is structured as a prospective observational study, allowing for the collection of real-time data and insights. Additionally, the study demonstrated meticulous adherence to the enrollment criteria, ensuring the inclusion of appropriate participants. However, there are certain limitations that need consideration. Participants were required to undergo frequent hospital visits for transvaginal ultrasounds to assess endometrial thickness and follicular growth, potentially introducing inconvenience and affecting adherence. Moreover, the study's focus was confined to exploring the impact of endometrial thickness on pregnancy outcomes, limiting the scope of its findings. The sample size employed in the study was relatively small, possibly affecting the generalizability of the results. Lastly, it's worth noting that the study was conducted exclusively within a single center, which could influence the diversity and representativeness of the study population.

CONCLUSION

The administration of estradiol valerate along with ovulogens showed improvement in endometrial thickness but did not improve the pregnancy rate.This should be confirmed with studies of larger sample size.

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