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Comparative Study between the Effect of Vaginal Sildenafil citrate and Estradiol Valerate on Endometrial Thickness in Women Undergoing Induction of ovulation by Clomiphen Citrate

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ABSTRACT

Background: Endometrial thickness (ET) is one of the best predictors of implantation rate and continued success rate for pregnancy. There were possible beneficial effects of sildenafil citrate or estradiol on endometrial receptivity. The aim of this study was to compare the effect of Vaginal Sildenafil versus Oral Estradiol Valerate on Endometrial Thickness and Pregnancy Rate in infertile women undergoing induction of ovulation by clomiphen citrate. **Patients and Methods:** This Randomized control study was conducted on 44 infertile women undergoing induction by Clomiphen Citrate attending infertility and U/S unit, Obstetrics & Gynecology Department, Zagazig University Hospital, during the period from December 2018 to August 2019. Patients were randomized into 2 groups (22 in each group); group (1) received Sildenafil and group (2) received oral Estradiol Valerate. **Results:** The results of present study showed that there was no statistically significant difference between the studied groups regarding age, Type of infertility, body mass index (BMI), follicle stimulating hormone (FSH), luteinizing hormone (LH), Thyroid stimulating hormone (TSH), prolactin, ovulation rate, follicles number and size, results of pregnancy test and fetal pulse detection between studied group. But there was a statistically significant difference between them in endometrial thickness on the day of triggering. **Conclusion:** It could be concluded from this study that vaginal use of vaginal sildenafil citrate 20 mg or oral Ethinyl Estradiol in infertile females increase endometrial thickness and support embryo growth but Ethinyl Estradiol has better results on endometrial thickness than sildenafil. But both treatments have the same effect on pregnancy rate.

Keywords: Infertility, Sildenafil, Estradiol valerate, Endometrial thickness

INTRODUCTION

Infertility is a worldwide public health issue; infertility affects around 13 per cent of couples. Implantation failure occurs despite the efforts of fertility clinics in the field of assisted reproductive technology (ART); thus, the successful implantation requires high-quality embryos and adequate receptive endometrial development [1].

The thickness of the endometrium depends on a variety of factors including reproductive age, menstrual cycle phase, concentration of ovarian hormones (estrogen and progesterone), and density of endometrial hormone receptors. There are several causes of thin endometrium: permanent endometrial injury, decreased blood flow, endometrial resistance to estrogen, decreased blood flow, and testosterone overexposure [2].

The endometrium, being a hormone-dependent tissue, proliferates in response to estrogen that further induces the development of progesterone receptors. As a consequence, estradiol (E2) treatments were given to infertile patients who presented thin endometrium, in an effort to improve endometrial proliferation [3].

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Sildenafil is considered a type 5-specific phosphodiesterase inhibitor; therefore, it increases the nitric oxide vasodilatory effects through the degradation prevention of cGMP. Vascular smooth muscle is relaxed during a cGMP-mediated pathway by Nitric oxide (NO) and NO synthase isoforms is found in the uterus. Some researchers studied the vaginal sildenafil effect on the thickness of endometrial of infertile patients who underwent IVF treatment and suffered from poor endometrial development. They showed an improvement in the uterine artery blood flow and in the endometrial growth with higher implantation and ongoing pregnancy rates following vaginal sildenafil administration [4].

In the treatment of recurrent implantation failure patient, vaginal sildenafil citrate has been attempted. Sildenafil citrate is a powerful and selective phosphodiesterase-5(PDE-5) inhibitor responsible for cGMP degradation, thus increasing the vasodilatory impact of nitric oxide by preventing cGMP degradation, contributing to vascular relaxation and increased uterine blood flow and enhancing endometrial efficacy. This results in vascular relaxation and increased blood flow and enhanced endometrial thickness [5].

The aim of this study was to compare the effect of Vaginal Sildenafil versus Oral Estradiol Valerate on Endometrial Thickness and Pregnancy Rate in infertile women undergoing induction of ovulation by clomiphen citrate

PATIENTS AND METHODS

This Randomized control study was conducted on 44 Infertile women undergoing induction by Clomiphen Citrate attending infertility and U/S unit, Obstetrics &Gynecology Department, Zagazig University Hospital, during the period from December 2018 to August 2019

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (International review board ZU-IRB# 4995-18-11-2018). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Ovulatory dysfunction, Primary or secondary infertility, Age between 20 -35 years, Normal basal hormonal level (FSH, LH, TSH, prolactin). Patent both fallopian tube as confirmed by HSG or laproscopy, BMI less than 30kg/m^2 and Normal semen analysis according to (WHO) 2010**[6]**.

Exclusion criteria: Any congenital uterine anomaly (e.g., unicornuate uterus or infantile uterus) or acquired deformities of the uterine cavity (as Asherman Syndrome), Women who had contraindication for estrogen treatment (e.g., history of stroke) or sildenafil (liver disease) and Endocrine disorders (thyroid disease, diabetes mellitus).

2-All patients were subjected to the following:

1- Complete history including:

Personal history (age, residence, BMI and habits), Menstrual history (regularity, amount, duration, dysmenorrhea, date of Last normal menstrual period (LNMP), Obstetric history (Gravidity, parity, abortion, mode of delivery), Medical history, surgical history and history of drug intake, Family history and endocrine disease.

2- General examination:

Inspection of skin as hirsutism, acne and other sings suggesting hyperandrogenism (PCO)

Thyroid disease as goiter, Bradycardia. Breast Examination as bilateral spontenous galactorrhea. BMI (calculated by dividing body weight in Kg by height in squared meter).Local examination to exclude any abnormlities such as infection , local vaginal or cervical lesion.

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Transvaginal ultrasound (TVS):

Transvaginal ultrasound (TVS): basic U/S on the cycle day two was done to detect endometrial thickness and exclude ovarian lesion (like cyst) and uterine (like endometrial polyp) .

Patients were randomly allocated into two groups, using a computer-generated randomization list and sequentially numbered opaque sealed envelopes, each containing the allocation information written on a card. Envelopes were opened sequentially by a study nurse to allocate patients to the assigned group. These patients were divided into 2 groups

Group (1): Included 22 women were given sildenafil (Silden® 25, E.I.P.I.CO.) was given every 8 hour from 2nd day of the cycle till the day of trigger of ovulation [3].

Group (2): Included 22 women received oral Estradiol Valerate (Cyclo-Progynova 2mg, white tablets, BAYER Schering pharma), one tablet every 12 hour from day 8th of the cycle till triggering of ovulation .

Follow up was done for both studied group by TVS at cycle day 12 to detect ovarian response and endometrial thickness. The transducer was introduced into the vagina for approximately 5cm . The tip of the transducer was normally angled up-ward through the anterior vaginal wall to visualize the anatomy of the uterus and ovaries. The transducer was manipulated by the user from side to side and up and down to image the entire area of interest, detecting the number of follicles on both ovaries form up down and from side to side [7].

Measurement of ovarian follicles, the follicle could be seen in the ultrasound device as a circular bubble filled with liquid with thin wall containing the egg. for round follicle , only one measurement was required, for oval follicles, the mean of two diameters was calculated (greatest diameters and greatest diameter perpendicular to it).

Measurement endometrial thickness :

The thickness of the Endometrium was measured (maximum distance between each Myometrial/Endometrial interface through the longitudinal axis of the uterus) using two dimensional Transvaginal Ultrasound.

Follow up continued until day of ovulation triggering (follicle size >17mm and endometrial thickness >8mm) on all cases.

Ovulating Triggering was done by hCG, 10.000IU (Choriomon, IBSA Switzerland) I.M administration. Then all cases in both groups were instructed to follow a regular time intercourse.

Ovulation was detected 48h after triggering by Ultrasound evidence of free fluid in Douglas pouch disappearance of follicles or decreasing its size.

B-hCG was done14 days after ovulation triggering.

For pregnant cases ultrasound was done 2 week after positive pregnancy test to detect fetal heart pulsation .

E- Outcome Measures

Primary Outcome Measures: Endometrial thickness

Secondary outcome measures: Number and size of follicles. Positive Pregnancy test by measurement of B-hCG 14 day after triggering of ovulation . Ultrasound detection of fetal pulsation 2 weeks after positive pregnancy test.

Statistical analysis

Statistical analysis was performed using **SPSS** version 25 software. Results were presented by tables and graphs. Results were expressed as the mean, Standard deviation and range for Continuous variables, number and percentage for categorical variables. **Chi-square test** was used to test differences for categorical variables. Independent samples **Student's t-test** or **Mann-Whitney U test** was used, as appropriate, to test differences for continuous variables between two groups. A P-value of **≤0.05** was accepted as statistically significant.

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RESULTS

Table (1), showed that the mean age was 29.1 ± 6.8 in group 1 while it was 27.6 ± 6.2 in group 2 with no statistical significant difference between the studied groups regarding age and the IBM was 24.3 ± 3.6 in group 1 while it was 24.7 ± 3.3 in group 2 with no statistical significant difference between the studied groups regarding BMI.

Table (2), showed that The mean FSH was 5.6 ± 0.9 in group 1 while it was 5.4 ± 1.0 in group 2, The mean LH was 9.4 ± 3.0in group 1 while it was 8.4 ± 3.0 in group 2, The mean TSH was 2.3 ± 0.7 in group 1 while it was 2.3 ± 0.7 in group 2, The mean Prolactin was 13.4±2.4 in group 1 while it was 14.3 ± 2.8in group 2 with no statistical significant difference between the studied groups regarding FSH, LH, TSH and prolactin level.

Table (3), showed that the mean Follicles number was 2.3 ± 1.8 in group 1 while it was 2.7 ± 1.2 in group 2 and the mean Follicles size (mm) was 20.3 ± 3.4 in group 1 while it was 21.4 ± 2.6 in group 2 with no statistical significant difference between the studied groups regarding follicles number and size.

Table (4), showed that the mean Endometrial thickness (mm) at the cycle day 8th was 6.4 ± 2.2 in group 1 while it was 6.0 ± 2.3 in group 2 with no statistical significant difference between both group, and the mean Endometrial thickness (mm) at the day of triggering was 8.2 ± 3.4 in group 1 while it was 8.8 ± 4.1 in group 2 with a statistical significant difference between the studied groups; where Group 2 had higher endometrial thickness than group 1**.**

Table (5), showed that ovulation was positive 16 (72.7%) in group 1 and 14 (63.6%) in group 2, while it was negative in 6 (27.3%) in group 1 and 8 (63.4%) in group 2 with no statistical significant difference between the studied groups regarding occurance of ovulation.

Table (6), showed that the pregnancy test was positive 6 (27.2%) in group 1 and 7 (31.8%)in group 2, while it was negative in 16 (72.2 %) in group 1 and 15 (68.1%) in group 2, Fetal pulse was positive 5 (83.3%) in group 1 and 6 (85.7%)in group 2, while it was negative in 1 (16.6 %) in group 1 and 2 (14.2%) in group 2 with no statistical significant difference between the studied groups regarding occurrence of pregnancy and fetal heart beat .

Table (1): Comparison between the studied groups regarding Age distribution, Type of infertility and BMI:

Variables	Group1(n=22)	Group2(n=22)	Test of sig.	*p*
Age (years):			T	
Mean ± SD	29.1 ± 6.8	27.6 ± 6.2	0.7	0.5
Median	29.0	28.0		
Range	20.0 – 35.0	21.0 - 32.0		
Type of fertility:			χ^2	
Primary	17 (77.3%)	13 (59.1%)	1.7	0.1
Secondary	5 (22.7%)	9 (40.9%)		
BMI (Kg/m^2):			T	
Mean ± SD	24.3 ± 3.6	24.7 ± 3.3	0.4	0.6
Median	25.5	25.4		
Range	18.8 – 29.1	19.2 – 29.3		

BMI: body mass index

Table (2): Comparison between the studied groups regarding basal hormonal level:

Variables	Group 1 (n=22)	Group 2 (n=22)	Test of	*p*

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			sig.	
FSH:			T	
Mean ± SD	5.6 ± 0.9	5.4 ± 1.0	0.9	0.3
Median	5.1	5.0		
Range	4.4 – 7.5	4.2 – 8.0		
LH:			MW	
Mean ± SD	9.4 ± 3.0	8.4 ± 3.0	1.2	0.2
Median	9.2	9.5		
Range	3.2 – 14.4	4.7 – 15.1		
TSH:			MW	
Mean ± SD	2.3 ± 0.7	2.3 ± 0.7	0.2	0.8
Median	2.4	2.1		
Range	1.3 – 3.8	1.0 – 3.5		
Prolactin:			T	
Mean ± SD	13.4 ± 2.4	14.3 ± 2.8	0.8	0.4
Median	13.0	14.5		
Range	10.6 – 19.3	10.2 – 20.7		

FSH : follicle stimulating hormone; LH : luteinizing hormone; TSH: Thyroid stimulating hormone

Table (3): Comparison between the studied groups regarding Follicles number and size:

Follicles number	**Group 1**	**Group 2**	**MW**	***p***
Mean ± SD	2.3 ± 1.8	2.7 ± 1.2	1.7	0.5
Median	3	2		
Range	0 - 5	0 - 4		
Follicles size (mm)	**Group1 (n=22)**	**Group2 (n=22)**	**T**	**p**
Mean ± SD	20.3 ± 3.4	21.4 ± 2.6	1.1	0.2
Range	12.0 – 24.0	17.0 – 25.0		

(MW)= Man Wittney Test

Table (4): Comparison between the studied groups regarding Endometrial thickness at the cycle day 8th and at the day of triggering

Endometrial thickness (mm) at the cycle day 8th	**Group 1**	**Group 2**	**MW**	***p***
Mean ± SD	6.4 ± 2.2	6.0 ± 2.3	2.0	0.2
Median	6.5	6.2		
Range	5.3 – 7.8	4.8 – 7.5		
Endometrial thickness (mm) at the day of triggering	**Group 1**	**Group 2**	**MW**	**p**
Mean ± SD	8.2 ± 3.4	8.8 ± 4.1	3.1	**0.003 S**
Median	8.6	9.5		
Range	8.3 – 9.4	8.8 – 11.5		

(MW)= Man Wittney Test

Table (5): Comparison between the studied groups regarding ovulation:

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Ovulation	Group 1 (n=22)	Group2 (n=22)	χ^2	*P*
Positive	16 (72.7%)	14 (63.6%)		
Negative	6 (27.3%)	8 (36.4%)	0.1	0.7

Table (6): Clinical pregnancy rates of the studied groups:

Variables	Group 1 (n=22)	Group2 (n=22)	Test of sig.	*p*
Pregnancy test:			χ^2	
Positive	6 (27.2%)	7 (31.8%)	0.2	0.8
Negative	16 (72.2 %)	15 (68.1%)		
Fetal pulse:			χ^2	
Positive	5 (83.3%)	6 (85.7%)	0.1	0.9
Negative	1(16.6 %)	2 (14.2%)		

DISCUSSION

Endometrial thickness (EM) is one of the strongest predictors of implantation rate and ongoing pregnancy success rate. The endometrial growth is dependent on the uterine blood flow and angiogenesis. Recently, some reports discussed the possible beneficial effects of sildenafil citrate on EM. Sildenafil citrate leads to smooth muscle relaxation and vasodilation. Because of these biological properties, it is a potential candidate for female infertility, especially in the management of thin endometrium, which leads to low implantation and pregnancy rates **[8].**

This study showed that there was no statistical significant difference between the two group in number of follicles >17 mm (p value 0.5) , mean in sildenfil group (2.3 +1.8) and mean in Estradiol group(2.7 +1.2) . This was in agreement with the study of **Dawood et al., [3]** who concluded that the difference in size and number of dominant follicles at HCG day between studied groups (A&B) was statistically insignificant (P>0.05)..

Additionally, our results are in agreement with result reported by a study of **Mangal and Mehirishi [5]**, as they found that the mean of number of follicles >18 mm at the time of HCG trigger was 1.52 in the group who took vaginal sildenfil and 1.68 in the group who took oral estradiol, the difference was statistically insignificant.

In contrary to current results, **Reddy et al., [9]** reported that though a slight increase in the number of follicles was observed with the use of vaginal Sildenafil, it was statistically insignificant with a P value of 0.09.

Our results of the current study proved that both Estradiol and Sildanfil increase endometrial thickness on day of triggering. Estradiol was more better and effective in increasing endometrial thickness in comparsion with sildanfil in which the difference between both group was stastically significant (P = 0.003). Estradiol increase endometrial thickness by mean (8.8+4.1) but sildanfil group increases by (8.2 +3.4).

Takasaki et al [10] used 100 mg sildenafil intravaginal starting first day of cycle till day of ovulation and 92% patients showed improvement in endometrial thickness

Another study carried by **Jerzak et al., [11]** in which they used 25 mg Sildenafil four times a day for 3 to 6 days as intra-vaginal suppository. Endometrial thickness was significantly increased.

Furthermore, **Cetinkaya et al., [12]** used vaginally administered local oestrogen 25 mcgms from 4th day for 15 days in clomiphene citrate induced cycle. They reported

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significant increase in endometrial thickness on the day of ovulation (7.6+/- 1.4 mm versus 8.3+/-2.1 mm) than the group where only clomiphene citrate was used, but there was no change in pregnancy rate.

In a study carried by **Satirapod et al., [13],** in which they examined the effects of Estradiol Valerate on the thickness of Clomiphene citrate -stimulated endometrium. They concluded that the administration of Estradiol Valerate following the Clomiphene citrate treatment can prevent the endometrial thinning.

Additionally, another study carried by **Malinova et al., [14], in** which they examined the role of sildenafil citrate and serophen in infertile women and they reported that vaginal consumption of sildenafil citrate and serophene can be used as an effective treatment method for ovulation induction by increasing uterin blood flow and increased endometrial thickness.

Also, a study carried by **Ataalla et al., [15]** as they found that there was a statistically significant increase in endometrial thickness on day of HCG in the sildenafil group compared to the control group although endometrial thickness was within the acceptable range in both groups.

In contrary of our results a study by **Mangal and Mehirishi [5],** in which they compare endometrial thickness between two groups (sildenafil and estradiol) and they found that there was no statistical significant difference between them in endometrial thickness. Mean endometrial thickness on day 7 was 5.42 mm in sildenafil group whereas it was 5.76 mm in estradiol group .

Pregnancy is the final goal of any infertility workup, In the study in our hands regarding to occurrence of pregnancy, pregnancy rate was higher in estradiol group than in sildenafil group . Despite this, the difference not reaching significant level and there was no statistically significant difference between the studied groups in regarding occurrence of pregnancy, which in agreement with the study carried by **Ataalla et al ., [15]** as they found that the increase in pregnancy rate, 6 cases in the sildenafil group versus 4 cases in the control group, which was not statistically significant difference..

Dawood et al [3], reported that the endometrial thickness and pattern was evaluated at the day of HCG trigger which was improved in both estradiol and sildenafil treatment. There was no significant different regard these parameters between studied groups however the pregnancy rate was significantly higher in sildenafil treated group

In a comparative prospective study performed by **Mangal and Mehirishi, [5]** that conclude: Mean endometrial thickness at the day of HCG trigger are higher in estradiol group than in sildenafil group however Sildenafil when compared to estradiol valerate has better consequences to the grade that endometrial vascularity is concerned and improved pregnancy result.

For a prospective study on fifty patients with unexplained 1ry infertility, **El-Shourbagy et al [16]** were conclude that the patients treated with sildenafil citrate saw a statistically significant increase in endometrial thickness and a higher pregnancy rate than control group.

In addition , our result showed that there was no statically significant difference between the studied group in fetal pulse detection , sildanfil group 5 cases of 6 (83.3%) positive fetal heart beat but Estradiol group 6 cases of 7(85.7%) positive fetal heart beat (P = 0.9).

Conclusion: It could be concluded from this study that vaginal use of vaginal sildenafil citrate 20 mg or oral Ethinyl Estradiol in infertile females increase endometrial thickness and support embryo growth but Ethinyl Estradiol has better results on endometrial thickness than sildenafil. But both treatments have the same effect on pregnancy rate.

Recommendation: Further studies should be done on large number of cases to compare oral estradiol valerat and vaginal sildenafil citrate regarding pregnancy rate and fetal outcome in pregnant women to confirm and validate the current results.

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