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Effect of Oral Estradiol Valerate versus Vaginal Sildenafil on Endometrial Receptivity in Clomiphene-Induced Cycle Infertile Females

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Abstract

Background: Female causes account for 30 percent of the overall infertility cases, five percent were attributed to uterine factors. 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 so some reports discussed these potential effects.

Aim of Study: Was to compare the effect of vaginal Sildenafil citrate and Estradiol valerate on endometrial receptivity in clomiphene-induced cycle infertile females.

Patients and Methods: This Randomized control study was conducted on 44 infertile women undergoing induction by Clomiphen Citrate attending infertility and ultrasound (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 (Respatio 20mg/8hr film coated tablets vaginally for 5 days starting from day 8 th) and group 2 received oral estradiol valerate (Cyclo-Progynova 2mg, white tablets, BAYER Schering pharma), one tablet every 12 houre from day 8 th till triggering of ovulation).

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 sildenafil citrate 20mg or oral Ethinyl Estradiol in females undergoing induction of ovulation lead to increase endometrial thickness and support embryo growth. Both have the same effect on pregnancy rate but Ethinyl Estradiol has better results on endometrial thickness than sildenafil.

Key Words: *Infertility – Sildenafil – Estradiol valerate – Endometrial thickness.*

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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]**.

Sildenafil citrate is a potent and selective inhibitor of cGMP-specific phosphodiesterase 5 (PDE-5), hence augment the vasodilatory effect of nitric oxide by preventing the degradation of cGMP, which leads to increased uterine blood flow and thicker endometrium. Alternatively, sildenafil may have an effect on vasoactive cytokines that regulate endometrial development or implantation. Sildenafil increases uterine receptivity by the development of spiral arteries and by increasing the uterine arterial blood flow. The effect of estrogen on endometrium occurs not via direct or regional transmission from the neighboring ovaries but rather through the systemic circulation **[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

Abbreviations:

BMI	: Body mass index.
FSH	: Follicle stimulating hormone.
LH	: Luteinizing hormone.
TSH	: Thyroid stimulating hormone.
PRs	: Clinical pregnancy rates.
U/S	: Ultrasound.
LNMP	: Last normal menstrual period.
TVS	: Transvaginal ultrasound.

thin endometrium, in an effort to improve endometrial proliferation [3].

The aim of this study was to compare the effect of vaginal Sildenafil citrate and Estradiol valerate on endometrial receptivity in clomiphene-induced cycle infertile females.

Patients and Methods

This non randomized clinicl trial study has been carried out to study and compare the effect of vaginal Sildenafil citrate and Estradiol valerate on endometrial thicknessin infertile women undergoing induction by clomiphen citrate attending infertility and ultrasound (U/S) unit, Obstetrics & Gynecology Department, Zagazig University Hospital, the study was conducted on 44 cases (22 in each group); group 1 received Sildenafil (Respatio 20mg/8hr film coated tablets vaginally for 5 days starting from day 8th) and group 2 received oral estradiol valerate (Cyclo-Progynova 2mg, white tablets, BAYER Schering pharma), one tablet every 12 houre from day 8 th till triggering of ovulation) 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.

Inclusion criteria: Ovulatory dysfunction that underwent induction of ovulation by Clomiphen Citrate, Primary or secondary infertility, Age between 20-35 years, Norml 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 [4].

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 and Benign) or sildenafil (liver disease) and Endocrine disorders (thyroid disease, diabetes mellitus).

All patients were subjected to the following:

Complete history including:

- Personal history (age, residence, BMI and habits).
- Menstrual history (regularity, amount, duration, dysmenorrheal, 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.

General examination:

- Inspection of skin as hirsutism, acne and other sings suggesting hyperandrogenism (PCO).
- Thyroid disease as goiter, Delay reflex, 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.

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).

Non randomization table generalized research randomizer program puls Annex (randomization in clinical trials at (www.statmed.com) was used to divide the cases into 2 groups:

- Group (1): Included 22 women received Sildenafil (Respatio 20mg/8hr film coated tablets) vaginally for 5 days starting from day 8 th.
- Group (2): Included 22 women received oral Estradiol Valerate (Cyclo-Progynova 2mg, white tablets, BAYER Schering pharma), one tablet every 12 houre from day 8 th till triggering of ovulation.

Follow-up was done for both studied group by TVS at cycle day 12 to detect ovarian responce and endometrial thickness. The transducer was introduced into the vagina for approximately 5cm. The tip of the transducer was normally angled upward 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.

Measurement of ovarian follicles, the follicle could be seen of the ultrasound device as a circular bubble filled with liquid with thin wall containing the egg for round follicle, only one measurement

was requied, 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 Switzeland) 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 fluide in Douglas pouch disappear of follicles or decreasing it is size.

B-hCG was done14 days after ovulation triggering.

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

Outcome measures:

1- Primary outcome measures:

- Endometrial thickness.

2- 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.

Results

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

Variables	Group 1 (n=22)	Group 2 (n=22)	Test of sig.	*p*
Age (years):				
Mean ± SD	29.1±6.8	27.6±6.2	*t*	0.5
Median	29.0	28.0	0.7	
Range	20.0-35.0	21.0-32.0		
Type of fertility:				
Primary	17 (77.3%)	13 (59.1%)	χ^2	0.1
Secondary	5 (22.7%)	9 (40.9%)	1.7	
BMI (Kg/m ^{2}):				
Mean ± SD	24.3±3.6	24.7±3.3	*t*	0.6
Median	25.5	25.4	0.4	
Range	18.8-29.1	19.2-29.3		

Table (1) showed that there was no statistical significant difference between the studied groups in age, type of infertility and BMI.

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

Variables	Group 1 (n=22)	Group 2 (n=22)	Test of sig.	*p*
FSH:				
Mean ± SD	5.6±0.9	5.4±1.0	*t*	0.3
Median	5.1	5.0	0.9	
Range	4.4-7.5	4.2-8.0		
LH:				
Mean ± SD	9.4±3.0	8.4±3.0	MW	0.2
Median	9.2	9.5	1.2	
Range	3.2-14.4	4.7-15.1		
TSH:				
Mean ± SD	2.3±0.7	2.3±0.7	MW	0.8
Median	2.4	2.1	0.2	
Range	1.3-3.8	1.0-3.5		
Prolactin:				
Mean ± SD	13.4±2.4	14.3±2.8	*t*	0.4
Median	13.0	14.5	0.8	
Range	10.6-19.3	10.2-20.7		

FSH: Follicle stimulating hormone.
LH : Luteinizing hormone.
TSH: Thyroid stimulating hormone.

Table (2) showed that there was no statistical significant difference between the studied groups regarding FSH, LH, TSH and prolactin level.

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):	Group 1 (n=22)	Group 2 (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 (3) showed that there was no statistical significant difference between the studied groups regarding follicles number and follicles size.

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

Endometrial thickness (mm) at the cycle day 8 th	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) the day of triggering:				
Mean ± SD	8.2±3.4	8.8±4.1	3.1	0.003
Median	8.6	9.5		S
Range	8.3-9.4	8.8-11.5		

MW = Man Wittney Test.

Table (4) showed that there was no statistical significant difference between both group in endometrial thickness at the cycle day 8 th. But there was a statistical significant difference between both group in endometrial thickness on the day of triggering. Group B had higher endometrial thickness than group A.

Table (5): Clinical pregnancy rates of the studied groups.

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

Table (5) showed that there was no statistical significant difference between the studied groups regarding occurrence of pregnancy and fetal heart beat.

Discussion

Clomiphene citrate is considered the gold standard treatment in anovulatory women with polycystic ovary disease. It is efficient as an oral ovulation induction drug, with low cost, minimal side effects and low incidence of complications [5]. But many studies showed that it causes retardation of endometrial growth during the proliferative phase and delayed endometrial development based on textural patterns [6].

Vaginal Sildenafil citrate has been suggested for its ability to relax vascular smooth muscle through a cyclic guanosine monophosphate-mediated pathway, and improve uterine artery blood flow. Changes in the endometrial vascularity appear on color Doppler examination, which may reflect the histologic changes described by the pathologists [7].

This study showed that there was no statistical significant difference between the two group in number of follicles >17mm (*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 Ahmed et al., [1] in which they reported that a mean increase in number of follicles with the use of oral sildenafil aganist placebo drug which was again insignificant. Also agree with astudy carried by Ataalla et al., [8] as they found that number of mature follicles were insignificant between two groupe (Sildenafil group, Placebo group) with *p*-value 0.561.

Additionally, our results are in agreement with result reported by a study of Mangal and Mehirishi [3], as they found that the mean of number of follicles >18mm at the time of HCG trigger was 1.52 in group take vaginal sildenfil and 1.68 in group take oral estradiol The difference is statistically insignificant.

Furthermore 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.

Being important in infertility treatment it was a must to measure and compare endometrial thickness between both group. 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*-value 0.003).

Estradiol increase endometrial thickness by mean (8.8±4.1) but sildanfil group increases by (8.2 ±3.4).

In another study, it was found that vaginal administration of sildenafil, in addition to a 70% increase in ET in the studied women, also caused pregnancy in infertile women to persist [10]. Also, a study carried by Unfer et al., [11] have studied administering oral estrogen for 10 days in addition to CC and found no significant change in the FSH, LH and estrogen levels, while there was a significant increase in ET in the estrogen group.

Another study carried by Jerzak et al., [12] in which they used 25mg Sildenafil four times a day for 3 to 6 days as intra-vaginal suppository. Endometrial thickness was significantly increased.

Furthermore, Cetinkaya et al., [13] used vaginally administered local oestrogen 25 mcgms from 4th day for 15 days in clomiphene citrate induced cycle. They reported significant increase in endometrial thickness on the day of ovulation (7.6 ± 1.4mm versus 8.3±2.1mm) 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., [14], 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., [15], 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., [8] 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 [3], 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 5.42mm in sildenafil group whereas it was 5.76mm in estradiol group.

Pregnancy is the final goal of any infertility workup, In the study in our hands regarding to occurance 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 occurance of pregnancy.

In addition, our result showed that there was no stastically 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-value 0.9).

This was in agreement with a study done by Jerzak et al., [12] who reported that there was a good correlation between endometrial thickness and the prevalence of conception and that endometrial thickness greater than 9mm as determined by vaginal ultrasound in the late proliferative phase, correlates well with the pregnancy rate.

Different result was reported by a study carried by Ataalla et al., [8] 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. This difference could be due to the small number of cases or may be due to different inclusion criteria.

Conclusion:

It could be concluded from this study that vaginal use of sildenafil citrate 20mg or oral Ethinyl Estradiol in females undergoing induction of ovulation lead to increase endometrial thickness and support embryo growth. Both have the same effect on pregnancy rate but Ethinyl Estradiol has better results on endometrial thickness than sildenafil.

Recommendation:

Further studies shoued be done on large number of cases. To compare oral estradiol valerat and vaginal sildenafil citrate and vaginal sildenafil citrate regarding pregnancy rate and fetal outcome in pregnant women.

Declarations:

Ethics approval and consent to participate: 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.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: AMS, BSS, MRA and OAA collected patients' samples and clinical data. OAA prepared sample for laboratory investigations and wrote the paper. Statistical analysis, interpretation of data, and preparation the paper for submitting international was done by AMS. Critical revision of the manuscript was performed by all of the authors. All authors have read and approved the final manuscript.

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تأثير إستراديول فاليرات مقابل السيلدينافيل المهبلى على تقبل بطانة الرحم فى السيدات اللآتى يخضعن للتحريض على التبويض بواسطة كلوميفين

خلفية الدراسة: يعرف العقم أنه عدم حدوث حمل مع علا قة زوجية منتظمة مدة عام على الأقل دون استخدام وسيلة لمنع الحمل والعقم قد يكون نتيجة أسباب ذكورية أو أنثوية أو أسباب مشتركة أو غير مبررة. وصعوبة عدم الأباضة قد تحدث نتيجة لمشاكل فى افراز الهرمونات التكاثرية من الغدة النخامية ، أو مشاكل فى المبيض. وقد وجد أن النشاط المضاد للاستروجين من قبل كلوميفين سيترات قد يؤدى إلى إنخفاض معدل الحمل. وإن إضافة هرمون الاستروجين الخارجى إلى سيترات الكلوميفين فى تنظيم الحث على التبويض هى استراتيجية من الممكن أن يؤدى إلى زيادة معدلات الحمل. أيضاً استخدام سترات السيلدنيافبل المهبلية تعتبر وسيلة أخرى لزيادة فرصة حدوث الحمل عند استخدامه للسيدات اللآتى يخضعت لتحريض الاباضة بالكلو ميفين سيترات ولديهن بطانة رحم رقيقة وذلك لقدرته على تحسين تدفق الدم فى الشريان الرحمى مما قد يؤدى إلى زيادة سمك بطانة الرحم وزيادة نسبة حدوث الحمل.

الهدف من الدراسة: مقارنة الفرق بين تأثير عقار ايثينيل الاستراديول وعقار سترات السيلدينافيل المهبلى على سمك بطانة الرحم ومعدلات حدوث الحمل للسيدات اللآتى يخضعن لتحفيز التبويض باستخدام عقار الكلومفين سترات.

المريضات وطرق الدراسة: شملت هذه الدراسة ٤٤ سيدة تعانين من العقم تم اختيارهن من المترددات على وحدة العقم والموجات فوق الصوتية، قسم أمراض النساء والتو ليد، مستشفى جامعة الزقازيق، خلال الفترة من ديسمبر ٢٠١٨ إلى أغسطس ٢٠١٩. تم تقسيمهم عشوائياً إلى مجموعتين: المجموعة الأولى: شملت ٢٢ سيدة ثم أعطائهن السيلدينافيل ٢٠ مجم مهبلى ٣ مرات يومياً من اليوم الثامن لمدة ٥ أيام لنفس الدورة. والمجموعة الثانية: شملت ٢٢ سيدة تم إعطائهن ايثينيل الاستراديول ٢ مجم مرتين يومياً وكان عبارة عن أقراص البيضاء من عقار السيلكوبروجينوفا من اليوم الثامن حتى يوم التحريض على الاباضة.

نتائج الدراسة: عند استخدام عقار السيلدينافيل والايثينيل استراديول للسيدات الآتى يخضعن لتحفيز التبويض بعقار سترات الكلوموفين نجد الآتى زيادة سمك بطانة الرحم، وزيادة معدل نبض الجنين مع عقار الاستراديول مقارنة بعقار سترات السيلدينافيل. مما يؤدى إلى ارتفا ع معدلات حدوث الحمل لتكون ٣١.٨٪ لعقار الاستراديول مقارنة ب ٢٧.٢٪ لعقار سترات السيلدينافيل ونبض الجنين لتكون ٨٥.٧٪ لعقار الاستراديول مقارنة ٨٣.٣٪ لعقار سترات السيلدينافيل.

ونسبة الاباضة بعد استخدام الكلوميفين للمجموعة التى أخدت عقار سترات السيلدينافيل حوالى (٧٢.٧٪) أعلى بقليل من التى أخدت عقار الاستراديول بنسبة (٦٣.٦٪). بينما لا يوجد أى تأثير فى حجم وعدد البويضات عند استخدام العقارين.

الاستنتاج: نستنتج من هذه الدراسة أن عقار الاستراديول وسترات السلدينافيل يوديان إلى زيادة سمك بطانة الرحم مما يؤدى ارتفا ع معدلات حدوث الحمل للسيدات التى يخضعن لتحفيظ التبويض باستخدام سترات الكلو موفين م ولكن الاستراديول يعطى نتائج أفضل بشأن تحسن بطانة الرحم وفرصة حدوث الحمل.