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THE EFFECT OF SILDENAFIL VERSUS ESTRADIOL VALERATE ON ENDOMETRIAL THICKNESS AND PATTERN IN INFERTILE FEMALES

Dalia Ibrahim MD*[1], Nadia Abozied MD[2], Samy Makary MD[1] and Hamsa Rashwan[3]

[1]Department of Physiology, Suez Canal University.
[2]Pharmacology, Suez Canal University.
[3]Obstetrics and Gynecology, Cairo University.

***Corresponding Author: Dalia Ibrahim MD**

Department of Physiology, Suez Canal University.

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ABSTRACT

Background and aim: Female causes account for 30% of the total infertility cases of these causes 5% are due to uterine factors .very thin endometrium (< 7mm) seems to be accepted as a reliable sign of suboptimal implantation potential. Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP. Sildenafil is a selective inhibitor of the type V cGMP-specific phosphodiesterase. With the use of sildenafil, cGMP levels remain elevated, which leads to vascular relaxation and increased blood flow to improved the endometrial thickness. **Objective:** This case control study was designed to compare the use of estrogen alone or in combined with Sildenafil on the endometrial thickness and pattern in infertile women. **Methods:** 30 patients had primary or secondary infertility were attending to the outpatient infertility clinic. All patients undergo ovulation induction by clomiphene citrate and gonadotropins. And evaluated by TVS at day 8th, bad endometerium (thickness <6 mm) in 30 patients. Devided into 3 groups: G1: 10 patients of them did not receive any treatment to improve endometrial thickness. G2: 10 patients of them received Estradiol valerate 2mg 2 tab orally daily from day 8th of the cycle till ovulation, And G3: 10 patients of them received Estradiol valerate 2mg 2 tab orally daily and sildenafil citrate 25mg vaginally every 6 hours from day 8th of the cycle till ovulation. And those patients were reevaluated by TVS at day 13th of cycle for endometrial thickness and pattern with number and size of Graffian follicle. **Results:** In this study we found that a total of 30 infertile had a mean of endometrial thickness of 5.1±1.1 mm at 8th day of cycle. There was statistically significant increase in the endometrial thickness from day 8th to day 13th in G3 as compared to that of the patients in control group G1 and as compared to G2, the difference is highly significant. **Conclusion:** Sildenafil citrate with Estradiol valerate increase the endometrial thickness significantly as compared to control group or Estradiol valerate alone.

KEYWORDS: Sildenafil citrate, infertile female, endometrial thickness, Estradiol valerate.

INTRODUCTION

Female causes account for 30% of the total infertility cases[1] of these causes 5% are due to uterine factors.[2]

There are many causes of thin endometrium: Permanent damage to the basal endometrium, Endometrial resistance to estrogen, Reduced blood flow and Over-exposure to testosterone.

Potential functional markers of endometrial receptivity, although promising, but are expensive and invasive . So Transvaginal ultrasonography has been proposed as an alternative tool in the assessment of endometrial receptivity. It has been reported that endometrial thickness and pattern on the day before oocyte retrieval may be an indicator of achieving pregnancy.[3]

Ultrasound can be used to evaluate the endometrium, we need to look at endometrial thickness, endometrial pattern and color flow in spiral arteries.[4]

Estrogen induced endometrial proliferation is in large part dependent upon blood flow to the basal endometrium.[5]

A good correlation between endometrial thickness and the prevalence of conception has been found,[6] very thin endometrium (< 7mm) seems to be accepted as a reliable sign of suboptimal implantation potential.[5] Implantation and pregnancy rates are significantly reduced if the endometrial thickness is increased (> 14mm).[7] Endometrial thickness has a significant positive correlation with the duration of follicular stimulation, and an inverse correlation with age.[8]

An endometrial thickness of ≥9 mm in the late proliferative phase, as determined by vaginal ultrasound, correlates well with the chance of pregnancy after IVF, whereas a thinner endometrium is associated with poorer prognosis for success.[9]

Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP. Sildenafil is a selective inhibitor of the type V cGMP-specific phosphodiesterase. With the use of sildenafil, cGMP levels remain elevated, which leads to vascular relaxation and increased blood flow to improved the endometrial thickness.[10]

Also NO may have detrimental effects at the level of the endometrium during the implantation window.

The endometrium is normally a non-receptive environment for an embryo, except during the window. Implantation window is a period during which the endometrium is optimally receptive to implanting blastocyst within the cycle days 20 and 24. It is characterized by a refractory endometrial status.[3] Endometrial receptivity during the implantation window depends on Morphological Markers like Endometrial thickness, Endometrial echogenic pattern and Endometrial and sub endometrial blood flows. and also depend on Biochemical Markers like Endometrial adhesion molecules, Endometrial anti-adhesion molecules, Endometrial cytokines, Growth factors, Endometrial immune markers, Endometrial Glycodelin, Insulin like growth factor (IGF) and Leukemia inhibitory factor (LIF).[11]

During implantation window, the endometrial epithelium encompasses four cell types: microvilli-rich cells, pinopode cells, vesiculated cells, and ciliated cells.[12]

The process of embryo implantation having three phases:

- "unstable adhesion" of the transferred embryo to the surface of the uterine lining.
- "stable adhesion," believed to involve signaling back and forth between the embryo and the lining.
- Penetration (invasion): invasion of the trophectoderm cells from the embryo through the surface of the lining deeper the stroma of the uterine lining, forming a vascular connection to the mother.[13]

The achieved implantation depends on the blastocyst's ability to infiltrate the endometrium and develop blood supply, which requires the genes to produce the necessary proteins for digesting the endometrial cellular matrix, to regulate cell growth, and to induce angiogenesis like Tumor suppressor factor (p53), Plasminogen activator inhibitor 1 (PAI-1) and Vascularendothelial growth factor (VEGF).[14,15,16]

Sildenafil citrate was enhanced markedly in p53 and stimulated angiogenic responses with increased VEGF.[17,18]

Also Sildenafil citrate enhance the action of estrogen on the endometrium.

METHODS

A case control study on 30 patients had primary or secondary infertility were attending to the outpatient infertility clinic with inclusion criteria include: No history of PID or D&C and have Patent fallopian tubes, normal uterus by ultrasound examination and Exclusions criteria include: uterine fibroid, uterine congenital anomalies, and adenomyosis. Ultrasound examination and HSG was done for all patients to evaluate uterus, endometerium, ovaries and patency of fallopian tubes.

All patients undergo ovulation induction by clomiphene citrate and gonadotropins.

And evaluated by TVS at day 8^{th}, have bad endometrium (thickness <6 mm) in 30 patients.

Devided into 3 groups:
G1: 10 patients of them did not receive any treatment to improve endometrial thickness.
G2: 10 patients of them received Estradiol valerate 2mg 2 tab orally daily from day 8^{th} of the cycle till ovulation
And G3: 10 patients of them received Estradiol valerate 2mg 2 tab orally daily and sildenafil citrate 25mg vaginally every 6 hours from day 8^{th} of the cycle till ovulation. and those patients were reevaluated by TVS at day 13^{th} of cycle for endometrial thickness and pattern with number and size of Graffian follicle.

Statistical analysis

SPSS statistical software was used applying appropriate statistical method. Data are presented as mean ± SD. Differences between two groups were assessed by the Student's paired t test, chi square test Comparison among the two groups was performed by one way analysis of variance. Chi square test was also used. P value <0.001 is considered highly significant.

RESULTS

30 patients had primary or secondary infertility, all patients had normal HSG, and all received ovulation induction treatment, and they all have no gynecological problem.

All patients had a mean endometrial thickness by us at day 8^{th} of cycle 5.1±1.1.

Table-I shows the Effect of sildenafil+ Estradiol valerate (G3) versus Estradiol valerate only(G2) on endometrial thickness, there was statistically significant increase in endometrial thickness from day 8 to day 13 in patients received sildenafil+ Estradiol valerate 9.04±1.02. When we compared the endometrial thickness at day 13 for control group G1. it was higher in the study group compared with that in the control group 6.1±1.1 and the difference is highly significant
p-value 0.001.

Also When we compared the endometrial thickness at day 13th in patients received sildenafil+ Estradiol valerate G3 with that patients received Estradiol valerate only G2 7.14±1.02 the difference is highly significant p-value 0.003.

Table – I: Effect of sildenafil+ Estradiol valerate G3 versus Estradiol valerate only G2 on endometrial thickness.

Character	Day 8	Day 13	p-value between G3 &G2
Endometrial thickness G1 (control)	5.1±1.1	6.1±1.1	
Endometrial thickness G2	5.1±1.1	7.14±1.02	
Endometrial thickness G3	5.1±1.1	9.04±1.02	0.003 (HS) **
P-value between previous G1 and G3			0.001(HS) **

P value <0.001 is considered highly significant**

Table - II shows the Effect of sildenafil+ Estradiol valerate (G3) versus Estradiol valerate only(G2) on endometrial pattern, there was Triple line on day 13th in patients received sildenafil+ Estradiol valerate 77.9%of patients when we compared the endometrial pattern at day 13th in patients received Estradiol valerate only 30% the difference is highly significant p<0.0001.

The triple line pattern of the endometrium was significantly higher in the sildenafil citrate group (p<0.0001).

Table – II: Effect of sildenafil+ Estradiol valerate versus Estradiol valerate only on ultrasonic endometrial pattern.

Endometrial pattern	G2	G3	p-value
Triple line	30%	77.9%	<0.0001**

P value <0.001 is considered highly significant**

DISCUSSION

Endometrial development is regulated by steroid hormones mainly estrogen and various growth factors and cytokines. Some of these factors are produced locally and act via paracrine mechanisms. Sufficient blood supply is required for these factors to reach the endometrium especially the functional layer.[13]

In this study we use sildenafil to improve endometrial thickness and pattern and we found that it was effective in significantly increasing the thickness to a mean of 9.04±1.02 on day 13 of the cycle (day of hcG injection) and this was significantly higher than that in the control group 6.1±1.1 or when compared with group who received Estradiol valerate only 7.14±1.02 and this finding is similar to that reported by Sher & Fisch.[19]

K.Aisaka., et al[20] found that There are some elderly patients cannot respond to estrogen induced proliferation of the endometrium and reported that administration of oral sildenafil improve endometrial thickness during IVF program. This finding is similar to our study.

Endometrial echogenic pattern was said to be important in predicting the chance of implantation.

In our study, sildenafil citrate increased the triple line pattern of the endometrium. A combined analysis of endometrial thickness and pattern on the day of hCG administration proved to be better predictor of the outcome of IVF/ICSI-ET done by Chen., et al.[21]

In this study no patient reported any side effect after vaginal sildenafil application, which is also the same findings reported by Sher & Fisch.[19] This is probably explained by the fact that following vaginal administration, sildenafil immediately reaches the uterine blood system in a high concentration and then as it is absorbed in to the systemic circulation it dilutes out.

CONCLUSION

Sildenafil citrate with Estradiol valerate increase the endometrial thickness and patterns significantly as compared to control group or Estradiol valerate alone.

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