The effect of Sildenafil on endometrial characters in patients with infertility

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Abstract

Objective: To study the role of sildenafil on the echogenic pattern of endometrium in infertile patients with bad endometrium.

Setting: Infertility center in Basrah Maternity and Children hospital.

Design: Case control prospective study.

Methodology: 28 patients had primary or secondary infertility with mature Graffian follicle and bad endometrial thickness (control group) in the previous cycle . The same patients were considered as study group in the present cycle after giving them sildenafil citrate (Erasma) (Mepha company) 25 mg vaginally every 6 hours for 5 days from day 8th of the cycle and those patients were reevaluated by TVS (7.5 MHZ) at day 8th and 13 th of cycle for endometrial thickness and pattern with number and size of Graffian follicle.

Result : A total of 28 infertile women were included in this study. The control group had a mean of endometrial thickness of 5.21+2.8 mm at time of ovulation. There was statistically significant increase in the endometrial thickness from day 8th to day 13th in study group as compared to that of the same patients in control group and the difference is highly significant. Vaginal sildenafil increase endometrial thickness to >7mm in about 35.7% of patients in the study group without any side effect. 71.4% of patients in study group had hyperechogenic endometrium which was higher than those in the control group but the difference is statistically not significant and the percentage for those with isoechogenic is higher in control group compared to the study group.

Conclusion: Vaginal sildenafil was significantly effective in improving endometrial thickness in patients receiving ovulation induction therapy with bad endometrial thickness in previous cycle. It causes no systemic side effect.

Key wards: Vaginal sildenafil & endometrial thickness.

Introduction

Infertility is defined as the inability to conceive after one to two years of un protected enter course .(1) The 12-month prevalence rate ranged from 3.5% to 16.7% in more developed nations and from 6.9% to 9.3% in less-

developed nations, with an estimated overall median prevalence of 9%(2). Female causes account for 30% of the total infertility cases (3) of these causes 5% are due to uterine factors (1). Ultrasound can be used to evaluate the endometrium, we need to look at endometrial thickness, endometrial pattern and color flow in spiral arteries. Endometrial thickness is the maximum distance between the echogenic interfaces of the myometrium and the endometrium, measured in a plane through the central longitudinal axis of the uterus (4).

Potential functional markers of endometrial receptivity, although promising, are expensive, invasive and circumstantial. 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 the likelihood of achieving pregnancy. (5)

i. 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).

ii. It was found that the multilayered echogenic pattern, the so-called triple line appearance, was predictive of pregnancy (9,10). However, pregnancies can occur in absence of this pattern(8).

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(11). Sildenafil is contraindicated in patients who are hypersensitive to the active substance or any of the excipients contained in Viagra™ and in patients concurrently using nitric oxide donors (e.g. amyl nitrite) or nitrates in any form, as the drug has been shown to potentiate their hypotensive effects(12)

The **aim** of the study To study the role of seldinafil as a drug to improve the quality and thickness of endometerium in patients with previously bad endometerium.

Material and methods

This is a prospective case control study which was conducted at Basrah Maternity and Children hospital during the period from the 1st of January to the 30th of august 2011. 28 patients attending the infertility clinic of the hospital with primary or secondary infertility were selected.

The inclusion criteria include : Patent fallopian tubes, mature one or more graffian follicles either spontaneously or by ovulation induction, normal uterus by ultrasound examination and bad endometerium (thickness <6 mm and hyperechogenic pattern) at mid cycle before ovulation.

The Exclusions criteria include: Multiple uterine fibroid, uterine congenital anomalies, acute or chronic attack of PID, clinical and ultrasonic suspicion of endometriosis and adenomyosis and those with overian hyperstimulation at present cycle.

All 28 patients (the control group) were assessed by full history, full clinical examination including pelvic examination. Review of the patients record was done including the result of the HSG, hormonal analysis and present mid cycle ultrasound examination of the uterus and the Ovaries that confirm bad endometrium and mature one or more graffian follicles. The ovulation induction regimen which was used at the present cycle was recorded . Verbal consent was obtained and they were instructed to come back at the second day of the next cycle.

The same 28 patients, who accepted to participate in the study (the study group), came back at day2 of cycle when TVS was done for them to assess the endometrial thickness and echogenisity and to exclude any persistent graffian follicle from the previous cycle .

The same ovulation induction regimen which was used in the previous cycle was repeated and they were instructed to come back at day 8 when TVS was repeated to assess the thickness and character of endometrium and to assess graffian follicle growth. Seldinafil (Erasma) (Mepha company) was given to those patients in adose of 25 mg (half of 50 mg tablet was crushed and dissolved in 2cc of distilled water and injected in to vagina) administered every 6 hours for 5 days from day 8 of cycle and those patients were reevaluated by TVS at day 13 of the cycle for endometrial thickness and character and the number and sizes of graffian follicle using T.V.S. with frequency of 7.5 MHZ and was evaluated by same sonographer .

Data were analyzed by using the SPSS program and by using (Z-test and T-test) Significant difference was considered when the P-value is < 0.05.

Results:

A total of 28 women were included in this prospective study. Table 1 shows patients characteristic. 71.4% of patients were in age group from 20-40 years,

Half of patients had primary infertility and the other half had secondary infertility, all patients had normal HSG, and all received ovulation induction treatment, 67.9% of them received combination of clomiphen citrate and FSH (Gonal F) (Serono), 32.1% received only FSH, and they all have no gynecological problem except one had uterine fibroid (intramural about 3cm) which was not considered to has an effect on endometrium. All patients had a mean endometrial thickness of 5.21±1.28.

Table-II shows the effect of sildenafil on endometrial thickness, there was statistically significant increase in endometrial thickness from day 8 to day 13 in patients received sildenafil at present cycle .When we compared the endometrial thickness at day 13 for the same patients in previous and present cycles it was higher in the study group compared with that in the control group and the difference is highly significant.

Table-III shows effect of sildenafil on endometrial ultrasonic pattern at day 13 in both control and study group.71.4% of patients in study group had hyperechogenic endometrium which was more than those having hypoechogenic and isoechogenic for the control group patients with isoechogenic constituted the higher proportion (50%) although the hyperechogenic endometrium in the study group was higher than those in the control group, but the difference is statistically not significant, the same thing applied for those with isoechogenic, although the percentage of them is higher in control group compared to the study group. No patient reported any side effect after vaginal sildenafil application.

Discussion

In order for successful implantation to occur, an adequately prepared endometrium has to be build up during the menstrual cycle. Endometrial development is regulated by steroid hormones and various growth factors and cytokines. Some of these factors are produced locally and act via paracrine mechanisms. Other have to be transferred to the endometrium. Sufficient blood supply is required for these factors to reach the endometrium especially the functional layer(13). Most studies agree that the endometrium has to reach a certain thickness (>7mm) for successful pregnancy to occur (14). Sildenafil cause vascular relaxation and increase uterine blood flow (11).

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 (7.64±2.02mm) on day 13 of the cycle (day of hcG injection) and this was significantly higher than that in the control group (5.21±1.28mm) and this finding is similar to that reported by Sher & Fisch (2002) (15).

35.7% of patients in our study developed endometrial thickness to >7mm after the use of sildenafil while Sher & Fisch reported an endometrial thickness >9mm in 70% of cases. This difference could be due to the larger sample size (105) & the longer duration of sildenafil application (immediately after end of mensis)(15).

Regarding endometrial ultrasonic pattern the percentage of patients with hypoechogenic endometrium remain the same. The percentage of patients with isoechogenic endometrium was decreased and that of patients with hyperechogenic endometrium was increased in the study group compare to the control group. Although these changes were statistically not significant.

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

(16,17) but the majority of studies concentrate on endometrial thickness only (17,18). Pregnancy can occur even with hyperechogenic endometrium. So that it seems that endometrial echogenic pattern is not important in affecting the chance of pregnancy .

In this study no patient reported any side effect after vaginal sildenafil application, which is also the same findings reported by Sher & Fisch(15). 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:

Vaginal sildenafil was significantly effective in improving endometrial thickness in patients receiving ovulation induction therapy with no systemic side effects.

Recommendation:

As the number of studies evaluation the use of vaginal sildenafil are limited to 3 including this study. Case - control study evaluating larger sample size is recommended to confirm our findings.

References

1. Bhattacharya S. Infertility. In: Edmonds DK. Dewhurst's Textbook of Obstetrics and Gynaecology. 17th ed. Blackwell Publishing. 2007: 440.

2.Boivin J, Bunting L, John A., Collins, Karl G. et al. International estimates of infertility prevalence and treatment– seeking: Potential need and demand for infertility medical care in Oxford Medicine Human Reproduction. 2007; 22(6):P 1506-1512.

3.Regulate fertility service: a commissioning aid- Expert group on commissioning NHS infertility provision- 18. June. 2009. from the Department of Health UK.

4. Malhorta N and Malhorta J. Transvaginal Sonography in Infertility .In: Kamini Aroa and Howard Carp. The Infertility Manual. 3rd ed. JAPEE. 2009:P35-45 .

5.Gonen Y, and Casper RF. Predication of implantation by sonographic appearance of the endometrium during controlled ovarian stimulation for in vitro fertilization . J. Invitro Fertile & Embryo transfer .1990;7: P 146.

6.Fanchin R. Assessing uterine receptivity. In: Ultrasonographic glances at the new millenuium. Ann NY Acad Sci. 2001; 943: P185-202.

7.ELnashar A, Afifi A and Donia D. Endometrial thickness and pregnancy rates in infertile couples undergoing AIH. Benha MJ. 1995; 12: P1-9.

8.Elnashar A. M. and Aboul-Enein G.I. Endometrial receptivity. Middle East Fertility Society Journal. 2004; 9 (1): 16, 17.

9.Leibovit Z, Grinin V, Rabia R, Degani S. and Shapiro I. Assessment of endometrial receptivity for gestation in patients undergoing in vitro

fertilization, using endometrial thickness and the endometrium –myometrium relative echogenicity coefficient . Ultrasound obstet. Gynecol. 1999; 143: 194-199.

10.Fanchin R, de Ziegler D, Taieb J, Olivennes F, Frydman R, et al. Human chorionic gonadotropin administration does not increase plasma androgen levels in patients undergoing controlled ovarian hyper stimulation . Fertil . Steril. 2000; 73: 275-279.

11.Sher G and Fisch JD. Vaginal sildenafil (Viagra): A preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF. Hum . Reprod. 2000; 15: P806-809.

12.Viagra(™.) Summary of product characteristic .Pfizer. September . 1998.

13.Peter Kovacs .Endometrial Development, Sildenafil use Among infertile women .Medscape ob/gyn and Womens' Health. 2004;9(1).

14.Kovacs P, Matyas S, Bodak K and Kaali S G. The effect of endometrial thickness on IVF/ICS out come. Hum .Reprod. 2003; 18: P2337-2341.

15.Sher G and Fish JD. Effects of vaginal sildenafil on the outcome of in vitro fertilization(IVF) after multiple IVF failures attributed to poor endometrial development. Fertil. Steril. 2002; 78: P1073-1076.

16.Gonen Y and Casper RF. Prediction of implantation by sonographic appearance of the endometrium during controlled ovarian stimulation for IVF. J. in vitro fertilization embryo transfer . 1990; 7(3):P146-152.

17.Sundstorm P. Establishment of successful pregnancies in the IVF with an endometrial thickness of no more than 4 mm. Hum. Reprod. 1998; 13(6): P1550-1552.

18.Zaidi J, Campbell S, Pittrof R and Tan SL. Endometrial thickness , morphology, vascular penetration and velocimetry in predicting implantation in IVF fertilization program. Ultrasound obestet .Gynecol .1995;6(3):P191-198.

ENDOMETRIAL THICKNESS AND MENSTRUAL CYCLE[4]

PHASE	**APPEARANCE**
Menses (day 1-5) < 4mm	Hypoechoic area is blood.
Early follicular phase (day 6-10)	Distinct 'triple-line' pattern hypoechogenic endometrial thickness 7-9 mm.
Late follicular phase (day 11 ovulation)	Endometrial appearance similar to myometrium. Thickness 9-12 mm at ovulation.
Luteal phase	Bright, fluffy appearance. Absence of triple line. Thickness 10-14 mm.

Table -1. Patients´ characteristics

Character		NO.	%
Age	< 20	2	7.1
	20-40	20	71.4
	>40	6	21.4
Infertility	Primary	14	50
	Secondary	14	50
HSG		28	100
Method of ovulation induction	Clomid	0	0
	FSH	9	32.1
	Clomid+FSH	19	67.9
Gynecological problem	Fibroid	1	0.28
	Endometeriosis	0	0
	PID	0	0
	D&C	0	0
Endometrial thickness in previous cycle	Mean ± SD	5.21±1.28	

Table- II Effect of sildenafil on endometrial thickness

Character	Day 2	Day 8	Day 13	p-value between day 8 and day 13
Endometrial thickness at the previous cycle			5.21±1.29	
Endometrial thickness at the present cycle	5.64±1.41	6.35±1.41	7.64±2.02	0.003 (HS)
P-value between previous and present cycle			0.00(HS)	

Table- III Effect of sildenafil on ultrasonic endometrial pattern

Character	Hypoechogenic	Isoechogenic	Hyperechogenic
Endometrial pattern in the previous cycle	2 (7.14%)	14 (50%)	12 (42.9%)
Endometrial pattern in the present cycle	2 (7.14%)	6 (21.4%)	20 (71.4%)
P value	1 (NS)	0.24 (NS)	0.11 (NS)