RESEARCH ARTICLE

Effects of Vaginal Sildenafil Citrate on Ovarian Blood Flow and Endometrial Thickness in Infertile Women Undergoing Intra-uterine Insemination

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ABSTRACT

Background: Healthy blood circulation in the uterus and ovaries can affect the success of assisted reproductive therapy (ART). Ovarian Color Doppler and ultrasound blood flow assessment is a useful non-invasive technique that assesses ovarian vascular function by evaluating the ovarian stromal blood's resistance index and pulsatility index. The resistance index is a sign of resistance to blood circulation. The lower the resistance index value, the more blood circulation. The use of vaginal sildenafil is a promising treatment to improve endometrial circulation and ovarian Doppler blood flow index to treat infertile women.

Objective: To evaluate the effect of vaginal sildenafil citrate on ovarian blood flow and measured by two-dimensional Doppler ultrasound parameters (ovarian stromal blood resistance index and pulsatility index) and pregnancy of infertile women receiving termination of the intra-uterine insemination (IUI).

Subjects and Methods: A total of 50 infertile patients achieved IUI and were randomly divided into two groups, the sildenafil group, of which 25 patients were included in this study and received treatment with Sildenafil citrate 50 mg (group of sildenafil) and. The second group, 25 infertile women, did not receive sildenafil (group without sildenafil). Both groups of infertile women received letrozole to stimulate intrauterine insemination was followed by continuous transvaginal ultrasound to assess the number and size of mature follicles, the thickness of the endometrium, and the ovarian stromal blood flow to measure the resistance index (IR) and the pulsatility index (PI) of the dominant ovary.

Results: Patients in the sildenafil group showed (significantly) more mature follicles than the non-sildenafil group ($p = 0.028$). The mean endometrial thickness in the sildenafil group was also greater than the days of the human trophozoite. The group of without sildenafil was (8.90 ± 0.54 mm and 8.0 ± 0.91 mm) respectively and $p = 0.001$, and also had significantly lower resistance index and pulsatility index ($p < 0.001$) (0.41 ± 0.08 vs 0.58 ± 0.07) and (0.46 ± 0.08 vs 0.63 ± 0.07), respectively. The pregnancy rate in the sildenafil group was significantly higher than in the non-sildenafil group ($p = 0.032$).

Conclusion: Topical sildenafil treatment significantly improved ovarian interstitial blood flow, endometrial thickness, and pregnancy rate.

Keywords: Infertility, Pulsatility index, Resistance index, Sildenafil.

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INTRODUCTION

Infertility is described by the World Health Organization (WHO) as a disease of the reproductive system that results in the inability to achieve clinical pregnancy after unprotected intercourse for 12 months or more (unless there is no other reason, such as breastfeeding) or postpartum amenorrhea).[1] Successful pregnancy requires normal endometrium and ovarian function. Follicle formation in the human ovary is a complex process regulated by various endocrine and paracrine signals.[2] It has been suggested that the availability of sufficient vascular supply may play a key role in regulating the growth of follicles.[3] It has been observed that embryos derived from well-vascularized follicles have higher implantation rates than oocytes that develop in less vascularized follicles.[4] It turns out that increased ovarian stromal blood flow can lead to increased gonadotropin delivery to the granule cells of the developing follicle.[5] In addition to successful ovulation, clinical pregnancy requires sufficient endometrial growth to support ovum implantation during the menstrual cycle, so endometrial thickness (ET) is one of the strongest predictors of implantation.[6] Sildenafil Citrate (commercial Viagra) is the first phosphodiesterase 5 (PDE5) inhibitor approved by the US Food and Drug Administration (FDA) to prevent cyclic guanosine monophosphate (cGMP). It potentiates the effects of

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nitric oxide on vascular smooth muscle causing smooth muscle relaxation and an increase in blood flow circulation.[7] Sildenafil is also considered a possible drug for pregnant women with intrauterine growth retardation, pre-eclampsia, and uterine contractors (anti-contractants) that help maintain pregnancy.[8] Penn State College of Medicine assumes that Viagra's effect on blood flow makes it a possible treatment for periodic problems such as menstrual pain and cramps.[9]

MATERIALS AND METHOD

The present study was a randomized prospective comparative study conducted in the High Institute of Infertility Diagnosis and Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq from September 2019 to April 2020.Fifty infertile female patients who undergo stimulated intra-uterine insemination were randomized divided into two groups. The first group (Sildenafil group), 25 patients were included and given Sildenafil citrate 50mg vaginally every 12 hours from day 5 of the cycle for 8 days. The second group (non-sildenafil group), were 25 infertile females not given sildenafil. Infertile female patients in both groups underwent stimulated Intrauterine Insemination by letrozole 5 mg at cycle day 2 for 5 days. The patients follow up by serial transvaginal ultrasounds to assess the number and size of mature follicles. When at least one follicle reached the size equal to or more than 18 mm on cycle day 12 to 13en the human chorionic gonadotrophin trigger was given. Ultrasound and Doppler study was done to assess the number and size of mature follicles, endometrial thickness and ovarian stromal blood flow, which measured as RI and PI of the dominant ovary. After 34–36 hours of day of ovulation, sperm preparation technique and Intrauterine Insemination should be done. After 14 days β hCG test was done in blood to check biochemical pregnancy test.

RESULTS

The demographic features and hormonal levels of the studied groups were illustrated in Table 1, and the results demonstrated no statistically significant differences in all parameters between sildenafil and non-sildenafil groups with a *p-value* of less than 0.05.

The sonographic and Doppler blood flow of the ovaries show a significant difference in the number of dominant follicles (1.98 ± 0.92) and endothelial thickness (8.9 ± 0.54) in sildenafil group versus (1.44 ± 0.56) and (8.0 ± 0.91), respectively in a non-sildenafil group. However, there were no significant differences in the size of dominant follicles, even larger in the sildenafil group (19.42 ± 1.56 vs. 19.21 ± 1.08) in the non-sildenafil group with $p = 0.614$. There was also a significant difference between sildenafil and non-sildenafil groups regarding late follicular resistance index (0.41 ± 0.07 vs. 0.58 ± 0.08), respectively and pulsatility index (0.46 ± 0.08 vs. 0.63 ± 0.07), respectively with *p*-value less than 0.001.

The pregnancy rate was higher and significant in sildenafil group, 48% vs. 16% in the non-sildenafil group ($p = 0.032$), as presented in Table 2.

DISCUSSION

There were no significant differences between the two groups in terms of average age, body mass index, the average duration of infertility, type of infertility, and hormone levels (follicle stimulating hormone [FSH), luteinizing hormone (LH), E2, prolactin, and thyroid stimulating hormone (TSH)] as shown in Table 1. Further, no significant difference in the demographic characteristics of infertile women included in will limit any possible impact, interference, or bias in the results of ovarian blood flow index and pregnancy rate after adding sildenafil. The average number of dominant follicles detected by transvaginal ultrasound in the sildenafil group was significantly higher than that in the non-sildenafil group (Table 2). However, there was insignificantly higher in sildenafil group in the mean average size of the dominant follicle at the day of hCG trigger, as demonstrated in Table 2. This finding may lead to think that there may be a possible correlation between several dominant follicles and the administration of sildenafil. This observation may have been reversed. Although sildenafil was administered topically, it caused an overall increase in blood flow to the female reproductive system (including the ovaries), thereby

Table 1: Comparison of demographic and hormonal assay of the study groups

Parameters	*Sildenafil group (Mean ± SD)*	*Non-Sildenafil group (Mean ± SD*	*p-value*
Age (years)	28.44 ± 4.96	28.84 ± 5.71	0.346
BMI (Kg/m²)	24.61 ± 2.28	24.82 ± 2.27	0.074
Duration of infertility	4.48 ± 1.35	4.52 ± 1.76	0.914
Type of infertility	Primary = 9 Secondary =16	Primary = 8 Secondary = 17	0.756
FSH mU/L	7.14 ± 0.95	7.51 ± 3.15	0.665
LH mU/L	4.23 ± 1.39	4.11 ± 1.08	0.716
TSH mU/l	2.6 ± 0.73	2.88 ± 0.8	0.716
E2 pg/mL	59.47 ± 24.05	60.5 ± 22.31	0.875
Prolactin ng/mL	16.05 ± 3.15	16.5 ± 2.96	0.281

SD: Standard deviation; BMI: body mass index: FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; TSH: Thyroid stimulating hormone

Table 2: Comparison of clinical parameters of the study groups

Parameters	*Sildenafil group (Mean ± SD)*	*Non- Sildenafil group (Mean ± SD)*	*p-value*
No. of dominant follicles at hcg trigger	1.98 ± 0.92	1.44 ± 0.56	0.028*
No. of dominant follicles at hcg trigger	19.42 ± 1.56	19.21 ± 1.08	0.614
Endometrial thickness at hcg trigger	8.9 ± 0.54	8.0 ± 0.91	0.001*
Late follicular phase RI	0.41 ± 0.07	0.58 ± 0.08	0.001*
Late follicular phase PI	0.46 ± 0.08	0.63 ± 0.07	0.001*
Pregnancy rate	48% (12/25)	16% (4/25)	0.032*

SD: Standard deviation; ET:Endometrial thickness; RI: Resistance index; PI:Pulsatility index; *: $p<0.05$ (significant).

improving follicular development. Trakakis *et al.* concluded that sildenafil therapy could improve ovarian response in women. It has also been concluded that in an experimental study, the administration of sildenafil can increase ovarian angiogenesis, but in a negligible way.[10]

An experimental study by Celik *et al.* shows the effect of sildenafil on ovarian ischemia-reperfusion injury in rats was examined. The histopathological and biochemical results of their study confirmed that the mentioned damage improved with the administration of sildenafil.[11]

In a prospective study by Takasaki *et al.,* who stated that by using vaginal sildenafil, the thickness of the endometrium of the women in the study was significantly improved.[12] These results are also similar to Fetih *et al*. They noted that adding sildenafil to clomiphene significantly increased the thickness of the endometrium of women with thin endometrium was consistent with other authors in this regard.[13] Note that embryos derived from oocytes from well-vascularized follicles have a higher implantation rate than embryos derived from oocytes developed from the poorly vascularized follicle.[4] This study (Table 2) showed that the late follicular resistance index and the pulsatility index of the sildenafil group were significantly lower than those of the non-sildenafil group ($p=0.001$). This finding is that the angiogenic effect of sildenafil can lead to increased blood flow in the ovary.

Sildenafil is a vasodilator that causes vasodilation by inhibiting the PDE5 enzyme. This is due to the inhibition of cGMP hydrolysis and the increased availability of nitric oxide.[10] Therefore, due to local vasodilation, the possible improvement in blood flow is the reason. The Doppler parameters of women treated with sildenafil in this study were improved. The resistance index is a sign of resistance to blood circulation. The lower the resistance index value, the more blood circulation.[14] Some researchers have proposed the positive effect of sildenafil on ovarian function. Taskin *et al.* (2014) proved that sildenafil pretreatment could help protect the ovaries from cisplatin-induced histopathological damage in rats. The drug may be an option for preserving fertility after chemotherapy. Celik *et al*. experimental study showed that taking sildenafil increased ovarian angiogenesis, but not significantly.[10]

Therefore, there must be a correlation between ovarian perfusion and follicular oxygenation and oocyte maturation, ultimately translating into embryo quality. If other factors such as endometrial receptivity are controlled, implantation potential will also be affected. However, the theoretical linkage of oocyte quality, follicles and vascular networks, ovarian vascularization, and vascular endothelial growth factor (VEGF) levels may be true surrogate markers of oocyte quality.[15]

Data from this study showed that the overall pregnancy rate of women taking sildenafil was significantly higher than that of women not taking sildenafil (Table 2). These findings are consistent with the opinions of Fetih *et al*.[13] Mohamed TY 2019 found that the combination of oral sildenafil and letrozole significantly affects the pregnancy rate. The availability of multiple oocytes and the formation of an excellent endometrial thickness can be considered the cornerstone of the final pregnancy because better vascularization increases the likelihood of fertilization and implantation, thereby improving pregnancy outcomes.[12]

REFERENCES

1. World Health Organization. (2020). World Health Organization. [online] Available at: https://www.who.int/reproductivehealth/topics/en/ [Accessed 23 Jan. 2020].https://www.googleadservices.com/pagead/aclk?sa=L&ai=DChcSEwiNhJmt15TwAhWDuncKHYAQB-4YABABGgJlZg&ae=2&ohost=www.google.com&cid=CAESQeD2oyhl2Iw3R7cpFC647m0ewvPzDAjvujGohlrG4PeQ79b3RH8edhOgTQi0D-XhkRX5kL4oa8xEIaBbXhG1hSDv&sig=AOD64_31CtXoBX-OGegCvtqO5PIN8WTjfA&q&adurl&ved=2ahUKEwjzvYyt15TwAhXK_7sIHcWVC6wQ0Qx6BAgCEAE
2. McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. Endocr. Rev. 2000 Apr 1;21(2):200-214.
3. Redmer DA, Reynolds LP. Angiogenesis in the ovary. Rev. Reprod. 1996 Sep 1;1(3):182-192.
4. Naredi N, Singh SK, Sharma R. Does perifollicular vascularity on the day of oocyte retrieval affect pregnancy outcome in an In Vitro fertilization cycle?. J. Hum. Reprod. Sci. 2017;10(4):281.
5. Martelli A, Russo V, Mauro A, Di Giacinto O, Nardinocchi D, Mattioli M, Barboni B, Berardinelli P. Insights into ovarian follicle angiogenesis: morphological and chronological vascular remodeling from primordial to ovulating follicles. SM Vasc Med. 2017;2(1):1009.
6. Masrour MJ, Yoonesi L, Aerabsheibani H. The effect of endometrial thickness and endometrial blood flow on pregnancy outcome in intrauterine insemination cycles. Fam. Med. Prim. Care Rev. 2019 Sep;8(9):2845.

7. Elhwuegi AS. The Wonders of Phosphodiesterase-5 Inhibitors: A Majestic History. Ann Med Health Sci Res. 2016;6(3): 139-145.
8. Webb R, Garnsworthy PC, Campbell BK, Hunter MG. Intra-ovarian regulation of follicular development and oocyte competence in farm animals. Theriogenology. 2007 Sep 1;68:S22-S29.
9. Dmitrovic R, Kunselman AR, Legro RS. Sildenafil citrate in the treatment of pain in primary dysmenorrhea: a randomized controlled trial. Hum. Reprod. 2013 Nov 1;28(11): 2958-2965.
10. Golkar MH, Borujeni MJ, Rashidi B. The effects of administrated sildenafil citrate on uterine luminal epithelium height associated with ovarian angiogenesis: an experimental animal study. Adv. Biomed. Res. 2017;6.164.
11. Celik M, Aksoy AN, Aksoy H, Aksoy Y, Halici Z. Sildenafil reduces ischemia-reperfusion injury in rat ovary: biochemical and histopathological evaluation. Gynecol. Obstet. 2014;78(3):162-167.
12. Trakakis E, Vaggopoulos V, Sioulas VD, Panagopoulos P, Grammatikakis I, Ambatzi P, Kassanos D. The contribution of sildenafil (Viagra) to ovarian stimulation with gonadotropins in a woman with poor ovarian response. Gynecol. Endocrinol. 2014 Jul 1;30(7):478-480.
13. Fetih AN, Habib DM, Abdelaal II, Hussein M, Fetih GN, Othman ER. Adding sildenafil vaginal gel to clomiphene citrate in infertile women with prior clomiphene citrate failure due to thin endometrium: a prospective self-controlled clinical trial. Facts, views & vision in ObGyn. 2017 Mar;9(1):21.
14. Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction. Pharmacol. Ther. 2013;38(7):407.
15. Zhou Y, Zhang B, Han H, Mo X, Ma Y, Zhou Y. Objective: The purpose of this study was to explore the application of transvaginal two-dimensional and three-dimensional power Doppler ultrasound in pregnancy corpus luteum to predict the final outcome of early intrauterine pregnancy. Methods: This is a prospective observational cohort study. Six hundred early intrauterine pregnant women in Shanghai Changning Maternity and Infant Health Hospital were. Ultrasound for Precision Medicine: Diagnosis, Drug Delivery and Image-Guided Therapy. 2020 Aug 7.