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Research Article

Oral Sildenafil for Treatment of Female Infertility among PCO Patients: Randomized Comparative Study

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Abstract

Background: Anovulation is the most common cause of female infertility and endometrial thickness is an important determinant factor for successful pregnancy. Use of sildenafil in female infertility treatment is getting more and more attention.

Objective: To evaluate the role of oral sildenafil in addition to oral letrozole for treatment of female infertility in PCO women in comparison to letrozole alone.

Patients and Method: After approval of ethics committee, prospective randomized study was conducted among a total of 40 infertile females with PCO diagnosed to have anovulatory infertility. Patients were randomized into one of two treatment groups using simple randomization. Group A included 20 female patients who received letrozole alone 2.5mg twice daily from day 3 to day 7. Group B included 20 female patients who received letrozole 2.5mg twice daily from day 3 of the cycle to day 7 then sildenafil 50mg tab once daily from day 8 of the cycle till administration of Human Chorionic Gonadotrophin HCG. Patients of both groups were compared regarding follicular growth and number, endometrial thickness and clinical pregnancy rate.

Results: Endometrial thickness was significantly more among females receiving sildenafil (12.7mm versus 9.8mm; p-value < 0.001). Clinical pregnancy rate was 65% among sildenafil group compared to 15% among letrozole only group. No statistically significant difference was found regarding follicular number and diameter.

Conclusion: Oral sildenafil has significant effect in improving endometrial thickness and pregnancy rate when added to letrozole for treatment or anovulatory infertility among PCO women with tolerable mild side effect.

Keywords: Ovulation Induction; Endometrium; Fertility; Aromatase Inhibitors; Phosphodiesterase Inhibitors

Introduction

Polycystic ovary syndrome is one of the most important and prevalent causes of female infertility. PCO is characterized by ovulatory dysfunction and hyperandrogenism [1]. Approximately two-thirds of patients with PCOS, whether adolescent or adult, have anovulatory symptoms [2,3].

Letrozole is an anti-estrogenic aromatase inhibitor that was used as an ovulation inductor in anovulatory infertility women with more than 56mm endometrial thickness [4-6]. The other studies also reported that letrozole is effective in clomiphene-resistant patients, and also resulted in ovulation of 62% cases, and pregnancy of 14.7%. Additionally, no adverse events have been reported on fetus [7].

Besides successful ovulation, clinical pregnancy requires adequate growth of the endometrium to support the ovum implantation during menstrual cycle. Endometrial thickness (EM) is one of the strongest predictors of implantation [8].

Sildenafil citrate-The first PDE-5 inhibitor approved by the United States Food and Drug Administration (FDA)- is a type 5-specific Phosphodiesterase (PDE) inhibitor that act by preventing the breakdown of cyclic GMP (cGMP) and potentiates the effects of nitric oxide (NO) on vascular smooth muscle [9]. The recent advancing basic and clinical studies suggest some very promising new applications of PDE-5 inhibitors, far beyond their urological scope [10].

The current study was designed aiming to evaluate the role of oral sildenafil in addition to oral letrozole for treatment of female infertility in PCO women in comparison to letrozole alone.

Patients and Methods

After approval of ethics committee of Faculty of Medicine, Suez Canal University, the present prospective randomized study was conducted among a total of 40 infertile females with PCO diagnosed to have anovulatory infertility. Patients aged 18- to 40-year-old with PCO, normal baseline FSH, LH, with normal uterus and patent fallopian tubes on Hysterosalpingogram (HSG) and absence of any male factors of infertility were included into the study. Anovulation was diagnosed by ultrasonography and day-21 serum progesterone more than 5ng/ml. Females with significant cardiovascular, liver or renal diseases, endocrine abnormalities (as hyperprolactinemia or abnormal thyroid functions), prior ovarian or adnexal surgery,

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Table 1: Baseline patient characteristics.

Characteristic		Group A (n=20)		Group B (n=20)		p-value
Age (years)		27.8 ± 3.9		28.2 ± 4.5		0.8 (NS)
BMI (Kg/m²)		25.7 ± 4.6		26.1 ± 5.9		0.8 (NS)
Type of infertility	Primary	13	65%	15	75%	0.7 (NS)
	Secondary	7	35%	5	25%	
Duration of infertility (years)		3.2 ± 1.4		2.9 ± 2.5		0.6 (NS)
Day 2 Serum FSH (U/L)		5.3 ± 0.9		4.9 ± 1.1		0.2 (NS)
Day 2 Serum LH (IU/L)		8.9 ± 3.5		9.3 ± 2.8		0.7 (NS)
Baseline endometrial thickness (mm)		8.2 ± 1.2		7.9 ± 1.3		0.5 (NS)

NS: no statistically significant difference.

Table 2: Bycle characteristics and outcome among both groups.

Outcome measures		Group A (n=20)		Group B (n=20)		p-value
Number of follicles		3.8 ± 1.2		2.9 ± 1.7		0.06 (NS)
Follicular diameter		17.5 ± 1.9		18.1 ± 1.8		0.3 (NS)
Endometrial thickness		9.8 ± 1.1		12.7 ± 0.8		<0.001*
Clinical pregnancy rate N(%)		3	15%	11	55%	0.02*
Side effects	No	16	80%	13	65%	0.5 (NS)
	Headache	2	10%	4	20%	0.7 (NS)
	Flushing	1	5%	2	10%	0.9 (NS)
	Blurring of vision	0	0%	1	5%	0.9 (NS)
	GI upset	2	10%	2	10%	0.9 (NS)

NS: no statistically significant difference.
*Statistically significant difference.

or organic pelvic pathology (fibroids, adenomyosis, or congenital uterine anomalies) were excluded from the study.

All patients were subjected to full history taking and examination, baseline laboratory assessment, vaginal ultrasound and HSG.

After fulfilling inclusion criteria, enrolled patients were randomized into one of two treatment groups using simple randomization. Group A included 20 female patients who received letrozole alone 2.5mg twice daily from day 3 to day 7. Group B included 20 female patients who received letrozole 2.5mg twice daily from day 3 of the cycle to day 7 then sildenafil 50mg tab once daily from day 8 of the cycle till administration of human chorionic gonadotrophin HCG.

HCG was administered when leading follicle reached ≥ 18mm in diameter. 10000 IU of HCG was administered by IM injection for all patients in both groups. Folliculometry was assessed by transvaginal ultrasound on day 13 or day 14 of the cycle. Pregnancy was confirmed by beta subunit HCG test positive and confirmed by ultrasound assessment.

Outcome measures

Patients of both groups were compared regarding follicular growth and number, endometrial thickness and clinical pregnancy rate.

Statistical analysis

Collected data was processed using SPSS version (25) (SPSS Inc., chiago, IL, USA.). Quantitative data was expressed as means ± SD while qualitative data was expressed as number and percentages (%). Unpaired t test was used to test significance of difference for quantitative variables and chi square was used to test significance of difference for qualitative variables. A probability value (p-value) <0.05 was considered statistically significant.

Results

There was no statistically significant difference between both groups regarding age, BMI, and type or duration of infertility. Most of patients were found to have primary infertility (65% in group A and 75% in group B). Baseline FSH, LH, and endometrial thickness showed no statistically significant difference between both groups (Table 1).

Regarding number of follicles and average follicular diameter, there was no statistically significant difference between both groups. Endometrial thickness was found to be higher among patients received oral sildenafil with letrozole compared to patients received letrozole only (12.7mm versus 9.8mm; p-value <0.001). Clinical pregnancy was confirmed among 15% of patients of group A versus clinical pregnancy rate of 55% among patients of group B with statistically significant difference with risk ratio 3.7 (risk of pregnancy with letrozole and sildenafil is 3.7 times risk of pregnancy with letrozole alone). Side effects were tolerable in both groups with no statistically significant difference regarding their incidence (Table 2).

Discussion

Current study has studied systemic administration of sildenafil, while previous reports have used sildenafil local administration whether gel or vaginal suppositories. Despite different route of administration these reports have shown consistent results supporting the current finding of improved endometrial thickness and pregnancy rate with addition of sildenafil to treatment protocol. Moreover these studies have shown significant effect of local sildenafil on uterine artery Doppler findings as increased uterine blood flow and reduced uterine artery vascular resistance [11-17].

Fahmy et al., [18] have compared adding of oral sildenafil to clomiphene citrate regarding effect on endometrial thickness and pregnancy rate. They have shown that patients treated with sildenafil in addition to clomiphene citrate have increased endometrial thickness, follicular number and pregnancy rates. Although, Fahmy et al., [18] have used clomiphene citrate in their treatment protocol and current study have evaluated letrozole, both studies have shown consistent findings regarding positive effect of sildenafil in terms of endometrial thickness and pregnancy rate.

Also in accordance with current results, Paulus et al [19] and Fisch et al [20] reported that oral sildenafil citrate improved the sonographic endometrial thickness in patients with thin endometrial over clomiphene citrate alone.

A study failed to demonstrate the beneficial effect of sildenafil on thin endometrium, has been reported in women treated with estrogen and sildenafil citrate. Endometrial thickness was compared between the groups. Neither vaginal estrogen nor sildenafil significantly improved endometrial thickness or blood flow in the subsequent

frozen embryo transfer cycle [21]. Thus, the use of sildenafil cannot be expected to help all patients with a thin endometrial lining. Women with intractable damage to the basal endometrium may be less likely to respond to increased uterine blood flow. Response to sildenafil is also predicated on an adequate serum estrogen level [22].

The main reported side effects for sildenafil citrate are headache, flushing, blurring of vision, nausea and dyspepsia [23]. Side effects to sildenafil citrate are mild to moderate in nature and are dose related [24]. Side effects reported among patients of current study were tolerable with no statistically significant difference compared to clomiphene citrate-only group.

Few patients reported vaginal irritation [25]. Another study showed that vaginal sildenafil suppositories are free from side effects related to oral sildenafil [16].

Conclusion

Oral sildenafil has significant effect in improving endometrial thickness and pregnancy rate when added to letrozole for treatment or anovulatory infertility among PCO women with tolerable mild side effect.

Limitation of the study: The main limitation of the study is the small sample size and that current study didn't evaluate Doppler parameters of uterine artery.

References

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004; 89: 2745-2749.
2. King J. Polycystic ovary syndrome. J Midwifery Womens Health. 2006; 51: 415-422.
3. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19: 41.
4. Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018; 5.
5. Hu S, Yu Q, Wang Y, Wang M, Xia W, Zhu C. Letrozole versus clomiphene citrate in polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2018; 297: 1081-1088.
6. Rajan RK, SS M, Balaji B. Soy isoflavones exert beneficial effects on letrozole-induced rat polycystic ovary syndrome (PCOS) model through anti-androgenic mechanism. Pharm Biol. 2017; 55: 242-251.
7. Abu Hashim H, Shokeir T, Badawy A. Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Fertil Steril. 2009; 94: 1405-1409.
8. Ghahiri A, Mogharehabed N, Mamourian M. Letrozole as the first-line treatment of infertile women with poly cystic ovarian syndrome (PCOS) compared with clomiphene citrate: A clinical trial. Adv Biomed Res. 2016; 5: 6.
9. Boolell M, Gepi-Attee S, Gingell JC, Allen MJ. Sildenafil, a novel effective oral therapy for male erectile dysfunction. Br J Urol. 1996; 78: 257-261.
10. Dehghani-Firouzabadi R, Davar R, Hojjat F, Mahdavi M. Effect of sildenafil citrate on endometrial preparation and outcome of frozen-thawed embryo transfer cycles: a randomized clinical trial. Iran J Reprod Med. 2013; 11: 151-158.
11. Sher G, Fisch JD. Vaginal sildenafil citrate (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: 806-809.
12. Sher G, Fisch JD. Effect of vaginal sildenafil citrate on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. Fertil Steril. 2002; 78: 1073-1076.
13. Richter KS, Bugge KR, Bromer JG, Levy MJ. Relationship between endometrial thickness and embryo implantation, based on 1,294 cycles of in vitro fertilization with transfer of two blastocyst-stage embryos. Fertil Steril. 2007; 87: 53-59.
14. Das V, Agarwal A, Pandey A, V Jain. Evaluation of role of sildenafil in improving IUI success rates. Poster presentations/ International Journal of Gynecology & Obstetrics. 2009; 107: S413-S729.
15. Malinova M, Abouyta T, Krasteva M. The effect of vaginal sildenafil citrate on uterine blood flow and endometrium in the infertile women. Akush Ginekol (Sofiia). 2013; 52: 26-30.
16. Takasaki A, Tamura H, Miwa I, Taketani T, Shimamura K, Sugino N. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. Fertil Steril. 2010; 93: 1851-1858.
17. Fetih AN, Habib DM, Abdelaal I, 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 Vis Obgyn. 2017; 9: 21-27.
18. Fahmy AA, El Sokkary M, Sayed S. The Value of Oral Sildenafil in the Treatment of Female Infertility: A Randomized Clinical Trial. Life Science Journal. 2015; 12: 78-82.
19. Paulus WE, Strehler E, Zhang M, Jelinkova L, El-Danasouri I, Sterzik K. Benefit of vaginal sildenafil citrate in assisted reproductive therapy. Fertil Steril. 2002; 77: 846-847.
20. Fisch P, Casper RF, Brown SE, Wrixon W, Collins JA, Reid RL, Simpson C. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotrophin. Fertil Steril. 2003; 51: 828.
21. Check JH, Graziano V, Lee G, Nazari A, Choe JK, Dietterich C. Neither sildenafil nor vaginal estradiol improves endometrial thickness in women with thin endometria after taking oral estradiol in graduating dosages. Clin Exp Obstet Gynecol. 2004; 31: 99-102.
22. Benni JM, Patil PA. An overview on sildenafil and female infertility. Indian Journal of Health Sciences. 2016; 9: 131-136.
23. Berman JR, Laura AB, Steven MT, Jennifier G and Scoutt H; Sildenafil Study Group. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: A Double-blind, placebo controlled study. J Urol. 2003; 170: 2333-2338.
24. Basson R, Rosemery M, Mike DS, Gemma H, Naden K. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. J Womens Health Gend Based Med. 2002; 11: 367-377.
25. Kim KR, Sun Lee H, Ryu HE, Park CY, Min SH, Park C, et al. Efficacy of luteal supplementation of vaginal sildenafil and oral estrogen on pregnancy rate following IVF-ET in women with a history of thin endometria: A pilot study. J Womens Med. 2010; 3: 155-158.

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