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Original Research Article

Effect of combining estradiol valerate with sildenafil in increasing the thickness of the endometrium in infertile women before intrauterine insemination: a randomized clinical trial

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ABSTRACT

Background: Therapies available for thin endometrium are limited and are mostly performed experimentally which most of these treatments have a similar function and increase blood flow to the endometrium, causing it to thicken and develop. The aim of the study was to compare the effect of estradiol valerate in combination with sildenafil on endometrial thickness in infertile women before intrauterine insemination.
Methods: In this randomized clinical trial 100 infertile women referred to Reyhaneh Infertility Center in Ardabil were randomly divided into two groups. Patients' endometrial thickness was assessed by vaginal ultrasound before treatment and then on day 9 of the cycle. The intervention group received one tablet of estradiol valerate every 12 h from the ninth day of menstruation for 4 days and sildenafil as 25 mg orally daily from day 9 to 12, but in the control group, patients received placebo tablets orally in addition to estradiol.
Results: There was no statistically significant difference between the intervention and control groups before and after the intervention in term of endometrial thickness. The rate of increase in endometrial thickness was 1.35 mm in the intervention group and 1.37 mm in the control group, but the difference was not statistically significant.
Conclusions: Estradiol valerate alone or in combination with sildenafil resulted in a significant increase in endometrial thickness and increasing oral sildenafil supplementation with oral estradiol valerate had no significant effect on increasing endometrial thickness.

Keywords: Endometrial thickness, Infertility, Sildenafil, Estradiol valerate, Intrauterine insemination

INTRODUCTION

Infertility is defined as the inability to conceive after one year of unprotected intercourse. Although the endometrial factor and defects in replacement are among the known causes of female infertility, but the effect of interventions to improve them has not been widely studied in the infertile population undergoing intrauterine insemination (IUI). New clinical treatments such as biopsy or endometrial intentional damage have recently attracted much attention in the treatment of endometrial infertility but endometrial evolution in IUI cycles has been less studied.[1,2] One of the strongest predictors of replacement is the thickness of the endometrium. Several studies have shown that embryo replacement and pregnancy rate are much higher in people with an endometrial thickness of more than 9 mm.[3,4]

A thin endometrium, usually considered less than 7 mm, is less able to tolerate replacement and pregnancy.[5] The thickness of the endometrium depends on several factors, including the age of the mother, the phase of the menstrual cycle, the concentration of

ovarian hormones (estrogen and progesterone) and the density of the endometrial hormone receptor.[6,7] Treatments available for thin endometrium are limited and mostly empirical. These treatments include high doses of estrogen, human chorionic gonadotropin (HCG) and granulocyte colony stimulating factor.[8] Most of these treatments have similar functions and by increasing the blood flow to the endometrium, they cause it to thicken and develop. Considering that low endometrial thickness is related to lower pregnancy rate, the aim of the study was to investigate the effect of combining estradiol valerate with sildenafil on increasing the endometrial thickness in infertile women before IUI.

METHODS

Study design

This clinical trial study was conducted on 100 infertile women who referred to Reyhane Ardabil Infertility Center in 1400 for IUI. Infertile women aged between 20 and 40 years and BMI less than 30 kg/m^2 were included in the study. Women with any congenital uterine anomaly (unicorn uterus) or acquired uterine cavity deformity (for example, Asherman syndrome), women with tubal infertility (for example, tubal adhesions or previous ectopic pregnancy), women under treatment for which estrogen is contraindicated (for example, a history of stroke, DVT and benign liver disease) and women whose infertility was caused by a male factor (azoospermia, teratospermia) were excluded from the study.

Data collection

Patients were randomly divided into intervention and control groups. The endometrial thickness of the patients were evaluated by vaginal ultrasound before the treatment and after the intervention. Patients in the intervention group received one estradiol valerate tablet every 12 hours from the 9th day of menstruation until the start of ovulation (for 4 days) + Sildenafil 25 mg orally daily from the 9th day of the cycle and patients in the control group except for estradiol valerate, they also received placebo tablets orally daily from the 9th day of the cycle.

Statistical analysis

After completing the checklist, the information was entered into SPSS (version 26) and analyzed by using descriptive statistics and independent t-test to determine the difference in parametric variable like endometrial thickness, weight, height and BMI between experimental groups at the beginning and end of the intervention. Also paired t-test was used to determine the difference in endometrial thickness amounts in each group at the beginning and end of the study. A significance level of less than 0.05 was considered significant. This study was registered in the Ethics Committee of Ardabil University of Medical Sciences with the ethics code IR.ARUMS.REC.1399.571 and in the website of the National Clinical Trials Center with the code IRCT20210313050688N1.

RESULTS

In the intervention group, the average age was 31.4±5.22 years and in the control group was 30.1±4.5 years and the difference was no significant. There were no significant differences between two groups in terms of age, occupation, weight, height and BMI.

In terms of endometrial thickness, there was no statistically significant difference between the intervention and control groups before the intervention. Also, after the intervention, there was no significant difference between the control and intervention groups in terms of endometrial thickness (Table 1).

Table 1: The average thickness of the endometrium in the study groups before and after the intervention.

Group time of intervention	Control	Intervention	P value*
Before	6.11±0.7	6.29±0.62	0.18
After	7.458±0.7	7.64±0.71	0.21

The rate of increasing in endometrial thickness was 1.35 units in the intervention group and 1.37 units in the control group, and there was no statistically significant difference between the two groups (Table 2).

Table 2: The difference in endometrial thickness values in the participants according to the studied groups.

Group	Mean±SD	P value*
Estradiol valerate + sildenafil	1.35±0.75	0.92
Estradiol valerate + placebo	1.37±0.78	

DISCUSSION

Based on the results of similar clinical trial studies, endometrial thickness in sildenafil group appears to be higher in women undergoing IUI. In particular, a recent study has shown that delayed initiation of oral sildenafil administration may significantly increase the chance of obtaining a thicker endometrium and pregnancy. Further studies are needed to determine whether the sildenafil administration method has a significant effect on endometrial thickness and pregnancy rate. In different studies, in all trials except one trial, sildenafil was administered orally and in all these studies, no significant improvement in endometrial thickness achieved for sildenafil supplementation, so

in this sense, the study ours is also in line with the mentioned studies.[9-14] In one of these trials, the effect of sildenafil, like our study, has been compared with and without estradiol, while in other studies, sildenafil has been compared with no intervention.[10]

Regarding the improvement of endometrial thickness in women treated with sildenafil, it has been found that this molecule improves arterial blood flow by preventing the breakdown of cGMP, which leads to increased vasodilation.[15] A possible explanation for the effect of sildenafil on endometrium is that this molecule has a positive effect on endometrial growth and endometrial vascularization through the described mechanism. This mechanism works in cooperation with estrogens that secrete angiogenic factors to increase revascularization, perhaps the significant effect of sildenafil in combination with estradiol is due to this potential mechanism. This improvement in endometrial growth through increased vascularity has led to improved fertility rates in various studies.

Also, when sildenafil supplementation is started 7 to 8 days after ovarian stimulation, better results in terms of pregnancy rate have been reported which challenges the results of our study because in the current study, sildenafil was prescribed from the tenth day of menstruation until the start of ovulation but no significant results were obtained in increasing the thickness of the endometrium with oral sildenafil. Physiologically, endometrial vessels increase during the endometrial proliferation phase, which generally continues from the seventh day of the menstrual cycle under the influence of estrogens through the action of various angiogenic factors. Because NK cells release cytokines that contribute to failure of embryo implantation through the action of nitric oxide, administration of sildenafil may be beneficial only when spiral arteries are already formed to avoid high nitric oxide concentrations. In fact, if the assumption is to use sildenafil to increase the vascularity of the endometrium, the delayed administration of this molecule is better adapted to the physiology of the endometrial cycle and works in harmony with the increase of estrogen.

In summary, a biological explanation for the apparently different effects of sildenafil among women undergoing IUI compared with women undergoing IVF in the published literature may lie in the different estrogen levels achieved in different types of treatment.[15] Indeed, as previously reported, estrogen therapy is an option to achieve a thicker endometrium and high levels of endogenous estradiol may serve as an adjunctive therapy so that in the present study, the use of estradiol even in the control group caused a significant increase in the thickness of the endometrium. This aspect may explain the non-significant results in increased endometrial thickness in women following treatments requiring higher estradiol levels this is perhaps the reason why the intervention group of the present study achieved insignificant results in comparison with the control group.[16,17] Finally, understanding the mechanisms of endometrial angiogenesis and the role of angiogenic factors during ART treatments may provide new insights and clarify the effect of sildenafil on the endometrium at different stages of the endometrial cycle. Due to the limitations of the existing study, more trials are still needed to finally confirm or deny the real clinical effectiveness and also to determine the best time, dose and duration of sildenafil administration. One of the limitations of this study is the lack of comparison between sildenafil and the non-intervention group.

CONCLUSION

According to the results of this study, estradiol valerate alone or together with sildenafil led to a significant increase in the thickness of the endometrium. The increase of oral sildenafil supplement on oral estradiol valerate had no significant effect on the increase of endometrial thickness. This research showed that 12% in the control group and 14% in the intervention group had positive pregnancy results. It is suggested to conduct a similar study with other intervention groups including GnRH agonist and aspirin. It is also suggested to conduct a similar study with the non-intervention group to compare sildenafil and estradiol valerate with it and conduct similar clinical trials with vaginal sildenafil.

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