



The Comparison Between The Effect of Different Medical Drugs used To Improve Endometrial Receptivity in patients with Thin Poorly Vascularized Endometrium.

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In a perfect world, the peak of receptivity of the endometrial lining would occur simultaneously with the entry into the uterine cavity of a healthy blastocyst, which would then be able to adhere, attach, invade, and develop protected until the time of delivery. This would be the ideal scenario. The study was carried out on 200 infertile women who have thin, poorly vascularized endometrium, those patients were divided into five groups; 40 patients in each group, group A received estrofem oral, group B received vagifem vaginal tablets, group C received sildenafil citrate gel, group D received pentoxifylline oral and group E received 4 grams of pentoxifylline vaginal gel. The endometrial thickness, vascularity zones, sub endometrial flow, and both uterine arteries resistance and pulsatility indices were assessed at the middle of the menstrual cycle (day 11–14) on a monthly basis for six cycles or until a positive pregnancy test was obtained. Pentoxifylline vaginal gel, pentoxifylline+ vitamin E capsule, and sildenafil vaginal gel have improved the vascularity indices of endometrium and uterine arteries, while the vagifem and estrofem were less effective in terms of improving the vascularity indices of endometrium and uterine arteries. The study also showed that 57.5% of women succeed to get pregnant after six months of receiving pentoxifylline vaginal gel, 35% of women succeed to get pregnant after six months of Pentoxifylline+vit E, while 22.5% of women succeed to get pregnant after six months of sildenafil, about 10% of women got pregnant after six months of vagifem, and finally 2.5% of women got pregnant after six months of receiving estrofem tablets. It was discovered that pentoxifylline vaginal gel, pentoxifylline tablet plus vitamin E capsule, and sildenafil vaginal gel were able to improve the vascularity index of the endometrium, the uterine arteries and endometrial thickness, and enhance the pregnancy rates in patients with thin poorly vascularized endometrium.

ABSTRACT

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KEYWORD

Endometrial Receptivity; Thin Poorly; Vascularized Endometrium; Pentoxifylline.

1. Introduction

The process of reproduction is essential to the continued existence of mammalian species, and as a result, millions of sex genes have been conserved over the course of history **(Croft et al. 2015 [1])**. There are several challenges associated with describing the illness, which makes it impossible to obtain a global picture of infertility. In the body of academic research, the terms subfertility, sterility, childlessness, and infecundity are frequently interchanged with one another. Infertility is defined as "a disorder of the reproductive system characterized by an inability to conceive after 12 months or more of routinely unprotected sexual intercourse," as stated by the World Health Organization (WHO). **(WHO, 2020), (Szamatowicz and Szamatowicz, 2020 [2])**. An infertile pair accounts for around 15 percent of all couples in the world. In certain situations, both the female and male

partners are infertile or sub-fertile, and the infertility of the partnership is the result of a combination of several of the factors that have been discussed earlier. In some instances, the problem is thought to be due to immunological or genetic issues; this is the case when both partners are fertile on their own, but the pair is unable to have children together even with the assistance of various assisted reproductive technologies **(Shazadi et al., 2022 [3])**. The term "receptive endometrium" refers to a healthy uterine environment in which endometrial cells are converted into decidua cells, which are suited for blastocyst implantation, and the placenta develops fast. This allows for the successful implantation of the blastocyst **(Meyer and Zenclussen, 2020 [4])**. When there are no obvious abnormalities in the endometrium's physical appearance, these tests have been utilized as a sign of the receptivity of the endometrium **(Sadek et al., 2022 [5])**. It is commonly accepted that the endometrium must have the

appropriate thickness in order for a pregnancy to be successful, and several theses have revealed low pregnancy scores in women whose endometrium was fragile and poorly vascularized (Shokeir and Abdelshaheed, 2022 [6]). Endometrial thickness that is measured on ultrasound to be less than seven millimeters is generally regarded as sub-optimal for embryo transfer and is associated with a lower probability of becoming pregnant. This is a consensus amongst medical professionals, despite the fact that doctors disagree on the ideal endometrial thickness for conception (Alaa et al 2021 [7]). Endometrium that is thin and poorly vascularized is still a concern in the fields of gynecology and reproductive science, despite the fact that there has been very little progress made with the therapies that are now available (Bu et al., 2020 [8]). In this particular research project, the hypothesis focuses on developing and investigating viable treatments for refractory endometrium that are thin and undersupplied.

2. Patients and Methods

This study was carried out on 200 infertile women who have thin, poorly vascularized endometrium as assessed in their first visit at Tikrit City, Iraq.

Exclusion criteria:

- 1-Age <20 and > 40 years.
- 2-Patients who have an allergy to one or more of the study drugs (Esterofem, vagifem, sildenafil citrate, vitamin E, and pentoxifylline).
- 3-Patients with obvious intrauterine lesions that distorted the endometrium cavity, like myomas or polyps, that Diagnosed by transvaginal ultrasound.
- 4- Patients with Mullerian duct anomalies or uterine hypoplasia (infantile uterus).
- 5-Patients for whom study drugs are contraindicated.
- 6-Patients with premature ovarian failure.
- 7-Infertile male partner with azoospermia, sever oligo astheno terato spermia, and sexual dysfunction.

8- Patients with any tubal factor that is related to infertility (bilateral tubal blockage).

Consent procedure:

Every patient provided their permission after receiving appropriate information. An appropriate informed consent process was developed by the investigator in order to ensure that potential research subjects or their authorized representatives are fully informed about the nature and purpose of the clinical study, the potential risks, and benefits of participating in the study, as well as their rights as research subjects. Before carrying out any procedures that were unique to the study on a subject, the researcher ensured that they had the subject's written and signed consent, as well as the approval of any authorized representatives of the subject. The investigator made sure to keep a copy of the fully completed and original consent form. In order to obtain an alpha error of 5 percent and a beta error of 20 percent, each group needed to

have a minimum of 40 patients. Therefore, it was determined that 40 patients in each group was an adequate number. Data on patients who were enrolled (in the study), as well as their characteristics, are included in the "Case record form (CRF)": At the time of the initial consultation, each patient was subjected to a comprehensive clinical examination and thorough evaluation, which included taking their weight, height, body mass index, and detailed medical history, as well as performing hormonal testing, husband seminal fluid analysis, abdominal and transvaginal ultrasounds.

Drug preparation:

The following information was entered into the Case Record Form (CRF) that was assigned to each patient: The sample was made by dissolving 2000 mg of pentoxifylline and 500 mg of sildenafil citrate in 40g of Hypermellous (H.M) gel, respectively. All of the preparations were made with mechanical stirring, and the temperature was brought up to

60 degrees Celsius over the course of approximately 30 minutes before being lowered to 25 degrees Celsius with continuous mechanical stirring. After the gels had been made, they were placed in plastic containers with wide mouths, covered with parafilm, and

then covered with a plastic lid with a screw-on cap. A cool location was used to store the preparations (not above 25c)

Study Design: Randomized controlled prospective clinical trials.

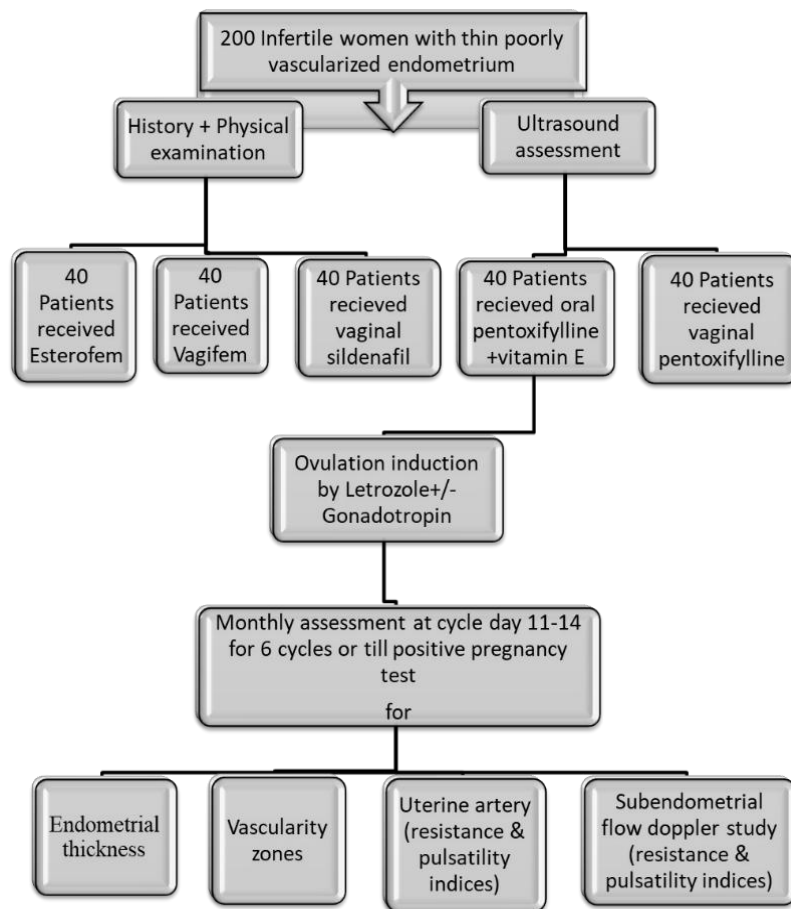


Figure 1: The study design

The procedure

200 infertile patients were included in the current study; all of them had endometrium that was thin and poorly vascularised, regardless of the cause; after determining whether or not they satisfied the inclusion and exclusion criteria, the women were randomly assigned to one of five groups, with forty patients in each group:

Group 1:

Is the study group that consists of 40 patients with thin, poorly vascularized endometrium who received Esterofem 2mg tablet every 12 hours from day 2 of the menstrual cycle till the day of ovulation trigger during the six cycles (the study period) /or till the patient gets pregnant.

Group 2:

Is the study group that consists of 40 patients with thin, poorly vascularized endometrium who received Vagifem vaginal tablets 25 micrograms self-administrated

vaginally at a fixed time daily from the fourth day of the menstrual cycle till the day of ovulation trigger during the six cycles (the study period) /or till the patient get pregnant.

Group 3:

Is the study group that consists of 40 patients with thin, poorly vascularized endometrium who received sildenafil citrate gel 3 gm, which containing 37.5 mg sildenafil every 12 hours administrated via prefilled syringe by self-administration in lithotomy position from the 2nd day of menstruation till the day of ovulation trigger during the six cycles (the study period) /or till the patient get pregnant.

Group 4:

Is the study group that consists of forty patients with thin, poorly vascularized endometrium. These patients were given pentoxifylline (oral 800 mg daily) and vitamin E (oral 400 mg twice daily) for the duration of the study, which lasted for six cycles or until the

patient became pregnant, whichever came first.

Group 5:

Is the study group that consists of 40 patients with thin, poorly vascularized endometrium who received 4 gm of pentoxifylline vaginal gel, which contains 200 mg pentoxifylline at a fixed time daily which was timed to be 3 hours before intercourse (that recommended to be every other day after menstruation till the next cycle) via prefilled syringe by self-administration in lithotomy position from the 7th day of menstrual cycle until day 21 of the cycle.



At the middle of their cycles, those patients underwent a two-dimensional transvaginal ultrasound examination to evaluate the thickness of their endometrium (the greatest distance between each myometrium-endometrium interface via the uterine longitudinal axis) in addition to an assessment of endometrial vascularity zones, uterine artery pulsatility, and resistance indices, and sub endometrial blood flow as pulsatility index and resistance index.



3. Results

According to the findings of the study, the average thickness of the endometrium prior to treatment for the group 1, group 2, group 3, group 4, and group 5 were 4.7700.842, 4.7250.933, 4.6630.996, 5.0020.993, and 4.8551.138 respectively. After one month of treatment, the means of the groups mentioned, While the means of endometrial thickness after 1-3 months of therapy for the stated groups respectively went to (5.593±0.6, 6.370±0.816, 5.882±0.985, 5.718±0.840 and 5.925±1.182), which was a very significant alteration.

Finally, after 3-6 months of treatment, the means of endometrium thickness for those mentioned groups respectively changed to (6.875±0.561, 7.76±0.549, 6.77±0.698, 7.1±0.509, and 6.823±0.703), which was again a highly significant change and obviously, the Vagifem group achieved the highest mean of endometrium thickness among the study drugs, table 4.6 and figure 4.1 below showed significant increase in endometrial thickness after treatment.

Table 1: The comparison of treatment coarse duration to achieve adequate endometrial thickness among different study groups

	Estrofe m Oral 1x2	Vagifem 25 mcg 1x1	Sildenafil 1 25mg 1x3 Vaginal	Pentoxi fylline+ vit E Oral	Pentoxifyl line Vaginal Gel	P value
Endometrial Thickness (mm)						
Pre-treatment	4.770±0.842	4.725±0.933	4.663±0.996	5.002±0.993	4.855±1.138	0.582
After 1 st month	5.173±0.736	5.620±0.776	5.425±1.016	5.403±0.864	5.373±1.095	0.299
After 1-3 months	5.593±0.6	6.370±0.816	5.882±0.985	5.718±0.840	5.925±1.182	0.002#
After 3-6 months	6.875±0.561	7.760±0.549	6.770±0.698	7.100±0.509	6.823±0.703	0.0001#
^Significant difference between the two independent means using the Students-t-test at 0.05 level. ^Significant difference between the two dependent means using a paired t-test at 0.05 level. #Significant difference among more than two independent means using ANOVA-test at 0.05 level.						

The study showed that the lowest mean of right uterine artery resistance index achieved after treatment was in the Pentoxifylline gel group, which was comparable to the results achieved by the pentoxifylline + vit E group, followed by sildenafil, then estrofem and vagifem groups who showed the highest resistance indeces for the right uterine artery among the study groups (unlike other drugs in the study vagifem and esterofem has shown to

increase the resistance index instead of improving it). While for The left uterine artery, the study showed that the lowest mean of resistance index was achieved by the pentoxifylline + vit E group, which was comparable to the results achieved by the sildenafil group, pentoxifylline gel, then estrofem and vagifem groups who showed the highest resistance indeces for the left uterine artery among the study groups (unlike other drugs in the study

vagifem and estrofem has shown to increase the resistance index instead of improving it).

For the mean of uterine artery resistance index, the study showed that the lowest mean of resistance index was achieved by the pentoxifylline + vit E group, which was comparable to the results achieved by the pentoxifylline gel group and vaginal sildenafil group, all those drugs gave significant decrease in the resistance indices of uterine artery during treatment course, then estrofem and vagifem groups who showed the highest resistance indices and gave significant increase in the resistance indices of uterine artery during treatment course among the study group, table 2. Regarding the uterine arteries pulsatility index, the study also showed that the lowest mean of right uterine artery pulsatility index achieved after treatment was in the pentoxifylline+ vit E group, followed by pentoxifylline gel group then by

vaginal sildenafil, while estrofem and vagifem groups showed the highest pulsatility indices for the right uterine artery among the study groups (unlike other drugs in the study vagifem and estrofem has shown to increase the pulsatility index instead of improving it). While for The left uterine artery, the study showed that the lowest mean of right uterine artery pulsatility index achieved after treatment was in the pentoxifylline + vit E group, followed by pentoxifylline gel group, then by vaginal sildenafil, while estrofem and vagifem group showed the highest pulsatility indices for the right uterine artery among the study groups (unlike other drugs in the study vagifem and estrofem has shown to increase the pulsatility index instead of improving it), the mean of uterine arteries pulsatility indices showed the same results as a significant decrease in the mean pulsatility indices scored by pentoxifylline + vit E, pentoxifylline

gel, and sildenafil during the treatment course, while estrofem and vagifem groups gave a significant increase in the

pulsatility indices of uterine artery during the treatment course, table 3.

Table 2. The comparison of uterine arteries resistance indeces among different study groups.

	Estrofem Oral 1x2	Vagifem 25 mcg1x1	Sildenafil 25mg 1x3 Vaginal	Pentoxifylline +vit E Oral	Pentoxifyllin e Vaginal Gel	P value
RT UA RI						
Pre-treatment	0.842 +0.057	0.816 +0.035	0.831 +0.043	0.837 ±0.043	0.851 ±0.041	0.001
After 1st month	0.857 +0.061	0.841 +0.039	0.778 +0.040	0.789 ±0.041	0.797 ±0.036	0.0001
After 1-3 months	0.863 +0.060	0.856 +0.037	0.755 +0.038	0.765 ±0.046	0.766 ±0.032	0.0001
After 3-6 months	0.874± 0.057	0.875 +0.041	0.732 +0.030	0.735 ±0.039	0.748 ±0.029	0.0001
LT UA RI						
Pre-treatment	0.809 +0.057	0.819 +0.043	0.835 +0.048	0.837 ±0.043	0.851 ±0.045	0.001
After 1st month	0.834 +0.052	0.847 +0.042	0.777 +0.043	0.783 ±0.045	0.798 ±0.039	0.0001
After 1-3 months	0.845 +0.048	0.857 +0.041	0.760 +0.041	0.767 ±0.045	0.772 ±0.042	0.0001
After 3-6 months	0.860 +0.048	0.877 +0.042	0.732 +0.040	0.732 ±0.041	0.750 ±0.037	0.0001
Mean UA RI						
Pre-treatment	0.825 +0.54	0.817 +0.037	0.833 +0.044	0.837 ±0.042	0.835 ±0.042	0.014
After 1st month	0.845±0.0 54	0.844 +0.039	0.778 +0.040	0.786 ±0.042	0.797 ±0.037	0.0001
After 1-3 months	0.854±0.0 52	0.856 +0.038	0.758 +0.039	0.766 ±0.045	0.769 ±0.035	0.0001
After 3-6 months	0.867±0.0 50	0.876 +0.040	0.732 +0.033	0.733 ±0.039	0.749 ±0.030	0.0001

Significant difference between the two independent means using students' T-test at 0.05 level.

Significant difference between two independent means using paired T-test at 0.05 level.

Significant difference among more than two independent means using ANOVA test at 0.05 level.

Table 3. The comparison of uterine arteries pulsatility indices among different study groups.

	Estrofem Oral 1x2	Vagifem 25 mcg1x1	Sildenafil 25mg 1x3 Vaginal	Pentoxifylli ne +vit E Oral	Pentoxifylline Vaginal Gel	P value
RT UA PI						
Pre-treatment	0.833 ±0.227	1.749 ±0.205	1.739 ±0.126	1.816 ±0.128	1.764 ±0.193	0.205
After 1st month	0.864 ±0.251	1.810 ±0.235	1.664 ±0.096	1.670 ±0.122	1.603 ±0.202	0.0001
After 1-3 months	0.869 ±0.260	1.832 ±0.231	1.582 ±0.153	1.581 ±0.152	1.506 ±0.228	0.0001
After 3-6 months	0.954 ± 0.293	1.876 ±0.246	1.486 ±0.149	1.405 ±0.140	1.415 ±0.197	0.0001
LT UA PI						
Pre-treatment	1.838 ±0.246	1.747 ±0.189	1.797 ±0.137	1.818 ±0.144	1.779 ±0.240	0.274
After 1st month	1.828 ±0.216	1.807 ±0.218	1.668 ±0.104	1.680 ±0.134	1.612 ±0.207	0.0001
After 1-3 months	1.889 ±0.253	1.835 ±0.251	1.597 ±0.146	1.589 ±0.161	1.506 ±0.230	0.0001
After 3-6 months	1.958 ±0.298	1.865 ±0.261	1.496 ±0.150	1.392 ±0.158	1.413 ±0.192	0.0001
Mean UA PI						
Pre-treatment	1.835 ±0.222	1.748 ±0.193	1.795 ±0.128	1.817 ±0.135	1.771 ±0.212	0.211
After 1st month	1.846 ±0.223	1.809 ±0.223	1.666 ±0.099	1.675 ±0.127	1.607 ±0.204	0.0001
After 1-3 months	1.879 ±0.241	1.834 ±0.238	1.589 ±0.148	1.585 ±0.154	1.506 ±0.228	0.0001
After 3-6 months	1.956 ±0.286	1.871 ±0.251	1.491 ±0.149	1.399 ±0.148	1.414 ±0.193	0.0001

Significant difference between the two independent means using students' T-test at 0.05 level.

Significant difference between two independent means using paired T-test at 0.05 level.

Significant difference among more than two independent means using ANOVA test at 0.05 level.

4. Discussion

In It is well knowledge that having a thin endometrium might have a detrimental effect on a woman's ability to have children. Since this illness is currently difficult to cure, further substantial research is going to be required in the future to better understand and manage persons who have a "thin" endometrium. A healthy embryo, a receptive endometrium, proper embryo endometrial cross-talk, and appropriate mother immune protection are all essential for successful implantation **(Afaf T and Mohamed, 2020 [9])**. In spite of advancements in assisted reproductive technologies, there has been hardly any improvement in the rates of implantation and conception **(Scarpellini and Sbracia, 2020 [10])**. Numerous studies are of the opinion that when infertility lasts for more than three years in both men and women, patients' core and overall fertility quality of life, psychological health,

and perceived treatment-related quality of life are all significantly diminished **(Zurlo et al., 2019 [11])**.

When it comes to the estrogen supplements, the findings of this study have been validated by the findings of Cetinkaya and colleagues, who administered estrogen vaginally at a dosage of 25 milligrams each day beginning on the fourth day of the cycle and continuing for the next 15 days. They found a significant increase in endometrial thickness in the estrogen + clomiphene citrate group compared to the estrogen + clomiphene citrate group on the day of ovulation, but there was no change in the pregnancy rate **(Cetinkaya and Kadanali, 2012 [12])**. Al-Kady et al. treated infertile individuals with thin endometrium with estradiol (E2) therapies to enhance endometrial growth regardless to the pregnancy rate **(Al-Kady et al., 2021 [13])**, Although the findings of the current study contradict those of Garcia-Velasco et al., 2016 **(Garcia-**

Velasco et al., 2016 [14]), who discovered that the oral route is the preferred prescription strategy for estradiol in patients with poorly receptive endometrium with regard to the endometrium thickness and pregnancy rate; this discrepancy may be explained by the fact that Garcia-Velasco et al. conducted their research by searching MEDLINE, E Concerning Sildenafil, the findings of the most recent research indicated that this medication, when administered vaginally to female patients whose endometriums were thin and poorly vascularized, resulted in an increase in both the endometrial thickness and the percentage of successful pregnancies. This discovery has been corroborated by Ranisavljevic et al., who published their findings in 2019, and they agreed with the findings of the present study in that sildenafil can enhance endometrial thickness (**Ranisavljevic et al., 2019 [15]**).

On the other side, Acharya and

colleagues reported that the endometrial thickness of those who were treated with pentoxifylline and vitamin E increased, and they also found that the pregnancy rate was increased to forty percent (**Acharya et al. 2009 [16]**). Despite the fact that Cicek and colleagues discovered that vitamin E supplementation might increase endometrial thickness in women with unexplained infertility but not implantation or continued pregnancy rates (**Cicek et al., 2012 [17]**), which goes against the study results, the increasing in the implantation and pregnancy rates in the current study could be explained by the effect of oral pentoxifylline that has been added to vitamin E.

6- Conclusion

The endometrial thickness was discovered to be a poor indicator of endometrial receptivity. On the other hand, the uterine and the sub-endometrial flow resistance indices were discovered to be good indicators

of endometrial receptivity. Finally, the uterine artery and the sub-endometrial flow pulsatility indices were discovered to be perfect indicators of endometrial receptivity.

The medications that make the endometrium thicker don't always make it more vascular or receptive to fertilized eggs.

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Author Contribution

Alaa T. Tawfeeq performed the study, and Muayad S. Abbood Mufeda A. Jwad supervised the work .

Conflict of Interest

The authors declare no conflict of interest .

Ethical Clearance

The study was approved by the Ethical Approval Committee.

Financial Disclosure

There is no financial disclosure.

Ethical Clearance

The study was approved by the Ethical Approval Committee

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