

Correlation Between Vascularity Index And Pregnancy Rate During Improve Endometrial Receptivity In Thin Poorly Vascularized Endometrium Therapy

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Abstract

Background: Pregnancy has been one of life's great mysteries. The endometrium is where life begins, and a receptive endometrium lies at the crossroads of menstruation and pregnancy.

Aim of the study: To evaluate the effects of different medical drugs used routinely to improve endometrial thickness, vascularity, and pregnancy rates and to find out the best medical protocol could be used to improve endometrial thickness, vasculature, and pregnancy rate for patient with thin and poorly vascularized endometrium regardless the cause.

Materials and methods: The study was carried out on 200 infertile women who have thin, poorly vascularized endometrium, after they matched the inclusion and exclusion criteria, those patients were divided randomly into five groups; 40 patient in each group, group A received esterofem oral 2mg tablet every 12 hours from day 2 of menstrual cycle till the day of ovulation trigger, group B received vagifem vaginal tablets 25 microgram from the fourth day of menstrual cycle for 15 days or till the day of ovulation trigger, group C received sildenafil citrate gel 3 gm which containing 37.5 mg sildenafil every 12 hours from the 2nd day of menstruation till the day of ovulation trigger, group D received pentoxifylline (oral 800 mg daily) with vitamin E (oral 400 IU daily) during the 6 cycles (this study period), and group E received 4 gm of pentoxifylline vaginal gel which is containing 200 mg pentoxifylline daily which was timed to be 3 hours before intercourse from the 7th day of menstrual cycle till day 21 of the cycle. The endometrial thickness, vascularity zones, sub endometrial flow and both uterine arteries resistance and pulsatility indices measured at mid cycle (day 11-14) on monthly basis for 6 cycles or till positive pregnancy test was achieved.

Results: The study showed that the mean of endometrial thickness before starting treatment for esterofem, vagifem, vaginal sildenafil, pentoxifylline + vitamin E, and vaginal pentoxifylline gel groups were (4.770±0.842, 4.725±0.933, 4.663±0.996, 5.002±0.993, and 4.855±1.138) respectively, after one month of treatment the means of the mentioned groups respectively changed to (5.173±0.736, 5.620±0.776, 5.425±1.016, 5.403±0.864, and 5.373±1.095) which was a significant change. 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 pentoxifylline+vit E group, followed by sildenafil, then esterofem and vagifem groups who showed the highest resistance indexes 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 esterofem and vagifem groups who showed the highest resistance indexes for the left uterine artery among the study groups. 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 esterofem and vagifem groups showed the highest pulsatility indexes for the right uterine artery among the study groups.

Conclusions: Pentoxifylline vaginal gel, pentoxifylline tablet plus vitamin E capsule, and Sildenafil vaginal gel are found to be able to improve the vascularity indexes of endometrium and uterine arteries, improve the endometrial thickness, and enhance the pregnancy rates for patients with thin poorly vascularized endometrium with no serious adverse events.

Keywords: Endometrial Receptivity; Thin Poorly; Vascularized Endometrium; Pentoxifylline

INTRODUCTION

One of the great mysteries of life has long been pregnancy. Life originates in the endometrium, and a receptive endometrium is situated where menstruation and pregnancy meet (Afaf T. and Mohamed, 2020). When a healthy blastocyst enters the uterus, the endometrial lining reaches its greatest receptivity synchronously, allowing it to adhere, attach, invade, and develop in safety until parturition. (Scarpellini and Sbracia, 2020). However, it is not always a

perfect world, especially when it comes to human reproduction. For every successful pregnancy, there are numerous fertilized eggs that either implant as clinical or subclinical pregnancies or never have the opportunity to interact with the endometrium, leading to infertility. (Jayakumaran, et al., 2021). Failure to implant an embryo may result from uterine, embryonic, or particular infertility treatment protocol issues (Abbas, et al., 2020). A unique, nearly immortal tissue called the endometrium regenerates repeatedly for the precise purpose of ensuring the survival of our species. (Guo, et al., 2022). Despite advances in assisted reproductive technologies over the past four decades, some patients remain who fail to achieve healthy receptive endometrium (Cicinelli, et al., 2021). The receptive endometrium is a healthy uterine environment in which endometrial cells are transformed into decidua cells, which are suitable for blastocyst implantation, and the placenta grows rapidly (Meyer and Zenclussen, 2020). When there is no visible physical abnormality in the endometrium, these measures have used as an indicator of the receptivity of the endometrium receptivity (Sadek et al., 2022), (Krief et al., 2019). It's generally understood that the proper thickness of endometrial and vascularity are required for a successful pregnancy, and multiple theses have reported poor pregnancy scores in women with weak, poorly vascularized endometrium (Kaye et al., 2021). Although physicians disagree on the ideal endometrial thickness for conception, there is agreement that endometrial thickness less than 7 mm on ultrasound is typically regarded sub-optimal for embryo transfer and is linked to a lower chance of pregnancy (Alaa, et al., 2021).

The aim of this study: was to evaluate the effects of different medical drugs used routinely to improve endometrial thickness, vascularity, and pregnancy rates.

Patients, Materials & 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 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 (Partners with azoospermia, sever oligo astheno terato spermia, and / or male partner with sexual dysfunction).
- 8- Patients with any tubal factor that is related to infertility (bilateral tubal blockage).

Consent procedure:

Informed consent was given to every patient. To confirm that potential research subjects or their authorized representatives are fully informed about the nature and purpose of the clinical study, the possible risks and benefits of participating in the study, as well as their rights as research subjects, the investigator set up an appropriate informed consent process. Prior to completing any study-specific procedures on a subject, the investigator received written, signed informed permission from each subject, or the subject's authorized representative. The original, duly-signed consent form was kept by the investigator. 40 patients were required in each group to achieve an alpha error of 5% and beta error of 20%. Thus ,40 patients in each group was considered sufficient. Enrolled (recruitment) Data, patient characteristics {Case record from (CRF)}: During first visit, all patients was undergoing complete clinical examination and full assessment including weight, Hight, body mass index, detailed history, hormonal assay, husband seminal fluid analysis, and abdominal and transvaginal ultrasound. Each patient had a Case Record From (CRF) in which the following data was recorded: Sample was prepared by dissolving 2000 mg of pentoxifylline in 40 Hypermellous (H.M) gel ,500 mg of sildenafil citrate in 40g of H.M gel. All preparations were prepared with mechanical stirring and temperature gradually increased to 60C for about 30 min and then cooling to 25C with continuous mechanical stirring, The prepared gels were placed in wide-mouth plastic containers with parafilm over the mouth, and a screw-capped plastic lid was placed on top. the preparations were kept in cool place (not above 25c)

Study Design:

Randomized controlled prospective clinical trials.

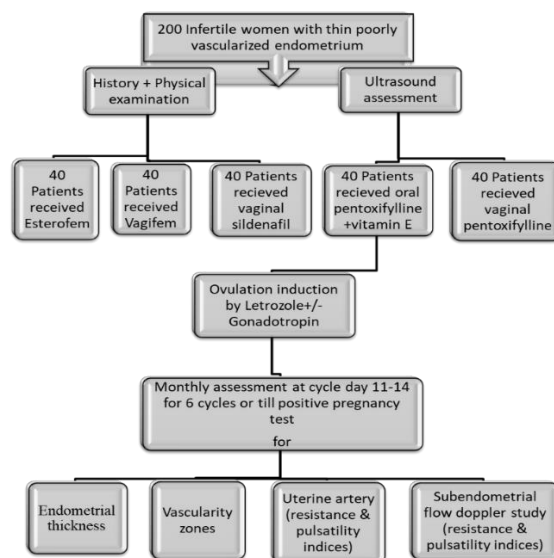


Figure3.1. The Study Design.

The procedure

In the present study, 200 infertile patients were included, all had thin poorly supplied endometrium regardless of the cause, after they matched the inclusion and exclusion criteria, these ladies were divided into five groups randomly; 40 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 menstrual cycle till the day of ovulation trigger during the 6 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 microgram self-administered vaginally at fixed time daily from the fourth day of menstrual cycle for 15 days or till the day of ovulation trigger during the 6 cycles (the study period) /or till the patient gets 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 contains 37.5 mg sildenafil every 12 hours administered via prefilled syringe by self-administration in lithotomy position from the 2nd day of menstruation till the day of ovulation trigger during the 6 cycles (the study period) /or till the patient gets pregnant.

Group 4:

Is the study group that consists of 40 patients with thin poorly vascularized endometrium who received pentoxifylline (oral 800 mg daily) with vitamin E (oral 400 mg twice daily) during the 6 cycles (the study period) /or till the patient gets pregnant.

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 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 till day 21 of the cycle during the 6 cycles (the study period) /or till the patient gets pregnant.

Those patients were assessed for endometrial thickness using the two-dimensional transvaginal ultrasonography at midcycle, (the greatest distance between each myometrium-endometrium interface via the uterine longitudinal axis).

RESULTS

The study showed that the mean of endometrial thickness before starting treatment for esterofem, vagifem, vaginal sildenafil, pentoxifylline + vitamin E, and vaginal pentoxifylline gel groups were (4.770±0.842, 4.725±0.933, 4.663±0.996, 5.002±0.993, and 4.855±1.138) respectively, after one month of treatment the means of the mentioned groups respectively changed to (5.173±0.736, 5.620±0.776, 5.425±1.016, 5.403±0.864, and 5.373±1.095) which was a significant change.

While the means of endometrium thickness after 1-3 months of treatment for the mentioned groups respectively turned to (5.593±0.600,6.370±0.816, 5.882±0.985, 5.718±0.840, and 5.925±1.182) which was a highly significant change. Finally, after 3-6 months of treatment the means of endometrium thickness for those mentioned groups respectively changed to (6.875±0.561,7.760±0.549, 6.770±0.698,7.100±0.509,and6.823±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 positive correlation between endometrial thickness and month of treatment by each of the study groups drugs (estrofem, vagifem 25 mcg 1x1, vaginal sildenafil 25mg 1x3, oral pentoxifylline+vit E and pentoxifylline vaginal gel).

Table 1: The Comparison Of Treatment Course Duration To Achieve Adequate Endometrial Thickness Among Different Study Groups

	Estrofem Oral 1x2	Vagifem 25 mcg 1x1	Sildenafil 25mg 1x3 Vaginal	Pentoxifylline+vit E Oral	Pentoxifylline Vaginal Gel	P value
Endometrial Thickness (mm)						
Pre-treatment	4.770±0.84	4.725±0.93	4.663±0.99	5.002±0.99	4.855±1.13	0.582
After 1 st month	5.173±0.73	5.620±0.77	5.425±1.01	5.403±0.86	5.373±1.09	0.299
After 1-3 months	5.593±0.60	6.370±0.81	5.882±0.98	5.718±0.84	5.925±1.18	0.002
After 3-6 months	6.875±0.56	7.760±0.54	6.770±0.69	7.100±0.50	6.823±0.70	0.000
	2	3	6	3	8	
	6	6	6	4	5	
	0	6	5	0	2	#
	1	9	8	9	3	1#

^Significant difference between two independent means using Students-t-test at 0.05 level.
^Significant difference between two dependent means using Paired-t-test at 0.05 level.
#Significant difference among more than two independent means using ANOVA-test at 0.05 level.

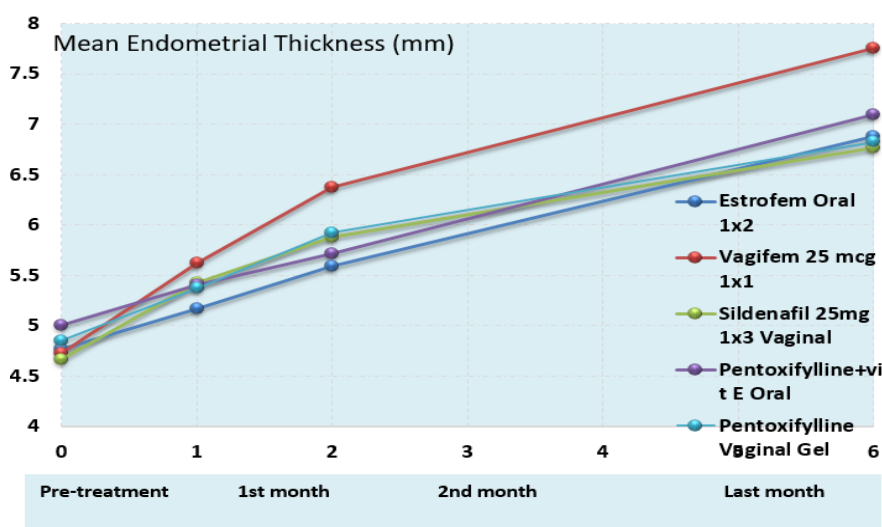


Figure 1: The Comparison Of Treatment Course Duration To Achieve Adequate Endometrial Thickness Among Different Study Groups

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 pentoxifylline+vit E group, followed by sildenafil, then estrofem and vagifem groups who showed the highest resistance indices for the right 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). 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 indices 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 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 indexes of uterine artery during treatment course among the study group, table 2 figures 2,3, and 4.

Table 2 The Comparison Of Uterine Arteries Resistance Indexes Among Different Study Groups.

	Estrofem Oral 1x2	Vagifem 25 mcg 1x1	Sildenafil 25mg 1x3 Vaginal	Pentoxifylline +vit E Oral	Pentoxifylline 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	0.010#
After 1 st 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 1 st 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±0.054	0.817±0.037	0.833±0.044	0.837±0.042	0.851±0.042	0.014#
After 1 st month	0.845±0.054	0.844±0.039	0.778±0.040	0.786±0.042	0.797±0.037	0.0001#
After 1-3 months	0.854±0.052	0.856±0.038	0.758±0.039	0.766±0.045	0.769±0.035	0.0001#
After 3-6 months	0.867±0.050	0.876±0.040	0.732±0.033	0.733±0.039	0.749±0.030	0.0001#

^Significant difference between two independent means using Students-t-test at 0.05 level.
^Significant difference between two dependent means using Paired-t-test at 0.05 level.
#Significant difference among more than two independent means using ANOVA-test at 0.05 level.

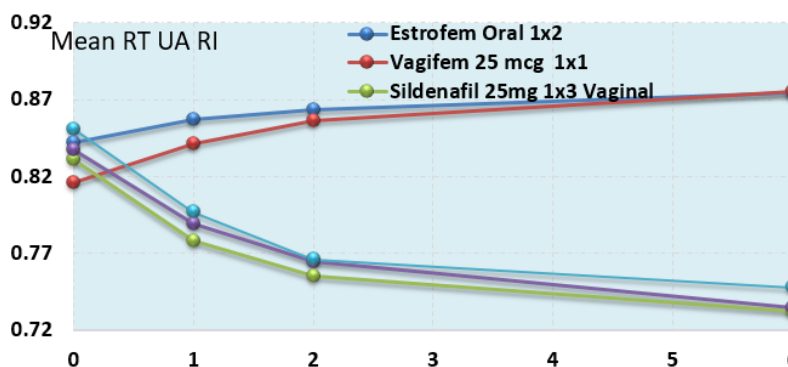


Figure 2. The Comparison Of The Mean Of Right Uterine Arteries Resistance Indexes Among Different Study Groups.

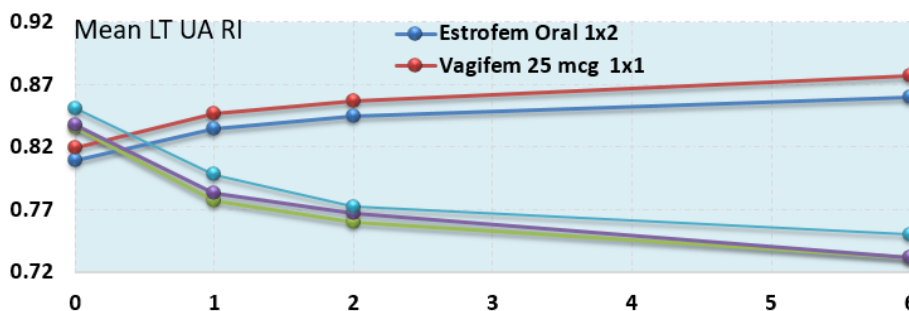


Figure 3. The Comparison Of The Mean Of Left Uterine Arteries Resistance Indexes Among Different Study Groups.

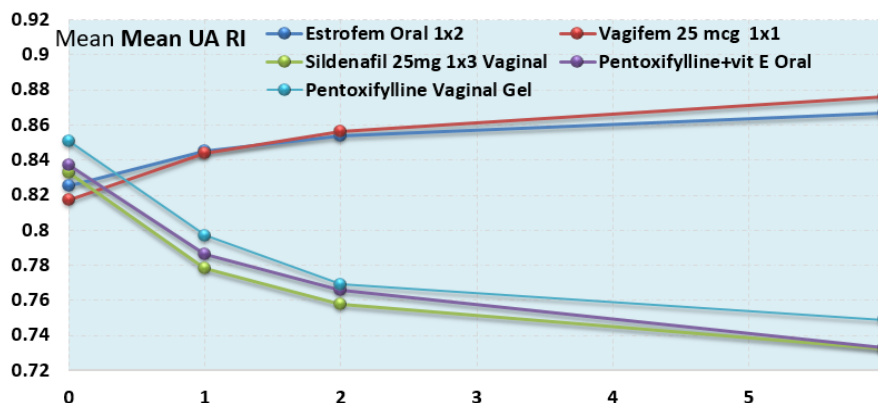


Figure 4. The Comparison Of The Mean Of Uterine Arteries Resistance Indexes Among Different Study Groups.

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 indeces for the right uterine artery among the study groups (unlike other drugs in the study vagifem and esterofem 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 indeces for the right uterine artery among the study groups (unlike other drugs in the study vagifem and esterofem has shown to increase the pulsatility index instead of improving it), the mean of uterine arteries pulsatility indeces showed the same results as a significant decrease in the mean pulsatility indeces scored by pentoxifylline + vit E, pentoxifylline gel, and sildenafil during treatment course, while estrofem and vagifem groups gave significant increase in the pulsatility indeces of uterine artery during treatment course, table 3.

Table 3: The Comparison Of Uterine Arteries Pulsatility Indeces Among Different Study Groups.

	Estrofem Oral 1x2	Vagifem 25 mcg 1x1	Sildenafil 25mg 1x3 Vaginal	Pentoxifylline +vit E Oral	Pentoxifylline Vaginal Gel	P value
RT UA PI						
Pre-treatment	1.833±0.227	1.749±0.205	1.793±0.126	1.816±0.128	1.764±0.193	0.205
After 1 st month	1.864±0.251	1.810±0.235	1.664±0.096	1.670±0.122	1.603±0.202	0.0001#
After 1-3 months	1.869±0.260	1.832±0.231	1.582±0.153	1.581±0.152	1.506±0.228	0.0001#
After 3-6 months	1.954±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 1 st 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 1 st 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 two independent means using Students-t-test at 0.05 level.						
^Significant difference between two dependent means using 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 sub endometrial flow resistance indeces achieved after treatment was in the pentoxifylline gel group followed by the results achieved by pentoxifylline+vit E group, then by vaginal sildenafil, and finally, vagifem, and estrofem, groups who showed the highest resistance indeces for the sub endometrial flow 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 sub endometrial flow pulsatility indeces, the study showed that the lowest mean of sub endometrial flow pulsatility index achieved after treatment was in the pentoxifylline gel group followed by the results achieved by pentoxifylline+vit E group, then by vaginal sildenafil, and finally, vagifem, and estrofem, groups who showed the highest pulsatility indeces for the sub endometrial flow among the study groups (unlike other drugs in the study vagifem and esterofem has shown to increase the pulsatility index instead of improving it), table 4

Table 4: The Comparison Of Subendometrial Blood Flow Indeces Among Different Study Groups.

	Estrofem Oral 1x2	Vagifem 25 mcg 1x1	Sildenafil 25mg 1x3 Vaginal	Pentoxifylli ne+vit E Oral	Pentoxifylli ne Vaginal Gel	P value
Sub Endometrial Flow RI						
Pre-treatment	0.745±0.033	0.752±0.032	0.790±0.021	0.793±0.022	0.808±0.023	0.0001#
After 1 st month	0.771±0.037	0.767±0.035	0.805±0.230	0.761±0.042	0.777±0.028	0.397
After 1-3 months	0.780±0.043	0.779±0.031	0.743±0.034	0.739±0.036	0.741±0.039	0.0001#
After 3-6 months	0.815±0.045	0.797±0.033	0.729±0.038	0.695±0.052	0.705±0.046	0.0001#
Sub Endometrial Flow PI						
Pre-treatment	1.392±0.188	1.308±0.113	1.366±0.086	1.373±0.084	1.443±0.136	0.0001#
After 1 st month	1.441±0.158	1.346±0.135	1.300±0.078	1.284±0.088	1.352±0.140	0.0001#
After 1-3 months	1.460±0.182	1.374±0.121	1.257±0.094	1.249±0.100	1.297±0.147	0.0001#
After 3-6 months	1.542±0.170	1.401±0.115	1.201±0.067	1.173±0.090	1.227±0.120	0.0001#
^Significant difference between two independent means using Students-t-test at 0.05 level.						
^Significant difference between two dependent means using Paired-t-test at 0.05 level.						
#Significant difference among more than two independent means using ANOVA-test at 0.05 level.						

The present study showed that no women with endometrial thickness of less than 7 mm got pregnant during the study period follow up. On other hand, for those women who succeeded to achieve endometrial thickness of equal or more than 7 mm, no one got pregnant after one month of treatment with any of the studied drugs, while 4.9% of them got pregnant after 2 months of treatment, and 18.8% , 9.7%, 2.1% ,2.9% of them got pregnant after 3,4,5,6 months of treatment in the study consecutively.

For estrofem group, 4 patients got pregnant which represents 19% of those who achieved endometrial thickness of equal or more than 7 mm (one after 5 months and three after 6 months which indicates that this modality of treatment is time consuming if compared to other drugs in the study).

For vagifem group, 4 patients got pregnant which represents 10.3% of those who achieved endometrial thickness of equal or more than 7 mm.

For sildenafil group, 9 patients got pregnant which represents 42.9% of those who achieved endometrial thickness of equal or more than 7 mm.

For pentoxifylline + vit E group, 18 patients got pregnant which represents 52.9% of those who achieved endometrial thickness of equal or more than 7 mm.

And finally, for Pentoxifylline gel group, 23 patients got pregnant which represents 79.3% of those who achieved endometrial thickness of equal or more than 7 mm, table 4.10.

Table 5: The Correlation Between Endometrial Thickness And Pregnancy Rates During Treatment Coarse Of Different Studied Drugs

		Post treatment Endometrial thickness				P value
		=>7.0mm		<7.0mm		
		No.	%	No.	%	
Total						
Pregnancy	Yes	58	40.3	-	-	0.0001*
	No	86	59.7	56	100	
Pregnancy after (month)	2	7	4.9			
	3	27	18.8			
	4	14	9.7			
	5	3	2.1	-	-	
	6	7	4.9	-	-	
Estrofem Oral 1x2						
Pregnancy	Yes	4	19.0	-	-	0.045*
	No	17	81.0	19	100	
Pregnancy after (month)	5	1	4.8	-	-	
	6	3	14.3	-	-	
Vagifem 25 mcg 1x1						
Pregnancy	Yes	4	10.3	-	-	0.736
	No	35	89.7	1	100	
Pregnancy after (month)	5	2	5.1	-	-	
	6	2	5.1	-	-	
Sildenafil 25mg 1x3 Vaginal						
Pregnancy	Yes	9	42.9	-	-	0.001*
	No	12	57.1	19	100	
Pregnancy after (month)	2	3	14.3	-	-	
	3	6	28.6	-	-	
Pentoxifylline+vit E Oral						
Pregnancy	Yes	18	52.9	-	-	0.016*
	No	16	47.1	6	100	
Pregnancy after (month)	3	5	14.7	-	-	
	4	7	20.6	-	-	
	5	2	5.9	-	-	
	6	4	11.8	-	-	
Pentoxifylline Vaginal Gel						
Pregnancy	Yes	23	79.3	-	-	0.0001*
	No	6	20.7	11	100	
Pregnancy after (month)	2	2	6.9	-	-	
	3	14	48.3	-	-	
	4	7	24.1	-	-	

*Significant difference between percentages using Pearson Chi-square test (χ^2 -test) at 0.05 level.

DISCUSSION:

The study showed that the lowest mean of resistance index among study groups was achieved by the Pentoxifylline + vit E group which was comparable to the results achieved by Pentoxifylline gel group and vaginal sildenafil group, all those drugs gave significant decrease in the resistance indeces of uterine artery during treatment coarse, then Estrofem and Vagifem groups who showed the highest resistance indeces and gave significant increase in the resistance indeces of uterine artery during treatment coarse among the study group Regarding the uterine arteries pulsatility index, the study also showed that the mean of uterine arteries pulsatility indeces showed a significant decrease in the mean

pulsatility indices scored by Pentoxifylline + vit E, Pentoxifylline gel, and Sildenafil during treatment course, while estrofem and vagifem groups gave significant increase in the pulsatility indices of uterine artery during treatment course.

Regarding the general effect of vascularity indices changes on pregnancy rates, the results showed that women who managed to get pregnant during the treatment period, were those who had achieved the lowest resistance and pulsatility indices for uterine arteries accompanied with endometrial thickness of equal or more than 7mm, while the women who scored higher resistance and pulsatility indices accompanied with endometrial thickness of equal or more than 7mm were less likely to get pregnant, and that explained the lower pregnancy rate among vagifem and estrofem groups comparing to the other groups (Pentoxifylline gel, Pentoxifylline + vit E, and sildenafil), this conclusion supported by the finding of Tong et al. who found that the ultrasonographic endometrial blood flow classification, spiral artery blood flow parameters, and uterine artery blood flow parameters can be effective indices for evaluating endometrial receptivity, and they have a certain clinical significance in evaluating the pregnancy outcome as the RI and PI of the spiral artery and uterine arteries in the non-pregnancy group were higher than those in the pregnancy group, besides the differences in the endometrial classification and sub endometrial blood flow classification between the two groups were statistically significant, and Wang et al. who found that the endometrial vascularization index, flow index and vascularization flow index have significant value in evaluation the endometrial receptivity, also it agreed with the finding of Maged et al. who found that the higher endometrial volume and sub endometrial flow perfusion were associated with pregnancy (Tong et al., 2020), (Wang et al., 2020), (Maged et al., 2019). The current result also supported by Ibrahim, El-Mandooh, Mohammed Gad and Al Hariri, who found that the Doppler parameters are useful tools to assess endometrial receptivity in unexplained infertility patients and their study found that Uterine, Ovarian, subendometrial arteries pulsatility index (PI) and resistance index RI measured on the day of embryo transfer higher than fertile women and have value in judging endometrial receptivity and predict the final outcome of IVF/ ICSI- ET. Uterine, ovarian and sub endometrial blood flow assessed by measuring PI, RI of these arteries was impaired in unexplained infertility patients compared to fertile women. Also, uterine arteries PI, ovarian and sub endometrial arteries PI, RI differ in pregnancy outcome in unexplained infertility patients undergoing ICSI (Ibrahim et al., 2020). Besides to what we have mentioned above to support the current study finding regarding the value of the doppler study for uterine arteries and sub endometrial flow in assessment the endometrial receptivity, a more interesting theory proposed by the Indian researcher Sindhu 2021 who found that the uterine artery doppler is a non-invasive, cost-effective useful add-on tool for routine endometrial evaluation and can be a good predictor for screening intrauterine pathology and valuable in decision making for pre-IVF hysteroscopy, in his study he categorized the women who have endometrial pathology by hysteroscope as group 1 and women who had normal endometrial cavity by hysteroscope as group 2, Both the groups were compared for pre hysteroscopy uterine artery Doppler parameters, resistivity index and pulsatility index, further clinical pregnancy rate and miscarriage rate were determined in both groups, he found that both the groups were comparable for age, body mass index, duration, and type of infertility. Mean RI and PI was significantly higher in group 1 as compared to group 2, and since not all endometrial pathology could be assessed by ultrasound and since the endometrial pathology could decrease the receptivity of endometrium regardless the thickness, this may explain the poor pregnancy outcome for some of the patients in the current study who had good endometrial thickness with high uterine arteries pulsatility and resistivity indices (Sindhu, 2021), and based on that we could strongly recommend the uterine arteries doppler study as a predictor for endometrial receptivity and as an easy tool that help us dispense with the more complicated methods of diagnosis, and we can conclude that the drugs used in the current study that actively reduced the uterine arteries pulsatility and resistivity indices may also minimize the effect of some undiagnosed endometrial pathology on the receptivity and overcomes its effects.

Regarding exogenous estrogen supplements groups (estrofem and vagifem) who had the highest resistance and pulsatility indices with poor pregnancy rates among study groups in spite of the good endometrial thickness that could be achieved especially for vaginal form, speaking about this finding, Dogan, Yildiz, Temizkan and Pulatoglu also found that there is statistically significant difference between endometrial, ovarian, uterine artery blood flow resistance in ovulatory and anovulatory cycles, blood flow resistance was found to be increased in anovulatory patients and increased E2 levels in anovulatory cycles were related to endometrial line thickness and endometrial volume, which support the current study finding and could explain the poor pregnancy rates for the estrogen supplement groups in the study by the anovulatory cycles, the uterine artery, and endometrial blood flow high resistance that combine the increased estrogen level (Dogan, et al, 2016), Dören, Rübige, Coelingh Bennink and Holzgreve on other had tested the effect tibolone (a synthetic estrogen replacement steroid) the vascular resistance and found that tibolone had increased the resistance index of arcuate arteries (Dören, Rübige, Coelingh Bennink and Holzgreve, 2000), Patil, Venkatappa and Patil used two forms of estrogen supplement oral and local (transdermal) and found that there was no statistical difference in the endometrial blood flow between the study groups which also agreed with the results of the current study since two estrogen forms in this study shows a comparable uterine arteries and subendometrial flow dynamics among other drugs used in the study (Patil, et al, 2021). Several other studies disagreed with the current study result regarding increase the resistance and pulsatility indices after exogenous estrogen supplement forms like De Ziegler, Bessis and Frydman, and Doren, Schwenkhagen, Schneider and Holzgreve, this may be due to most of these studies were carried out on either post-menopausal women or women with inactive or nonfunctioning ovaries who have very low endogenous estrogen level unlike the women in the current study or could be due to the short course and lower dose of estrogen used in this study may be not enough to cause the sufficient vasodilation effect of estrogen supplement that improve the uterine and endometrial blood supply (De Ziegler, et al 1992; Doren et al, 1995).

Regarding sildenafil, many studies have shown that it could widen the endometrial vasculature by its effects on the smooth muscles of the arteries and improve uterine and endometrial blood flow dynamics, which agreed with the current study results (Moini A. et al., 2020; Abbas et al., 2021). About pentoxifylline, it used in two forms in this study: as vaginal gel alone and as oral tablet with vitamin E capsule, both forms improved endometrial receptivity as we mentioned above and the vaginal gel scored the best regarding the pregnancy rates among this study drugs followed by oral form combined by vitamin E capsule. Regarding pentoxifylline oral tablet and vitamin E capsule several studies supported the current findings, Akbari-Fakhrabadi et al. had reported that for treating a thin hypovascularized endometrium, vitamin E was combined with pentoxifylline a methylxanthine derivative can cause vasodilatation and highly improved the endometrial condition (Akbari-Fakhrabadi et al., 2018), El Nashar, Salama, El-Deen and Fayez, Patel and McGurk, on other hand also agreed with this finding, Patel and McGurk has reported that pentoxifylline with vitamin E represents an excellent option for treating radiation-induced fibrosis and has been used clinically to address vascular problems of endometrium (El Nashar, et al, 2021), (Patel and McGurk, 2018). while Ledee-Bataille et al., Cicek and colleagues documented that individuals who utilize vitamin E have enough endometrial thickness, expansion of the glandular epithelium, an increase in the number of blood vessels which add more support to the current study findings regarding the improvement of endometrial thickness and vasculature for the study group who used it (Ledee-Bataille et al., 2002). Regarding the Pentoxifylline's effect on improving the peripheral blood supply and vasculature, it has been approved as a therapy for a number of vascular diseases for more than 30 years, both orally and intravenously as it represents a non-specific inhibitor of phosphodiesterase and is part of a class of medications known as vasoactives. It increases peripheral blood flow, which improves the oxygenation of peripheral tissues, and the main medical application of pentoxifylline was to treat intermittent claudication, a kind of muscular discomfort brought on by peripheral artery disorders, these facts about its effects support the current study findings regarding improve the endometrial vasculature and uterine artery blood supply (Afaf and Mohamed, 2020; Alaa et al, 2021; Al-Kady et al, 2021; Archer et al.,2020)

Arora et al. at 2019 had compared the effect of vaginal micronized estradiol with a combination of Pentoxifylline and tocopherol (vitamin E), his study comprised 18 oocyte recipients who received vaginal micronized estradiol but did not see an improvement in endometrial conditions then for six months, the patients took Pentoxifylline (800 mg/day) and vitamin E and just like the current study findings, he decided that the later combination has a better effect on endometrial receptivity than vaginal micronized estradiol. While regarding the vaginal pentoxifylline gel, it positively improved the quality of both endometrium and sperms, first by vaginal absorption of pentoxifylline which provides the same systemic effects with lower dose and less side effects, as Peak plasma concentrations of the active metabolite (5-hydroxi Pentoxifylline) were three times higher after vaginal administration of gel than the parent medication (Pentoxifylline), this parent drug to metabolite ratio is consistent with other studies following Pentoxifylline oral (Cetinkaya and Kadanali, 2012) and intravenous administration (Cicinelli et al., 2021), (Davar et al., 2020), and second as topical formulation of pentoxifylline administered intravaginally before or after sexual activity could improve sperm mobility and increase the likelihood of pregnancy (Demir et al. 2018; Dong et al., 2021), (Espinós et al., 2021), these two ways of action may explain the high pregnancy rates for pentoxifylline vaginal gel group in the current study.

Fahmy, et al (2019) have tested the pentoxifylline PKB171 gel's local tolerability when applied intravaginally in a group of healthy female volunteers. The pharmacokinetics, safety, and acceptability of PKB171 vaginal gel in this group are being assessed for the first time in this trial. PKB171 gel administered vaginally had a favorable safety and tolerability profile, and no significant adverse events were noted at all of the trial dosages, they discovered that Pentoxifylline was quickly absorbed following vaginal delivery at dosages ranging from 100 to 200 mg, reaching peak plasma concentrations (after dose adjustment) of around 90 ng/mL at 1.5–2 h for all three doses. Peak plasma concentrations of the active metabolite (after dose adjustment) of about 200 ng/mL were reached at 2-3.3 h for the three dosages examined (Fetih et al., 2019), which agreed with the current thesis results as the pentoxifylline vaginal gel gave the best pregnancy rate after it used by female partner 3 hours before intercourse.

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