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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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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 (day11-14) on monthly basis for 6 cycles or till positive pregnancy test was achieved. Results: The study showed that 97.5% of women who received Vagifem succeed to achieve endometrial thickness ≥7.0mm, followed by 85% of group who received Pentoxifylline+vit E, 67.5% of group who received pentoxifylline vaginal gel and 52.5% of group who received sildenafil vaginally and oral estrofem (P. value: 0.0001. Pentoxifylline vaginal gel, pentoxifylline+ vitamin E capsule, and sildenafil vaginal gel have improved the vascularity indeces of endometrium and uterine arteries after starting treatment, while the prolongation of treatment period gave significant improvement of the vascularity indeces for those groups, while the vagifem and esterofem were less effective in terms of improving the vascularity indeces 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. Conclusions: Pentoxifylline vaginal gel, pentoxifylline tablet plus vitamin E capsule, and Sildenafil vaginal gel are found to be able to improve the vascularity indeces of endometrium and uterine arteries, improve the endometrial thickness, and enhance the pregnancy rates for patients with thin poorly vascularized endometrium with no seriuos 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 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

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

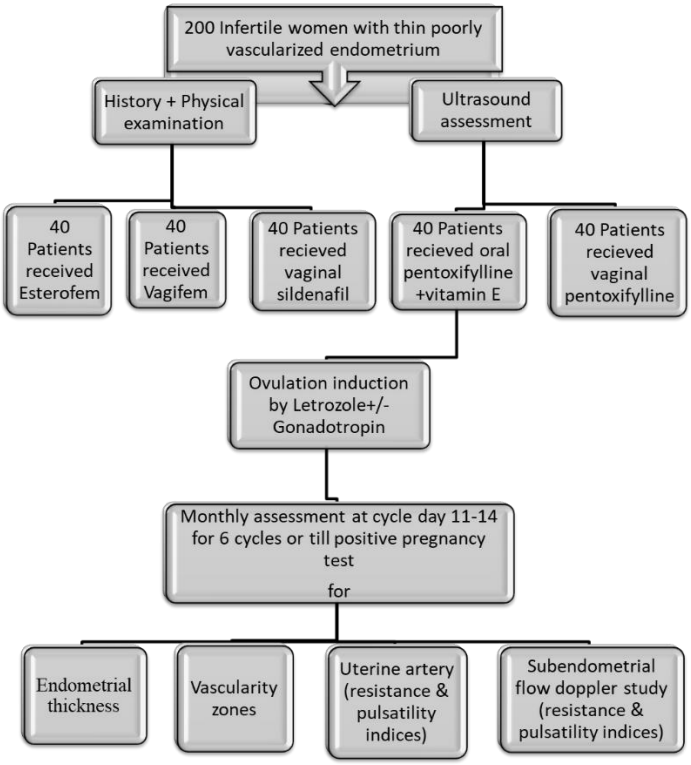

Figure 3.1. The study design

The procedure

In the present study, 200 infertile patients was included, all had thin poorly supplied endometrium regardless the cause, after they matched the inclusion and exclusion criteria, those ladies were divided into five groups randomly; 40 patient in each group:

Group 1

Is the study group that consist 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 get pregnant.

Group 2

Is the study group that consist of 40 patients with thin poorly vascularized endometrium who received Vagifem vaginal tablets 25 microgram self administrated 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 get pregnant.

Group 3

Is the study group that consist 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 6 cycles (the study period) /or till the patient get pregnant .

Group 4

Is the study group that consist 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 get pregnant.

Group 5

Is the study group that consist of 40 patients with thin poorly vascularized endometrium who received 4 gm of pentoxifylline vaginal gel which is containing 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 get 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 there was no significant difference between the four studied groups regarding the age and BMI, Table 1.

Table 1
The comparison of age and BMI among different study groups

		Estrofem Oral 1x2		Vagifem 25 mcg 1x1		Sildenafil 25mg 1x3 Vaginal		Pentoxifylline +vit E Oral		Pentoxifylline Vaginal Gel		P value
		No.	%	No.	%	No.	%	No.	%	No.	%	
Age years	20---24	14	35.0	12	30.0	9	22.5	11	27.5	7	17.5	0.327
	25---29	9	22.5	6	15.0	9	22.5	14	35.0	14	35.0	0.327
	30---34	10	25.0	11	27.5	11	27.5	12	30.0	9	22.5	0.255
	35---39years	7	17.5	11	27.5	11	27.5	3	7.5	10	25.0	0.287
	Mean±SD (Range)	28.5±5.5 (20-38)		30.0±5.9 (21-39)		30.2±5.6 (20-39)		28.1±5.0 (20-39)		30.4±5.7 (21-39)		0.224
BMI Kg/M2	Normal (<25)	9	22.5	16	40.0	12	30.0	13	32.5	14	35.0	0.545
	Overweight(=>25)	31	77.5	24	60.0	28	70.0	27	67.5	26	65.0	0.560
	Mean±SD (Range)	26.5±2.7 (20.6-29.9)		26.0±3.2 (20.0-29.8)		26.0±3.0 (20.2-29.9)		25.9±3.2 (20.0-29.8)		26.2±3.2 (20.0-29.9)		0.922

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.
^Significant difference between two independent means using Students-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 there was no significant difference between the four studied groups regarding vascularity zone before treatment and most of cases were in zone 2 (80% of esterofem group,87.5% of vagifem group,77.5% of sildenafil group, pentoxifylline oral+vit. E had75% of cases at zone 2, and 77.5 of pentoxifylline gel was in zone2) and no patients in zone 4 at all study groups. After one month from receiving the different medications, ultrasound examination was done for all participated females and showed that 82.5% of women was with 2nd zone of vascularity after one month of receiving estrofem and no one in the 4th zone. The study also showed that 87.5% of women was with 2nd zone of vascularity after one month of receiving vagifem and no one in the 4th zone. While the study showed that 82.5% of women was with 3rd zone of vascularity after one month of receiving sildenafil, 80% of women was with 3rd zone of vascularity after one month of receiving pentoxifylline+vit E and 67.5% of women was with 3rd zone of vascularity after one month of receiving pentoxifylline gel as shown in table 2.

The study also showed that 85% of women was with 2nd zone of vascularity after 1-3 months of receiving estrofem and no one in the 1st and 4th zone. The study also showed that 87.5% of women was with 2nd zone of vascularity after 1-3 months of receiving vagifem. While the study showed that 77.5% of women was with 3rd zone, and 22.5% at zone 4 of vascularity after 1-3 months of receiving vaginal sildenafil, 65% of women was with 3rd zone, and 35% on 4th zone of vascularity after 1-3 months of receiving pentoxifylline+vit E, while 32.5% of women were in 3rd zone , and 62.5% of women was with 4th zone of vascularity after 1-3 months of receiving pentoxifylline gel.

The study also showed that 82.5% of women was with 2nd zone of vascularity after 3- 6 months of receiving estrofem and no one in the 1st and 4th zone. The study also showed that 87.5% of women was with 2nd zone of vascularity after 3- 6 months of receiving vagifem. While the study showed that 75% of women was with 3rd zone and 25% on 4th zone of vascularity after 3-6 months of receiving sildenafil, 95% of women was with 4th zone, and 5 % on 3rd zone of vascularity after 3-6 months of receiving pentoxifylline+vit E and 92.5% of women was with 4th zone, and 7.5% on 3rd zone of vascularity after 3-6 months of receiving pentoxifylline gel, which indicate that the later 3 drugs has improved the vascularity zone of endometrium after starting treatment, while the prolongation of treatment period gave significant improvement of the vascularity zones as about the whole treatments groups for these drugs located in between zone 3 and 4 at the last month of treatment, unlike the estrogen drug forms (the esterofem and vagifem pills), Table 4.2.

Table 2
The Relation between the vascularity zone of endometrium and different medical drugs before and after treatment

Vascularity zone		Estrofem Oral 1x2		Vagifem 25 mcg 1x1		Sildinafil 25mg 1x3 Vaginal		Pentoxifylline+vit E Oral		Pentoxifylline Vaginal Gel		P value
		No.	%	No.	%	No.	%	No.	%	No.	%	
Pre-treatment	1	3	7.5	2	5.0	8	20.0	6	15.0	9	22.5	0.089
	2	32	80.0	35	87.5	31	77.5	30	75.0	31	77.5	0.089
	3	5	12.5	3	7.5	1	2.5	4	10.0	-	-	0.089
After 1st month	1	1	2.5	2	5.0	-	-	-	-	-	-	0.0001*
	2	33	82.5	35	87.5	6	15.0	8	20.0	2	5.0	0.0001*
	3	6	15.0	3	7.5	33	82.5	32	80.0	27	67.5	0.0001*
	4	-	-	-	-	1	2.5	-	-	11	27.5	0.0001*
After 1-3 months	1	-	-	2	5.0	-	-	-	-	-	-	0.0001*
	2	34	85.0	35	87.5	-	-	-	-	2	5.0	0.0001*
	3	6	15.0	3	7.5	31	77.5	26	65.0	13	32.5	0.0001*
	4	-	-	-	-	9	22.5	14	35.0	25	62.5	0.0001*
After 3-6 months	1	-	-	2	5.0	-	-	-	-	-	-	0.0001*
	2	33	82.5	35	87.5	-	-	-	-	-	-	0.0001*
	3	7	17.5	3	7.5	30	75.0	2	5.0	3	7.5	0.0001*
	4	-	-	-	-	10	25.0	38	95.0	37	92.5	0.0001*

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

The study showed that all women in the studied groups didn't get pregnant after one month and 1-3 months of receiving estrofem, vagifem, sildenafil, pentoxifylline plus vitamin E and pentoxifylline gel. While the study showed that 57.5% of women succeed to get pregnant after 3-6 months of receiving pentoxifylline vaginal gel, 35% of women succeed to get pregnant after 3-6 months of pentoxifylline+vit E, while 22.5% of women succeed to get pregnant after 3-6 months of sildenafil, about 10% of women got pregnant after 3-6 months of vagifem, and finally 2.5% of women got pregnant after 3-6 months of receiving estrofem tablets, Table 3

Table 3
The comparison of post treatment pregnancy rate among different studied groups

Got pregnant at		Estrofem Oral 1x2		Vagifem 25 mcg 1x1		Sildenafil 25mg 1x3 Vaginal		Pentoxifylline E Oral		Pentoxifylline Vaginal Gel		P value
		No.	%	No.	%	No.	%	No.	%	No.	%	
After 1st month	Yes	-	-	-	-	-	-	-	-	-	-	-
	No	40	100	40	100	40	100	40	100	40	100	
After1-3 months	Yes	-	-	-	-	-	-	-	-	-	-	-
	No	40	100	40	100	40	100	40	100	40	100	
After 3-6 months	Yes	1	2.5	4	10.0	9	22.5	14	35.0	23	57.5	0.0001*
	No	39	97.5	36	90.0	31	77.5	26	65.0	17	42.5	

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

Got pregnant at	Estrofem Oral 1x2		Vagifem 25 mcg 1x1		Sildenafil 25mg 1x3 Vaginal		Pentoxifylline E Oral		Pentoxifylline Vaginal Gel		P value
	No.	%	No.	%	No.	%	No.	%	No.	%	
After 1st month	-	-	-	-	-	-	-	-	-	-	-
After1-3 months	-	-	-	-	-	-	-	-	-	-	-
After 3-6 months	1	2.5	4	10.0	9	22.5	14	35.0	23	57.5	0.0001*

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

The study showed a significant difference in endometrial thickness that achieved after treatment among different studied groups with (P. value: 0.0001), 97.5% of women who received vagifem succeed to achieve endometrial thickness ≥7.0mm after treatment, followed by 85% of group who received pentoxifylline+vit E, 67.5% of group who received pentoxifylline vaginal gel and 52.5% of group who received vaginal sildenafil and estrofem. The study showed that 4 patients of each of esterofem and vagifem groups got pregnant between the 5th and 6th month of treatment, 9 patients of vaginal sildenafil group got pregnant between the 2nd and 3rd month of treatment, 18 patients of oral pentoxifylline+ vit. E got pregnant between the 3rd and 6th month of treatment, while 23 patients of vaginal pentoxifylline gel got pregnant between the 2nd and 4th month of treatment as shown in Table 4.

Table 4
The comparison of endometrial thickness that achieved after treatment among different studied groups

		Estrofem Oral 1x2		Vagifem 25 mcg 1x1		Sildenafil 25mg 1x3 Vaginal		Pentoxifylline+vit E Oral		Pentoxifylline Vaginal Gel		P value
		No.	%	No.	%	No.	%	No.	%	No.	%	
Post treatment endometrial thickness	=>7.0mm	21	52.5	39	97.5	21	52.5	34	85.0	27	67.5	0.0001*
	<7.0mm	19	47.5	1	2.5	19	47.5	6	15.0	13	32.5	0.0001*
Pregnancy	Yes	4	10.0	4	10.0	9	22.5	18	45.0	23	57.5	0.0001*
	No	36	90.0	36	90.0	31	77.5	22	55.0	17	42.5	0.0001*
Month of	2	-	-	-	-	3	33.3	-	-	2	8.7	0.0001*

pregnancy	3	-	-	-	-	6	66.7	5	27.8	14	60.9	0.0001*
	4	-	-	-	-	-	-	7	38.9	7	30.4	0.0001*
	5	1	25.0	2	50.0	-	-	2	11.1	-	-	0.0001*
	6	3	75.0	2	50.0	-	-	4	22.2	-	-	0.0001*

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

The study showed that all women who received of vagifem, vaginal sildenafil, pentoxifylline+vit E and pentoxifylline vaginal gel could get dominant follicle/s on lower doses of ovulation induction drugs (only letrozole), while all women who received estrofem needed higher doses of ovulation induction drugs (letrozole plus gonadotropins) to obtain dominant follicle/s. The study also showed that 2 of women who received estrofem suffered from withdrawal bleeding and endometrial polyp during treatment coarse. Also, the present study showed that 2 women of vagifem group, 4 women of vaginal sildenafil group, and 4 of women of pentoxifylline gel groupes developed vaginal itching. On other hand, the results showed that the women of vagifem, vaginal sildenafil, and pentoxifylline gel groupes developed vaginal discharge on the following rates 18, 8, and 12 respectively, Table 5.

Table 5
The comparison of side effects frequencies among different studied groups

		Estrofem Oral 1x2	Vagifem 25 mcg 1x1	Vaginal Sildenafil	Pentoxifylline+ vit E Oral	Pentoxifylline Vaginal Gel
Dose of ovulation induction	Higher	40	-	-	-	-
	lower	-	40	40	40	40
Dominant follicle	Obtained with high doses	40	-	-	-	-
	Obtained with lower doses	-	40	40	40	40
Side effect	Withdrawal bleeding	2	-	-	-	-
	endometrial polyp	2	1	-	-	-
	Vaginal itching	-	2	4	-	4
	Vaginal discharge	-	18	8	-	12

Discussion

It is well acknowledged that a thin endometrium has a negative impact on reproductive function. Future extensive study is needed to better understand and manage people with "thin" endometrium since this disorder is still challenging to treat. A viable embryo, a receptive endometrium, suitable embryo endometrial cross-talk, and appropriate maternal immune protection are all necessary for successful implantation (Afaf T and Mohamed, 2020). The implantation and pregnancy rates have barely changed despite breakthroughs in assisted reproductive technology (Scarpellini and Sbracia, 2020), (Guo, et al., 2022), (Goel,

et al., 2020). Numerous researchers contend that patients' core and overall fertility quality of life, psychological health, and perceived treatment-related quality of life are all considerably lowered when infertility persists for longer than three years in both men and women (Zurlo, et al., 2019). This stress is anticipated to worsen as the number of years of infertility rises, which might exacerbate psychological suffering and lead to sexual dysfunction, as shown by Dong et al. in 2021, thin and poorly vascularized endometrium is considered one of the main cause of female infertility that may lead to a long time infertility (Jayakumaran, Maldonado and Trolice, 2021), (Arora, et al. 2019) which is the main subject of this thesis.

There were no significant differences in the age, infertility years, body mass index (BMI), because all these findings were comparable among the current study groups to ensure statistical matching and reduce any variations that could affect the study's outcome so those prameters had no effects on the study results. The recent study showed that (Pentoxifylline + vit E, Pentoxifylline gel followed by sildenafil has improved the vascularity zone of endometrium after starting treatment, while the prolongation of treatment period gave significant improvement of the vascularity zones as about the whole treatments groups for these drugs located in between zone 3 and 4 at the last month of treatment, unlike the estrogen drug forms (the esterofem and vagifem pills) as vagifem tablet group had the worse vasculature zones followed by esterofem, since there is no known previous study had compared the effects of those drugs group on the vascularity zones of endometrium so we can not compare this result of current research with others. Since most of the known previous studies that dealt with the drugs studied in the current thesis had studied their effects on endometrial thickness and the pregnancy rates together, so we will discuss these two aspects together.

The current study showed that 97.5% of women who received vagifem succeed to achieve endometrial thickness ≥7.0mm, followed by Pentoxifylline+vit E group, then Pentoxifylline vaginal gel group, followed by the group who received sildenafil vaginally and oral estrofem, besides the study showed that more than half women who received Pentoxifylline vaginal gel succeed to get pregnant after 3-6 months of treatment , followed by 35% of women who treated with Pentoxifylline+vit E , then 22.5% of women who treated with Sildenafil, and about 10% of women got pregnant after 3-6 months of treatment with Vagifem, and finally 2.5% of women got pregnant after 3-6 months of receiving Estrofem tablets. Regarding the estrogen supplements, the results of this study has been supported by the findings of Cetinkaya and colleagues who had given estrogen vaginally 25 mg daily from the fourth day of the cycle for 15 days. They found a substantial increase in endometrial thickness in the estrogen + clomiphene citrate group compared to the estrogen + clomiphene citrate group on the day of ovulation, but no change in pregnancy rate (Cetinkaya and Kadanali, 2012) and Al-Kady et al. who had treated infertile individuals with thin endometrium with estradiol (E2) therapies to enhance endometrial growth regardless to the pregnancy rate (Al-Kady et al., 2021), besides, Gao et al. had found that vaginal estrogen add more beneficial effects regarding the endometrial thickness (Gao et al., 2019) and Davar et al. who considered the vaginal rout more beneficial than oral rout for estrogen

supplement (Davar, et al., 2020) regarding the endometrial thickness and pregnancy rates.

Demir et al. (2018) had found that exogeneous estrogen did not enhance clinical pregnancy rate, implantation rate, which is also supported the results of the current study which showed that the estrogen supplement groups (Esterofem and Vagifem groups) had the lowest pregnancy rates among the study drugs despite the improvement in endometrial thickness in those groups especially the vagifem group. Unlike Espinós et al. who found that there are no significant differences between micronized estradiol and estradiol valerate and oral administration of estradiol was the most effective approach for prescribing esterogen, (Espinós et al., 2021), the current study did not conduct on infertile women with chronic endometritis like them as chronic endometritis may be associated with vaginal infection which may affect the quality of vaginal rout absorption, and this may explains why the current study result went against their conclusion. Regarding Sildenafil, the current study results showed that this drug when has been used vaginally for women with thin poorly vascularized endometrium, it has improved the endometrial thickness, and pregnancy rate. This finding has been supported by Ranisavljevic et al., at 2019 who agreed with the current study findings in that sildenafil can improve endometrial thickness (Ranisavljevic et al., 2019), and Fahmy, M and S. who found that because the vascular relaxation effects of sildenafil, it can increase the thickening of the endometrium and improve the pregnancy rate (Fahmy, M and S, 2019). Also the study showed that women of vagifem, sildenafil, and pentoxifylline gel groupes developed vaginal itching on rate 5%,10%, and 10% respectively, and on other hand those women of vagifem, sildenafil, and pentoxifylline gel groupes developed vaginal discharge on the following rates respectively 45%, 20%, and 30% , these adverse effects again had been reported by many of the previous studies (Santen, et al.,, 2019;Archer et al., 2020).

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