

Effect of Sildenafil Citrate on Endometrial Preparation and Uterine Artery Blood Flow in Infertile Patients Undergoing Induction of Ovulation

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Abstract

Background: Sildenafil citrate improves the uterine artery blood flow and the endometrial thickness in women with a prior failed assisted reproductive cycle due to poor endometrial response. Sildenafil citrate can be used orally or by vaginal to improve endometrial receptivity.

Aim of Study: To evaluate the efficacy of the orally administered sildenafil citrate on the endometrial thickness and pattern, number of follicles, uterine artery blood flow and pregnancy rate in infertility patients undergoing induction of ovulation.

Patients and Methods: The study included one 150 patients who were randomized into two groups: Group A included 75 patients who were given sildenafil citrate 20mg from 8th day to 13th day of the cycle 3 times per day orally and Letrizole 2.5mg from 2nd day till 6th day of the same cycle two times per day orally, and Group B included 75 patients who were given Letrizole 2.5mg from 2nd day to 6th day of the cycle two times per day orally and placebo tablets from cycle day 8 till day 13 three times/day orally.

Results: Percentage in change in both RI and PI in both groups founded that it was statistically significant in both groups with p -value <0.001 . Biochemical pregnancy rate in both study groups was founded to be higher in group A (Sildenafil Group) than group B (Placebo Group) and was statistically significant between both groups with p -value 0.020.

Conclusion: Use of oral sildenafil in endometrial preparation for patient with poor endometrial vascularity showed better endometrial development.

Key Words: Sildenafil citrate – Endometrial – Uterine artery blood flow – Infertile patient.

Introduction

WORLD health organization defined Infertility as failure of a couple to conceive after 12 months of

regular intercourse without use of contraception in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older [1].

Infertility is growing at an alarming pace, especially in the cities according to a survey conducted by an International Institute of Population Sciences. Out of 250 million individuals estimated to be attempting parenthood at any given time, 13 to 19 million couples are likely to be infertile. Nearly 30 million couples in the country suffer from infertility, making the incidence rate 10% [1].

Embryo implantation requires an appropriate embryonic development coincident with a receptive endometrium. In clinical practice, adequate endometrial growth is required for successful implantation. The minimal endometrial thickness required for embryo transfer is 7mm at the end of follicular phase. Thin endometrium non-responsive to standard treatments is still a challenge in assisted reproductive technique (ART), which usually results in cycle cancellation and unplanned embryo cryopreservation [2].

Various strategies have been developed for the treatment of thin endometrium, including extended use of exogenous estrogen, use of low-dose aspirin, vitamin E and vaginal sildenafil citrate, electroacupuncture and application of granulocyte colony stimulation factor (G-CSF). However, a number of women with thin endometrium remain nonresponsive even these remedies have been performed [2].

Sildenafil is a specific inhibitor of type 5 phosphodiesterase so it prevents the breakdown of (cGMP) and potentiates the effects of NO on vascular smooth muscle [3]. Studies used sildenafil to improve uterine artery blood flow and sonographic

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endometrial appearance in patients with prior failed assisted reproductive cycles due to low endometrial response. Some of these studies showed a beneficial effect of sildenafil [4,5].

In the present study was to evaluate the efficacy of the orally administered sildenafil citrate on the endometrial thickness and pattern, number of follicles, uterine artery blood flow and pregnancy rate in infertility patients undergoing induction of ovulation.

Patients and Methods

This was a randomized controlled trial which was conducted at the infertility outpatient clinic in Al Hussein University Hospital from Dec. 2019 – Dec. 2021. One hundred and fifty patients were involved in our study.

The patients were divided into two groups:

Patients who were incorporated in the study were randomly allocated using a randomized computer number generation by the closed envelope method into 2 groups:

- 1- Group A: Which included 75 infertile women who received:
 - Aromatase inhibitor (Letrizole 2.5mg) for induction of ovulation for 5 days, starting from the second day of the cycle, in a dose of twice daily.
 - Sildenafil citrate (Respatio 20mg) from cycle day 8 till cycle day 13 in dose of 20mg every 8 hours.
- 2- Group B: Which included 75 infertile women who received:
 - Letrizole 2.5mg for induction of ovulation for 5 days, starting from the second day of the cycle, in a dose of twice/day.
 - Placebo tablets from cycle day 8 till cycle day 13 orally every 8 hours.

Inclusion criteria: Age: 18-35 years old, body mass index (BMI): 20-29 Kg/m², normal uterine-cavity proven by HSG or hysteroscopically, and patent both tubes proven by HSG or laparoscopically.

Exclusion criteria: Age: Less than 18 years or more than 35 years old, male factor infertility, tubal block, uterine congenital anomalies, and any contraindication to sildenafil citrate or any of the components of its formulation including: Concurrent use of organic nitrites and nitrates. Severe hepatic impairment. Severe renal impairment.

Hypotension. Recent stroke or heart attack. Hereditary degenerative retinal disorders.

All of the following done to all candidate women:

- 1- Informed consent obtained from all cases.
- 2- History taking with special emphasis to menstrual history, duration of infertility, cause of infertility.
- 3- Type of infertility whether it's primary or secondary, previous assisted reproductive techniques attempts and their outcome and history of contraception.
- 4- Physical examination: Including general examination, abdominal and pelvic examination.
- 5- Review of the patients' record including the result of HSG and or hysteroscopy or laparoscopy reports and hormonal analysis.
- 6- Treatment protocol: Patients received Letrizole 2.5mg oral dose from day 2 to day 6 of the menstrual cycle, then oral dose of sildenafil citrate 20mg 3 times daily from the day 8 of the menstrual cycle till day 13 of the same cycle.

On the day 8 of the cycle: A baseline endometrial thickness and number of follicles measured by 2D TVS. Uterine artery Doppler measured by colored doppler ultrasound.

On the day 13 of the cycle: 2D TVS was done on the day 13 to detect endometrial thickness, number of follicles. Uterine artery doppler measured by colored doppler ultrasound.

Finally a serum β hCG 2 weeks after the supposed time of ovulation to verify pregnancy.

The primary outcome measures were the endometrial thickness, number of mature follicles, uterine artery flow indices.

The secondary outcome measure was the pregnancy rate.

Statistical methods:

Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to examine the normality of numerical data distribution. Normally distributed numerical variables were presented as mean and SD and inter-group differences were compared using the unpaired *t*-test. Paired comparisons for normally distributed numerical data were done using the paired *t*-test. Skewed numerical variables were presented as median and interquartile range and between-group differences were compared non-parametrically using the Mann-

Whitney test. Paired comparisons for non-normally distributed numerical data were done using the Wilcoxon signed ranks test. Categorical variables were presented as number (%) and differences were compared using Fisher's exact test. The z-test was used to test the significance of relative benefit and related number needed to treat. *p*-value <0.05 was considered statistically significant.

Results

In our study we found that age, BMI, duration of infertility were statistically insignificant between two groups with *p*-value 0.549, 0.974 and 0.845 respectively. We found that type of infertility was statistically insignificant between two groups with *p*-value 0.720. Cause of infertility in our study mainly was due to PCO in group A (Sildenafil Group) but in group B (Placebo Group) it was unexplained, cause of infertility was insignificant between two groups with *p*-value 0.289. 29.7% of the patients included in both groups had history of ICSI and it was statistically insignificant between two groups with *p*-value 1.00 (Table 1).

Primary outcome measured in both groups on day 8 and showed that follicular count was statistically insignificant between two groups with *p*-value 0.908. Endometrial thickness in both groups was statistically insignificant between two groups when measured in day 8 with *p*-value 0.415. Uterine artery RI and PI was measured in both groups on day 8 and founded that it was statistically insignificant between two groups with *p*-value 0.454, 0.460 respectively (Table 2).

Outcomes measured on day 13 in both groups and founded that follicular count was increased in

group A than group B but was statistically insignificant between both groups with *p*-value 0.196. Endometrial thickness on day 13 measured and founded that it was higher in group A (Sildenafil Group) than group B (Placebo Group) and it was statistically significant difference between two groups with *p*-value <0.001. Uterine artery RI and PI in both groups was statistically significant between both groups with *p*-value 0.014, <0.001 respectively (Table 3).

Measuring percentage in change in primary outcome in both groups we found that percentage change in follicular number in both groups was statistically insignificant with *p*-value 0.239. Percentage of change in endometrial thickness was statistically significant between two groups with *p*-value <0.001. Percentage in change in both RI and PI in both groups founded that it was statistically significant in both groups with *p*-value <0.001 (Table 4).

Paired comparison in primary outcome in both groups on day 8 and 13 we found that in group A (Sildenafil Group) changes in follicular count, endometrial thickness, uterine artery RI and API were statistically significant from day 8 and 13 with *p*-value <0.001. In group B (Placebo Group) founded that changes in primary outcome on day 8 and 13 were also statistically significant with *p*-value <0.001 (Table 5).

Biochemical pregnancy rate in both study groups was founded to be higher in group A (Sildenafil Group) than group B (Placebo Group) and was statistically significant between both groups with *p*-value 0.020 (Table 6).

Table (1): Characteristics of patients in both study groups.

Variable	Sildenafil group (n=75)	Placebo group (n=75)	<i>t</i>	df	<i>p</i> -value
Age (years)	26.3±4.9	25.8±4.5	0.601	126	0.549¶
BMI (kg/m ²)	24.8±2.7	24.8±2.6	0.033	126	0.974¶
Duration of infertility (years)	5.1±2.3	5.0±2.2	0.196	126	0.845¶
Type of infertility					0.720§
Primary	39 (60.9%)	36 (56.3%)			
Secondary	25 (39.1%)	28 (43.8%)			
Cause of infertility					0.289§
Unexplained	29 (45.3%)	36 (56.3%)			
PCO	35 (54.7%)	28 (43.8%)			
History of ICSI	19 (29.7%)	19 (29.7%)			1.000§

Data are mean ± SD or number (%). *t*: *t* statistic. df: Degree of freedom. ¶Unpaired *t*-test. §Fisher's exact test.

Table (2): Primary outcome measures on day 13 in both study groups.

Variable	Sildenafil group (n=75)		Placebo group (n=75)		t	df	P-value¶
	Mean	SD	Mean	SD			
Number of follicles on day 8	2.0	0.8	2.0	0.7	0.116	126	0.908
Endometrial thickness on day 8 (mm)	4.3	0.8	4.4	0.7	-0.818	126	0.415
Uterine artery RI on day 8	0.89	0.06	0.88	0.07	0.751	126	0.454
Uterine artery PI on day 8	2.86	0.52	2.92	0.48	-0.741	126	0.460

t: t statistic. df: Degree of freedom. ¶Unpaired t-test.

Table (3): Primary outcome measures on day 13 in both study groups.

Variable	Sildenafil group (n=75)		Placebo group (n=75)		t	df	P-value¶
	Mean	SD	Mean	SD			
Number of follicles on day 8	3.1	1.1	2.8	0.9	1.300	126	0.196
Endometrial thickness on day 8 (mm)	9.8	1.8	8.4	1.3	5.050	114.315	<0.001
Uterine artery RI on day 8	0.79	0.09	0.83	0.08	-2.488	126	0.014
Uterine artery PI on day 8	2.09	0.28	2.53	0.46	-6.515	104.494	<0.001

t: t statistic. df: Degree of freedom. ¶Unpaired t-test.

Table (4): Percentage of change in primary outcome measures in both study groups.

Variable	Sildenafil group (n=75)		Placebo group (n=75)		U	Z	P-value¶
	Median	IQR	Median	IQR			
Percentage of change in follicular number	50.0	0.0 to 100.0	33.3	0.0 to 100.0	1807.5	-1.177	0.239
Percentage of change in endometrial thickness	128.6	100.0 to 150.0	100.0	75.0 to 120.0	1056.0	-4.749	<0.001
Percentage of change in UtA RI	-9.7	-13.5 to -3.5	-5.1	-6.4 to -3.2	1324.5	-3.449	<0.001
Percentage of change in UtA PI	-26.7	-32.3 to -19.4	-11.8	-17.2 to -6.5	725.5	-6.305	<0.001

IQR: Interquartile range. U: U statistic. Z: Z statistic. ¶: Mann-Whitney test.

Table (5): Paired comparison of primary outcome measures in both study groups.

	Variable	Day 8		Day 13		Mean diff.	95% CI		t	df	P-value¶
		Mean	SD	Mean	SD		95% LCL	95% UCL			
Filgrou	Number of follicles	2.0	0.8	3.1	1.1	-1.1	-1.3	-0.8	-7.926	63	<0.001
	Endometrial thickness (mm)	4.3	0.8	9.8	1.8	-5.5	-5.9	-5.0	-25.835	63	<0.001
	Uterine artery RI	0.89	0.06	0.79	0.09	0.10	0.08	0.12	9.931	63	<0.001
Sildena	Uterine artery PI	2.86	0.52	2.09	0.28	0.77	0.68	0.85	17.470	63	<0.001
	Number of follicles	2.0	0.7	2.8	0.9	-0.9	-1.1	-0.6	-6.189	63	<0.001
	Endometrial thickness (mm)	4.4	0.7	8.4	1.3	-3.9	-4.2	-3.6	-25.279	63	<0.001
Piacebogr	Uterine artery RI	0.88	0.07	0.83	0.08	0.05	0.04	0.07	9.739	63	<0.001
	Uterine artery PI	2.92	0.48	2.53	0.46	0.39	0.32	0.47	10.175	63	<0.001

t : t statistic. 95% CI: 95% confidence interval. 95% UCL: 95% upper confidence limit.
 df: Degree of freedom. 95% LCL: 95% lower confidence limit. ¶Paired t-test.

Table (6): Biochemical pregnancy rate in both study groups.

Outcome	Sildenafil group (n=75)	Placebo group (n=75)	RB (95% CI)	NNT (95% CI)	Z	P-value¶
Biochemical pregnancy	14 (21%)	4 (6.3%)	3.5 (1.2 to 10.1)	6.4 (3.7 to 25.7)	2.326	0.020

Data are number (%). RB: Relative benefit. NNT: Number needed to treat (or to benefit). 95% CI: 95% confidence interval.

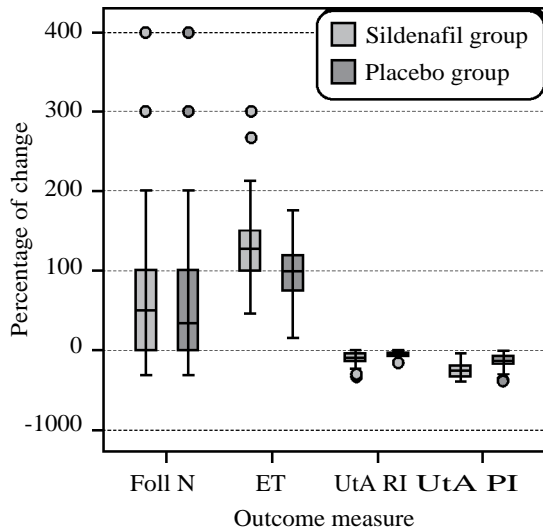


Fig. (1): Box plot showing the percentage of change in primary outcome measures in both study groups. Box represents the range from the first to third quartile (interquartile range). Line inside the box represents the median (second quartile). Whiskers represent the range between the minimum and maximum values excluding outliers and extreme observations. Number of follicles; ET, endometrial thickness; UtA RI, uterine artery RI; UtA PI, uterine artery PI.

Discussion

Age of the women was important factor due to the observed age related decline infertility as women approaches age 40 [6]. In our study age founded to be insignificant between two groups.

Infertility depends at large on the age of the female partner. As such, the ASRM states that an early evaluation and treatment is warranted after 6 months for women aged 35 years or older [7].

Ataalla et al., [3] they study the effect of Adjuvant sildenafil therapy in poor responders women and they agree as the age was insignificant between two groups involved in the study with *p*-value 0.54.

In our study the BMI was insignificant between both groups this comparable with Bozdog et al., [8] as they found that BMI was insignificant between studied groups. Zollner et al., [9] agree with our result as they found that BMI was insignificant in two groups.

Duration of infertility and type of infertility in our study were insignificant between two groups with *p*-value 0.845, 0.720 respectively this agree with Ataalla et al., [3] as they found that duration and type of infertility primary and secondary were insignificant between two groups with *p*-value 0.4, 0.77, 0.816 respectively.

Zollner et al., [9] agree with our result as they found that duration of infertility was insignificant in two groups.

There are many causes of infertility. In the majority of couples, an identifiable male or a female factor explaining their inability to conceive is usually found, in 10-25% there will be no explanation [10].

Cause of infertility in our study mainly was due to PCO in group A but in group B it was unexplained, cause of infertility was insignificant between two groups with *p*value 0.289 this agree with Liu et al., [11] as they found that cause of infertility was insignificant between two studied groups with *p*-value 0.901.

Ataalla et al., [3] agree with our result as they found that cause of infertility was insignificant between two studied groups.

In our study we evaluate the efficacy of the orally administered sildenafil citrate on the endometrial thickness and pattern, number of follicles, uterine artery blood flow and pregnancy rate in infertility patients undergoing induction of ovulation.

Primary outcome in our study measured on day 8 and day 13 and was included in it follicular number we found that on day 8 follicular number was insignificant between two groups also on day 13 there was insignificantly difference in follicular number between two groups.

This agree with Ataalla et al., [3] as they found that number of mature follicles were insignificant between two groups (Sildenafil group, Placebo group) with *p*-value 0.561.

Fahmy et al., [10] disagree with our result as they found significant differences in follicular number between two studied groups after sildenafil.

Regarding changes in endometrial thickness on day 8 and 13 in both groups we found that it was insignificantly changed between two groups on day 8 but on day 13 it was significantly increased due to effect of sildenafil with p -value 0.415, <0.001 respectively.

The percentage of changes in endometrial thickness between two groups in our study after administration of sildenafil founded to be significantly differences between two groups with improvement in group A with p -value <0.001 .

Fahmy et al., [10] agree with our result as they found that there was a significant statistical difference in endometrial thickness and number of follicles between treatment and placebo group which was higher in the treatment group. Thicker endometrium might be attributed to the vasodilator effect of sildenafil citrate which leads to increase uterine blood flow.

Moreover, Fisch et al., [12] found that sildenafil significantly increases endometrial thickness to >7 mm when used from day 8 to day 13 of the cycle. The effect of sildenafil citrate on endometrial thickness had also been reported using different route.

This agree with Ataalla et al., [3] as they found that there was a statistically significant increase in endometrial thickness on day of HCG in the sildenafil group compared to the control group although endometrial thickness was within the acceptable range in both groups. So, such increase in endometrial thickness may not be clinically significant in our groups of patients.

Dehghani-Firouzabadi et al., [13] also showed a beneficial role of oral sildenafil in improving endometrial thickness and endometrial receptivity in patients with previous IVF failure due to low endometrial thickness.

In our study we found that uterine artery RI and PI on day 8 was insignificantly difference between both groups with p -value 0.454, 0.460 respectively but it was significantly differences between two groups when measured on day 13 with p -value <0.001 and the percentage of change of uterine artery RI and PI after administration of sildenafil founded to be significantly differences between both groups with significant improvement in group A with p -value <0.001 .

Also in accordance with our results, Paulus et al., [14] reported that sildenafil citrate improved uterine artery blood flow and the sonographic

endometrial thickness in patients with thin endometrial.

Jerzek et al., [15] agree with our result also as they showed that Sildenafil citrate improves the uterine artery blood flow and the sonographic endometrial thickening in patients with a prior assisted reproductive cycle failing due to poor endometrial response.

Vascularity of the uterus affect myometrial and endometrial perfusion is directly related to the etiology of uterine factor infertility. Using dynamic methods like transvaginal color and power flow Doppler images as well as 3-D/4-D ultrasound, it has been demonstrated that detectable myometrial blood flow was associated with higher implantation and clinical pregnancy rates [16,17].

Regarding pregnancy rate in our study we found that biochemical pregnancy rate in both study groups founded that it was higher in group A than group B and was significantly between both groups with p -value 0.020.

In agreement with our result Fisch et al., [12] evaluated the effect of vaginal sildenafil citrate on the outcome of IVF after multiple IVF failure attributed to poor endometrial thickness in a cohort of 105 infertile women, with normal ovarian reserve and at least two consecutive prior IVF. They showed that sildenafil citrate enhanced endometrial development in 70% of the studied cases.

This is in agreement with a study done by Jerzek et al., [15] who reported that there was a good correlation between endometrial thickness and the prevalence of conception and that endometrial thickness greater than 9mm as determined by vaginal ultrasound in the late proliferative phase, correlates well with the pregnancy rate.

This disagree with Ataalla et al., [3] as they found that the increase in pregnancy rate, 6 cases in the sildenafil group versus 4 cases in the control group, was not statistically significant. This could be due to the small number of cases in their study and the non-significant difference in patients demographics in both groups. Another reason is although the endometrium was significantly thicker on day of HCG in the sildenafil group the thickness was within the acceptable range in both groups.

Dehghani-Firouzabadi et al., [13] also found that sildenafil citrate clearly increased endometrial thickness (9.8mm vs. 8mm), and the chemical pregnancy rates were higher in the sildenafil citrate group but not significantly.

Takasaki et al., [18] found that there was a positive linear correlation between endometrial thickness measured on the hCG day and pregnancy rate (PR) was identified.

Fahmy et al., [10] showed that in spite of non-statistical significant difference in pregnancy rate between both groups, we found that the pregnancy rate in the treatment group was higher by 2.5 than the placebo group.

Also, Kim et al., [18] detected that pregnancy rate was two folded higher in the study group although it was also statistically non-significant through a prospective randomized study done on twenty-one patient by luteal supplementation of sildenafil citrate 25mg/day.

Conclusion:

Use of oral sildenafil in endometrial preparation for patient with poor endometrial vascularity showed better endometrial development.

Sildenafil citrate increased pregnancy rate in women undergoing induction of ovulation by Letrozole 2.5mg in a dose of twice daily, which may be attributed to the increase in endometrial thickness and uterine artery blood flow.

Recommendations:

We, therefore recommend the use of oral sildenafil for improving endometrial perfusion in women with antecedent poor endometrial vascularity. Future studies to evaluate its effect on fetal outcome in pregnant women are needed.

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تأثير عقار سترات السيلدينافيل على تحضير بطانة الرحم وتدفق الدم فى الشريان الرحمى فى مرضى تأخر الحمل عند تنشيط المبيض

خلفية الدراسة: سيترات السيلدينافيل يحسن تدفق الدم فى الشريان الرحمى وسماكة بطانة الرحم لدى النساء اللواتى يعانين من فشل الدورة الإنجابية المساعدة بسبب ضعف استجابة بطانة الرحم. يمكن استخدام سيترات السيلدينافيل عن طريق الفم أو عن طريق المهبل لتحسين تقبل بطانة الرحم.

الهدف من الدراسة: تقييم فعالية سيترات السيلدينافيل التى يتم تناولها عن طريق الفم على سمك ونمط بطانة الرحم وعدد البصيلات وتدفق الدم فى شريان الرحم ومعدل الحمل فى مرضى العقم الذين يخضعون لتحريض الإباضة.

المرضى وطرق الدراسة: إشتملت الدراسة على ١٥٠ مريضة تم تقسيمهم عشوائياً إلى مجموعتين :

المجموعة اتضمنت ٧٥ مريضة تم إعطاؤهم ٢٠ ملغ من سيترات السيلدينافيل من اليوم الثامن إلى اليوم الثالث عشر من الدورة ٣ مرات فى اليوم عن طريق الفم وملغ و ٢٠٥ ملغ من اليوم الثانى حتى اليوم. اليوم السادس من نفس الدورة مرتين فى اليوم عن طريق الفم، وشملت لمجموعة ب ٧٥ مريضات تم إعطاؤهم ٢٠٥ ملغ من ليتريزولمن اليوم الثانى إلى اليوم السادس من الدورة مرتين فى اليوم عن طريق الفم وأقراص الدواء الوهمى من يوم الدورة ٨ حتى اليوم ١٣ ثلاث مرات / اليوم شفويًا.

نتائج الدراسة: تشير النسبة المئوية للتغير فى كل من مؤشر المقاومة ومؤشر النبض فى كلا المجموعتين إلى أنه كان ذا دلالة إحصائية فى كلا المجموعتين مع قيمة. $p < 0.001$ وجد معدل الحمل البيو كيميائى فى مجموعتى الدراسة أعلى فى المجموعة أ (مجموعة سيلدينافيل) من المجموعة ب (مجموعة الدواء الوهمى) وكان ذا دلالة إحصائية بين المجموعتين بقيمة احتمالية ٠.٠٠٢٠.

الاستنتاج: أظهر إستخدام السيلدينافيل عن طريق الفم فى تحضير بطانة الرحم للمرضى الذين يعانون من ضعف الأوعية الدموية فى بطانة الرحم تطور أفضل فى بطانة الرحم.