AUCTORES
Globalize your Research

Journal of Women Health Care and Issues

Dalia Mohammed Mohammed El-Khaldy *

Open Access

Research Article

Effect of Sildenafil in Endometrial Ripening with Induction of Ovulation by Clomiphene Citrate in Polycystic Ovarian Syndrome; Double Blinded; Randomized Controlled Trial

Mohamed Saeed Khallaf, Dalia Mohammed Mohammed El-Khaldy*, Ahmed Mohamed Nour Eldin Hashad, Ibrahim Shazly Mohamed Amen Elshazly

***Corresponding author:** Dalia Mohammed Mohammed El-Khaldy, Obstetrics & Gynecology Faculty of Medicine - Ain Shams University, Cairo, Egypt

Received date: November 06, 2019; **Accepted date:** December 05, 2019; **Published date:** December 11, 2019

Citation: Mohamed Saeed Khallaf, Dalia Mohammed Mohammed El-Khaldy, Ahmed Mohamed Nour Eldin Hashad, Ibrahim Shazly Mohamed Amen Elshazly. (2019) Effect of Sildenafil in Endometrial Ripening with Induction of Ovulation by Clomiphene Citrate in Polycystic ovarian syndrome; Double Blinded; Randomized Controlled Trial. *J. Women Health Care and Issues*. 2(3); **DOI:**10.31579/2642-9756/077

Abstract:

Back ground: World Health Organization (WHO) defines infertility as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Worldwide, 8 to 12 percent of couples experience fertility problems. Causes of infertility in women were as follows: menstrual disorders (disorders of cycle length and flow) 62.6%, diseases (obesity, thyroid diseases, diabetes) 58.7%, impaired ovulation (hormonal disorders, oligoovulation and anovulation) 50.3%, uterine causes 16.7%, tubal factor 15.4%, and cervical causes 7.9%. In the male factor fertility there was semen abnormalities (44.6%), genetic factors (29.8%), anti-spermatogenesis agents (11%), and vascular disorders (17.2%).

Aim of the Study: The purpose of this study is to evaluate the effect of sildenafil in endometrial ripening with induction of ovulation by clomiphene citrate in polycystic ovarian syndrome.

Patients and methods: It is a randomized controlled trial on 65 infertile women with polycystic ovarian syndrome; patients were randomly divided into two equal groups. In control group, 31 patients were given oral sildenafil, one tablet every 12 hrs. From 2nd day of the cycle till 12th day and clomiphene citrate, one tablet every 12 hours, for 5 days from 3rd day of the menstrual cycle. In study group, 34 patients were given oral placebo, one tablet every 12 hrs. From 2nd day of the cycle till 12th day and clomiphene citrate, one tablet every 12 hours, for 5 days from 3rd day of the menstrual cycle. A transvaginal ultrasound was performed to evaluated the endometrial thickness before and after treatment, the follicularometeric was measured on day 11 and day13. Uterine artery Doppler was then measured. Qualitative serum B-hCG level was checked 14 days after ovulation to assess clinical pregnancy rate.

Design: Prospective, Double blinded randomized controlled trial.

Setting: Obstetrics & Gynecology outpatient clinic, Ain Shams University Hospital. Study duration: 3 months.

Results: The present study was a double-blind, randomized, controlled study that was conducted on 65 women with PCOS who underwent induction of ovulation by Clomiphene citrate in outpatient clinic of Ain Shams University hospital.

Conclusion: Our systematic review and meta-analysis showed that follicular supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction. However, given the methodological limitations the current evidence does not support its use in clinical practice yet. Future high-quality RCT with large sample size to evaluate the sildenafil citrate effect in women undergoing assisted reproduction are needed. Future RCTs should focus on type of processing, stage of embryo, embryo quality, dosage, time of administration, type of control group, in order to identify the groups of patients who would benefit the most from this intervention and the most appropriate dosage, time, and type of sildenafil citrate which would have the most positive effect and the less possible side effects.

Recommendations: Follicular supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction. High-quality RCT with large sample size to evaluate the sildenafil citrate effect in women undergoing assisted reproduction are needed.

Keywords: clomiphene citrate; sildenafil; polycystic ovarian syndrome; ultrasound; endometrium

Introduction

Infertility is defined by the world health organization (WHO) as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Worldwide, 8 to 12 percent of couples experience fertility problems [2].

Causes of infertility in women were as follows: menstrual disorders (disorders of cycle length and flow) 62.6%, diseases (obesity, thyroid diseases, diabetes) 58.7%, impaired ovulation (hormonal disorders, oligoovulation and anovulation) 50.3%, uterine causes 16.7%, tubal factor 15.4%, and cervical causes 7.9%. In the male factor fertility there was semen abnormalities (44.6%), genetic factors (29.8%), anti-spermatogenesis agents (11%), and vascular disorders [3].

Polycystic ovarian syndrome (PCOS) is a common disorder in women that is characterized by hyperandro-genism (that is, evidence of excess male hormone or androgen effect; for example, clinically, such as hirsutism, and/or biochemically, such as hyper-andro-genaemia or excess levels of androgen), ovulatory dysfunction (including menstrual dysfunction) and polycystic ovarian morphology (PCOM; an excessive number of preantral follicles in the ovaries) [4].

Embryo implantation depends on the quality of the ovum and endometrial receptivity. Successful embryo implantation can take place only in a receptive uterus. Adequate growth of the endometrium is indispensable for successful pregnancy [5]. Patients with a thin endometrium showed low pregnancy rates [6].

Uterine blood flow is an important factor for endometrial growth and receptivity [7]. Nitric oxide (NO) leads to relaxation of vascular smooth muscles through a cyclic guanyl monophosphate (cGMP) mediated pathway. Nitric oxide synthase isoforms have been identified in the vascular muscles of both human endometrium and myometrium. Phosphodiesterase (PDE) is a family of isoenzymes that hydrolyze cyclic nucleotides, such as cGMP. The inhibitors of specific Phosphodiesterase (PDE) subtypes have been identified with an ability to augment the effects of cyclic nucleotides on target tissues as the endometrium [8].

Sildenafil citrate is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) that prevents the breakdown of cGMP and potentiates the effect of nitric oxide on vascular smooth muscles [9]. Sildenafil citrate could lead to an improvement in uterine blood flow and, in conjunction with estrogen, led to the estrogen-induced proliferation of the endometrial lining [8].

AIM OF THE STUDY:

The purpose of this study is to evaluate the effect of sildenafil in endometrial ripening with induction of ovulation by clomiphene citrate in polycystic ovarian syndrome.

Research question:

Is there a difference between the cases treated with sildenafil and clomiphene citrate to clomiphene citrate alone on endometrium thickness in females with polycystic ovarian syndrome?

Null hypothesis:

There is no difference regarding the response of endometrium in females with polycystic ovarian syndrome treated with Sildenafil and other available treatment option.

PATIENTS AND METHODS:

The present study was double blinded randomized controlled trial which was approved by the local Ethical and Research Committee, Ain-Shams University, Cairo, Egypt. It was conducted at the Infertility Outpatient Clinic in Ain Shams University Maternity Hospital .the study duration was 3 months. Eighty patients diagnosed as polycystic ovarian syndrome recruited from outpatient infertility clinic, Sixty five patients were fulfilling inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Age between 18-35 years. (2)Two of three diagnostic criteria of PCOS (Rotterdam Criteria) Biochemical and clinical hyperandrogenism ,Irregular cycles and ovulatory dysfunction ,Polycystic ovarian morphology.(3)All patients underwent full infertility investigation, such as: Hormonal tests (FSH, LH, Prolactin, TSH, free testosterone), trans-vaginal ultrasound, and Semen analysis. (4) Hysterosonography.

The exclusion criteria were (1) Women with myoma, adenomyosis or congenital uterine anomaly.(2)Chronic use of any medications including non-steroidal anti-inflammatory drugs.(3)Associated cases of infertility other than PCOs (male factor, tubal factor).(4) Cases with endometrial hyperplasia or endometrial polyp. (5)Discontinued patient for the full study time (3 cycles of treatment). (6)Presence of any medical contraindication to the medication like heart diseases.

Eighty opaque easy opening envelopes were numbered serially from 1-80 on each envelope. The corresponding number in randomization table written and when the patient comes to the clinic, she was examined for required criteria. On finding required criteria, the first envelope was opened and the patient received treatment according to the envelope. Recruited patients were divided into two groups (A and B) according to a sequence of random numbers created by a computer system.

We missed 15 cases from the total number of cases required. The number of cases become 65 of patients in this study due to discontinuation of treatment and follow up from some patients because of COVID 19 virus pandemic.

The 65 PCOS females were included in this study. They were divided into 2 groups; Group [A]: 31 patients were given oral sildenafil (Respatio®, 20 mg), one tablet every 12 hrs. From 2nd day of the cycle till 12th day and clomiphene citrate (clomid® 50 mg), one tablet every 12 hours, for 5 days from 3rd day of the menstrual cycle. Group [B]: 34 patients were given oral placebo, one tablet every 12 hrs. From 2nd day of the cycle till 12th day and clomiphene citrate (clomid® 50 mg), one tablet every 12 hours, for 5 days from 3rd day of the menstrual cycle.

All patients were subjected to: Full personal, family, maternal and medical history were taken, Serum of (FSH, LH, Prolactin,TSH and free testosterone levels), Full 2D Ultrasound examination was done and Hysterosalpingography. Also, transvaginal ultrasound was performed for all patients eligible for the study at Ain-Shams Fetomaternal Ultrasound Unit. The used machine was (Voluson pro 730 General Electric) machine; using 5-9 MHz probe. During the procedure, endometrial thickness was measured (maximum distance between each myometrial/endometrial interface through the longitudinal axis of the uterus). Using two dimensional (2D) transvaginal Doppler, flow velocity wave forms were

obtained from the ascending main branch of the uterine artery on the right and left side of the cervix before it enters the uterus.

The primary outcomes: To evaluate endometrial thickness in females with polycystic ovary syndrome who received sildenafil and who received ordinary treatment regimens.

The secondary outcomes: Positive pregnancy test (Time Frame: 14 days after triggering of ovulation) and Sub-endometrial blood flow (Time Frame: 9 days)

Figure 1: Voluson pro 730 General Electric machine.

Figure 2: 5-9 MHz probe.

Table 1: The demographic and clinical characteristics of the included patients

Variables	Sildenafil +CC (N =31)	CC +Placebo (N =34)	P-value
Age in years			
- Mean ±SD	26.6 ±3.2	26.8 ±4.0	0.818
- Range	22 – 35	21 - 35	
BMI in Kg/m2			
- Mean ±SD	27.4 ±3.1	25.8 ±3.5	0.064
- Range	19.5 - 30.2	19 - 30.2	

Parity, No (%)			
- 0	24 (77.4%)	24 (70.6%)	
- 1	6 (19.4%)	10(29.4%)	0.474
- 2	1 (3.2%)	0(0.0%)	

***Data are presented as mean ±SD, Range, number (%), P-value (>0.05).*

Table 1 shows the demographic and clinical characteristics of the included patients. There were no statistically significant differences between both groups in terms of age, BMI, and parity.

Table 2: Clinical Features of PCO

Variables	Sildenafil +CC (N =31)	CC+Plasebo (N =34)	X2	P-value
Clinical features of PCO				
Hirsutism	19 (61.9%)	20 (58.8%)	0.041	0.839
Acne	14 (45.2%)	17 (50.0%)	0.152	0.696
Irregular cycles	18 (58.1%)	19 (55.9%)	0.031	0.859
PCO by US	26 (83.9%)	23 (67.6%)	2.3	0.129

**Data are presented as number (%), X2, P-value (>0.05).*

Table 2 shows the clinical Features of PCO. There were no statistically significant differences between both groups in terms of any of clinical Features of PCO.

Table 3: The infertility characteristics of the included patients

Variables	Sildenafil +CC (N =31)	CC+Placebo (N =34)	P-value
Type of infertility, No (%)			
- Primary	24 (77.4%)	24 (70.6%)	0.531
- Secondary	7 (22.6%)	10(29.4%)	
Duration of infertility in years			
- Mean ±SD	1.4 ±0.83	1.6 ±1.0	0.395
- Range	0.5 -4.0	0.5 -5.0	

**Data are presented as mean ±SD, Range, number (%), P-value (>0.05).*

Table 3 shows the infertility characteristics of the included patients. There were no statistically significant differences between both groups in terms of type and duration of infertility.

Table 4: The laboratory parameters of the included patients

Variables	Sildenafil+CC(N =31)		CC+Placebo (N =34)		t-test	P-value
	Range	Mean±SD	Range	Mean±SD		
FSH (mIU/ml)	2- 12.9	6.0±1.9	3.9- 12.9	6.7±2.1 78	1.278	0.206
LH (mIU/ml)	2.5- 14.7	8.0±2.5	6.3 - 14.7	8.7±1.8 1.321	1.321	0.191
TSH (µIU/ml)	1- 4.8	2.3±.9	1.6 - 4.1	2.4±.8 0.482	0.482	0.631
Free testosterone (ng/dl)	0.7 - 4.5	2.9±1.0	0.8 - 4.3	3.2±.8 1.310	1.310	0.195
Prolactin (ng/ml)	10.1 - 23.5	17.1±3.0	10.1-23.1	16.5±3.3	0.694	0.490

***Data are presented as mean ±SD, Range, t-test, P-value (>0.05).*

Table 4 shows the laboratory parameters of the included patients. There were no statistically significant differences between both groups in terms of serum FSH, serum LH, serum TSH, serum testosterone, and serum prolactin.

Table 5: The Folliculometric measures of the included patients

Variables	Sildenafil +CC (N =31)		CC+Placebo (N =34)		t-test	P-value
	Range	Mean±SD	Range	Mean±SD		
Folliculometric measure on day 11 (mm)	11 - 18	13.8±2.26	10 - 18	14.4±2.27	1.024	0.310

Folliculometric measure 13 (mm)	13 - 20	16.3±2.17	12 - 20	16.3±2.13	0.885	0.380

**Data are presented as mean ±SD, Range, t-test, P-value (>0.05).*

Table 5 shows the folliculometric measures of the included patients. There were no statistically significant differences between both groups in terms of folliculometric measure on day 11 (mm) and folliculometric measure 13 (mm).

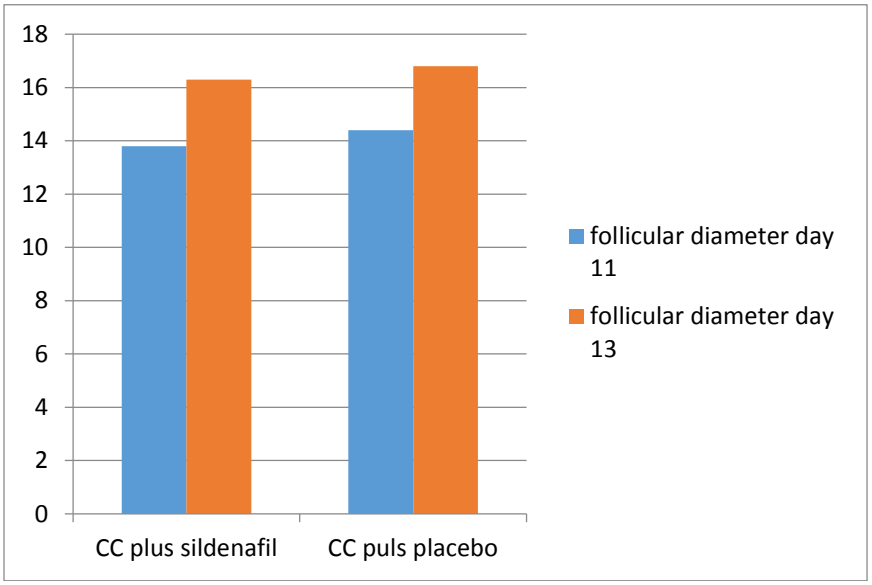

Figure 3: Follicular diameter in the two groups before and after intervention presented as mean and 95% confidence interval

Table 6: The endometrial thickness of the included patients

Variables	Sildenafil +CC (N =31)		CC+Placebo (N =34)		t-test	P-value
	Range	Mean±SD	Range	Mean±SD		
Endometrial thickness before intervention (mm)	1.5 - 4	3.1±0.88	1.5 – 4.5	3.0±0.94	0.417	0.678
Endometrial thickness after intervention (mm)	7.5 - 13	10.0±1.40	7 - 12	9.5±1.38	1.526	0.132

Data are presented as mean ±SD, Range, t-test, P-value (>0.05).

Table 6 shows the endometrial thickness of the included patients. There were no statistically significant differences between both groups in terms of endometrial thickness before intervention and endometrial thickness after intervention.

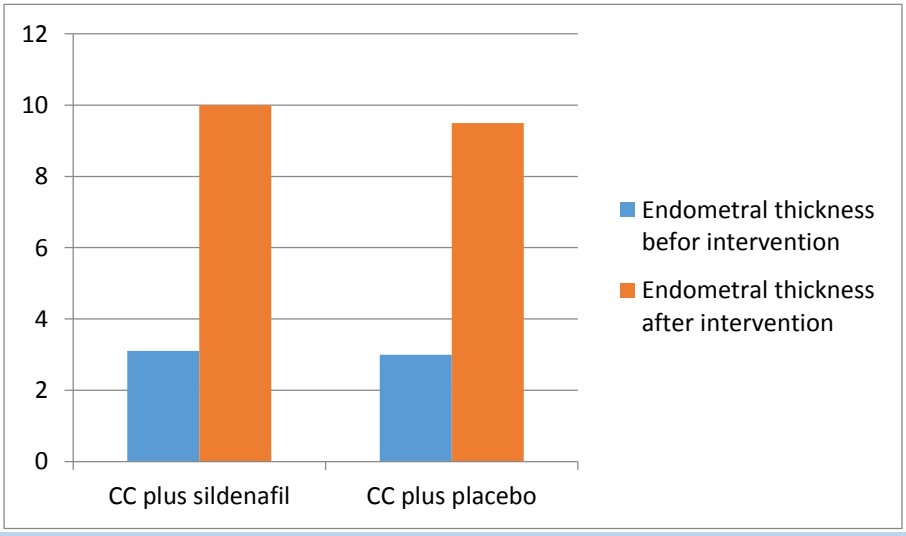

Figure 4: Endometrial thickness in the two groups before and after intervention presented as mean and 95% confidence interval.

Table 7: The UA Doppler measures of the included patients

Variables	Sildenafil +CC (N =31)		CC+Placebo (N =40)		t-test	P-value
	Range	Mean±SD	Range	Mean±SD		
Resistive index (RI)						
UA RI (right side)	0.66-0.82	0.7±0.06	0.72-1.06	0.9±.13	4.754	<.001
UA RI (left side)	0.67-0.83	0.8±0.06	0.74-1.09	0.9±.13	5.088	<.001
Pulsatility index (PI)						
UA PI (right side)	0.97-1.79	1.4±0.29	1.38-3.35	2.3±0.69	7.065	<.001
UA PI (left side)	1.05-1.81	1.4±0.27	1.43-3.46	2.3±0.76	6.209	<.001

***Data are presented as mean ±SD, Range, t-test, P-value.*

Table 7 shows the UA Doppler measures of the included patients. There were statistically significant differences between both groups in terms of Uterine artery PI right and Uterine artery PI left with higher values in the CC+Placebo group. But there is no statistically significant difference between the right and left in each group.

There were statistically significant difference between the two group regarding Uterine artery RI right and Uterine artery RI left with higher values in the CC+ Placebo group. But there is no statistically significant difference between the right and left in each group.

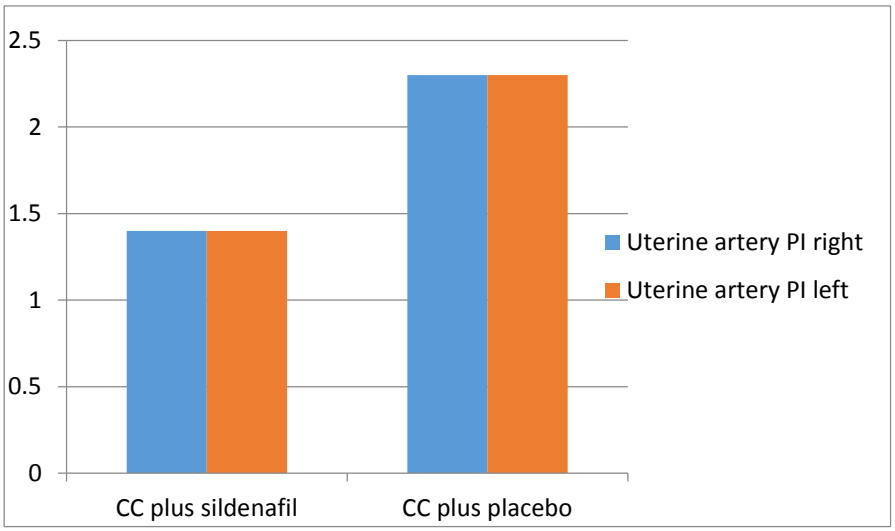

Figure 5: Uterine artery PI right versus left in the two groups presented as mean and 95% confidence interval

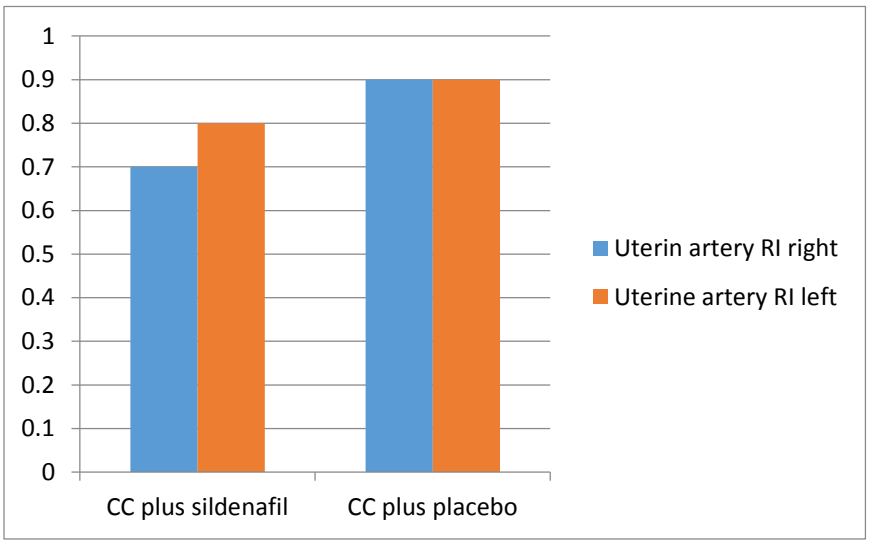

Figure 6: Endometrial RI right versus left in the two groups presented as mean and 95% confidence interval

Table 8: The clinical pregnancy rate per cycle of the included patients

Variables	Sildenafil +CC (N =31)	CC+Placebo (N =34)	X2	P-value
Clinical pregnancy, No (%)				
- Yes	13(41.9%)	11 (32.4%)	0.639	0.424
- No	18(58.1%)	23 (67.6%)		

***Data are presented as number or (%), X2, P-value (>0.05).*

Table 8 shows the clinical pregnancy rate per cycle of the included patients. There were no statistically significant difference between both groups in terms of clinical pregnancy rate per cycle.

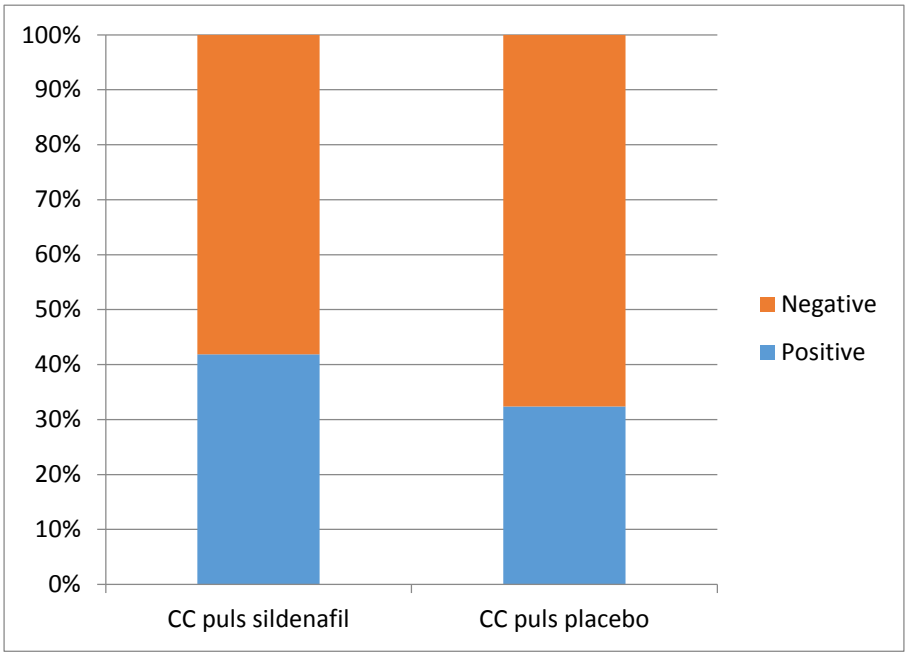

Figure 7: Pregnancy rate in the two study groups.

Table 9: The Repeated measure analysis of the follicular diameter and endometrial thickness of the included patients

Repeated measures				Between groups	
Variables	Replication	F test	P-value	F test	P-value
Follicular diameter	Day 11- Day13	620.551	<0.001	0.945	0.335
Endometrial thickness	Before -After	1461.492	<0.001	3.13	0.215

***Data are presented as replication, F test, P-value (<0.001).*

Table 9 Repeated measure analysis of the follicular diameter and endometrial thickness of the included patients. There confirmed the statistically significant increase in both diameters after either intervention but without statistically significant difference between the two interventions.

Table 10: Incidence of drug-related adverse effects in the two study groups

Variables	Sildenafil +CC(N=31)		CC + placebo (N=34)		X2	P-value
	n	%	n	%		
Drug-related adverse effects						
Nil	13	42.9%	32	95.2%	62.773	<.001
Mild side effects not requiring treatment	16	51.4%	2	4.8%		
Significant side effects requiring treatment	2	5.7%	0	0.0%		

***Data are presented as number (%), X2, P-value.*

Table 10 shows incidence of drug-related adverse effects of the included patients. There were statistically significance higher among the sildenafil group. The adverse effect was almost headache.

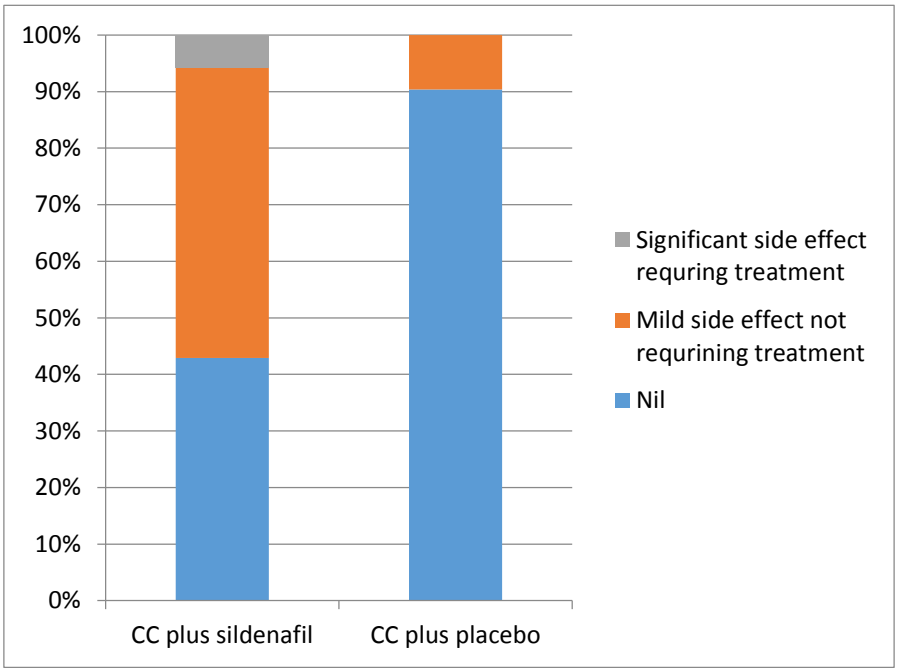

Figure 8: Incidence of drug-related adverse effects in the two study groups.

DISCUSSION:

This was a Double blinded randomized controlled trial conducted on 65 female patients with polycystic ovary syndrome (PCO); to evaluate the effect of sildenafil in endometrial ripening with induction of ovulation by clomiphene citrate in polycystic ovarian syndrome.

In our study we found no statistically significant difference between the two groups regarding basal demographic, hormonal and clinical characteristics as age, BMI, parity, types of infertility, duration of infertility in years, serum FSH, serum LH, serum free testosterone, TSH, Prolactin as well as clinical features of Pcos ($p > 0.05$ respectively). Which came in agreement with Ashoush & Abdelshafy, [10] and Selim & Borg, [11].

Ashoush & Abdelshafy, [10] reported that, no statistically significant differences were found between both groups regarding basal demographic, hormonal and clinical characteristics [10].

Selim & Borg, [11] reported that, a total of 201 cycles of ovulation induction were carried out, of which 102 cycles were in the sildenafil group and 99 cycles were in the CC group. There were no statistically significant differences in demographic characteristics of both groups of patients. The mean age, body mass index (BMI), the mean duration, and whether the patients had primary or secondary infertility were comparable between the two groups [11].

In our study we found there was no statistically significant difference between the two groups regarding Follicular diameter – day 11, Follicular diameter – day 13, Endometrial thickness before intervention as well as Endometrial thickness after intervention ($p > 0.05$ respectively). Which came in agreement with Ashoush & Abdelshafy, [10] and Fetih et al., [12].

Ashoush & Abdelshafy, [10] reported that, pre ovulatory follicumetric measurements didn't differ significantly between both groups [10].

Fetih et al., [12] reported that, endometrial thickness showed a statistically significant increase from a value of 6.6 +/- 1.4 mm with CC only treatment during the sixth cycle, to 9.3+/- 3.1mm with CC+ sildenafil vaginal gel in the seventh cycle. P value was <0.001[12].

In our study we found there was no statistically significant difference between the two groups regarding number of clinically pregnancy rate pre cycle ($p > 0.0$ respectively).Which came in agreement with Ashoush & Abdelshafy, [10].

Ashoush & Abdelshafy, [10] reported that, Clinical pregnancy rate was significantly higher in the sildenafil group (43.7% vs 34.5%) with a calculated number needed to treat (NNT) of 10.8 (95% CI: 6.36-37.84) [10].

In our study we found there is statistically significant difference between the two group regarding Uterine artery PI right and Uterine artery PI left with higher values in the placebo + clomid group. But there is no statistically significant difference between the right and left in each group ($p > 0.001$ respectively). Which came in agreement with Fetih et al., [12]

Fetih et al., [12] reported that, as an indicator of uterine blood flow, we used Doppler ultrasound to measure the pulsatility index in both uterine arteries. With the addition of the sildenafil vaginal gel, the uterine artery pulsatility index dropped from 2.4 +/- 0.8 to 1.6 +/- 1.3 (P value = 0.002) indicating a significant reduction in blood flow resistance in the uterine artery. PCOS women who ovulated under clomiphene citrate treatment had significantly higher uterine artery resistive index (RI), and increased impedance in endometrial and sub endometrial vasculature compared to healthy ovulatory women [12].

Repeated measure analysis in our study of the follicular diameter and endometrial thickness confirmed the statistically significant increase in both diameters after either intervention but without statistically significant difference between the two interventions. Which came in agreement with Fetih et al., [12], Selim & Borg, [11].

Fetih et al., [12] reported that, Follicular number and size (measured on the day of HCG injection), and number of cycle days until HCG injection were comparable for our cohort of women in their CC only cycle (6th cycle), and the CC + sildenafil vaginal gel cycle (7th cycle). Mean follicular number was 1.3 in the sixth cycle, and 1.4 in the seventh cycle (P value = 0.38). Mean follicular diameter was 17.8 versus 18.8 during the sixth and seventh cycle respectively (P value = 0.096) [12]

Selim & Borg, [11] reported that, the results of this study indicate that infertile women with PCOS experience no significant changes in the number of mature ovarian follicles (diameter = 18mm) and ovulation rate, although a significant increase in pregnancy rates was observed in patients who received sildenafil in comparison to CC [11] .

Our systematic review and meta-analysis showed that follicular supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction.

CONCLUSION:

Our systematic review and meta-analysis showed that follicular supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction. However, given the methodological limitations the current evidence does not support its use in clinical practice yet. Future high-quality RCT with large sample size to evaluate the sildenafil citrate effect in women undergoing assisted reproduction are needed. Future RCTs should focus on type of processing, stage of embryo, embryo quality, dosage, time of administration, type of control group, in order to identify the groups of patients who would benefit the most from this intervention and the most appropriate dosage, time, and type of sildenafil citrate which would have the most positive effect and the less possible side effects.

LIMITATIONS

- Poor methodological quality with small sample sizes, which may influence internal validity.
- Significant heterogeneity was found in some results, especially ET and pregnancy rates.
- Lack of follow up.

RECOMMENDATIONS

- Follicular supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction.
- High-quality RCT with large sample size to evaluate the sildenafil citrate effect in women undergoing assisted reproduction are needed.

REFERENCES:

1. Fernando Zegers-Hochschild, F., Adamson, G. D., de Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., ... and Van der Poel, S. (2009): The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. Human reproduction, 24(11): 2683-2687.
2. Christian Nordqvist, Debra Rose Wilson, RN, IBCLC, AHN-BC, CHT (2018):" Infertility in men and women" Thu 4 January.
3. Seyedeh Zahra Masoumi, Parisa Parsa, Nooshin Darvish, Sahar Mokhtari, Mahnaz Yavangi, M.D., and Ghodratollah Roshanaei (2015): An epidemiologic survey on the causes of infertility in patients referred to infertility center in Fatemieh Hospital in Hamadan"Iran J Reprod Med. Aug; 13(8): 513–516.
4. Yildiz, B. O., Knochenhauer, E. S., and Azziz, R. (2008): Impact of obesity on the risk for polycystic ovary syndrome. The Journal of Clinical Endocrinology and Metabolism, 93(1): 162-168.
5. Chen, S.-L. ;Wu, F.-R. ;Luo, C. ;Chen, X. ;Shi, X.-Y. ; Zheng, H.-Y., (2010): Combined analysis of endometrial thickness and pattern in predicting outcome of in vitro fertilization and embryo transfer: a retrospective cohort study." Reproductive Biology and Endocrinology,.8(1): 30.
6. Groenewoud, E. R.; Cantineau, A. E.; Kollen, B. J.; Macklon, N. S. and Cohlen, B. J (2013): "What is the optimal means of preparing the endometrium in frozen–thawed embryo transfer cycles? A systematic review and meta-analysis." Human reproduction update. 19(5): 458-470.
7. Ng, E. H. Y. ;Chan, C. C. W. ;Tang, O. S. ;Yeung, W. S. B. and Ho, P. C (2007): "The role of endometrial blood flow measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during in vitro fertilization treatment." European Journal of Obstetrics and Gynecology and Reproductive Biology. 135(1): 8-16.
8. Sher G, and Fisch JD (2002): Effect of vaginal sildenafil citrate on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. Fertil Steril; 78:1073–1076.
9. Sher G, and Fisch JD (2000): Vaginal sildenafil citrate (Viagra): a preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF. Hum Reprod; 15:806–809.
10. Ashoush, S., and Abdelshafy, A (2019): Sildenafil citrate adjuvant treatment in women with polycystic ovary syndrome following clomiphene failure: A randomized controlled trial. Evidence Based Women's Health Journal, 9(3): 487–493.
11. Selim, M. F., and Borg, T. F (2012): Letrozole and clomiphene citrate effect on endometrial and subendometrial vascularity in treating infertility in women with polycystic ovary syndrome. Journal of Gynecologic Surgery, 28(6): 405–410.
12. Fetih, A. N., Habib, D. M., Abdelaal, I. I., Hussein, M., Fetih, G. N., and Othman, E. R (2017): Adding sildenafil vaginal gel to clomiphene citrate in infertile women with prior clomiphene citrate failure due to thin endometrium: A prospective self-controlled clinical trial. Facts, Views and Vision in Obgyn, 9(1): 21.

DOI:10.31579/2642-9756/077