Clomiphene Citrate versus Clomiphene Citrate in combination with other drugs in Ovulation Induction in Patients with Polycystic Ovary Syndrome

Mostafa Khodary[a] , Yasser Ahmed Abuelwafa Abdellatif [a*] , Mahmoud Ibrahim Almolakab B-Alrashidy[b] , Sayed Ahmed Mohammed Taha[a]

[a]Obstetrics and Gynecology Department, Faculty of Medicine, South Valley University, Qena, Egypt.
[b]Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University (Assuit Branch), Assiut, Egypt

Abstract

Background: Polycystic ovary syndrome (PCOS) is the most prevalent cause of normogonadotrophic anovulation, also classified as World Health Organization group II anovulation.

Objectives: The aim of this study was to compare the effectiveness and clinical outcomes of clomiphene citrate alone and with different combinations (metformin , tamoxifen , letrozole and low dose gonadotrophins) in induction of ovulation in women with PCOS.

Patients and methods: The Obstetrics and Gynecology department at Qena University Hospital, South Valley University, was the site of this randomized study. The study included 400 infertile cases with PCOS divided on 5 groups . The duration of the study ranged from 12-24 months.

Results: In the studied groups, group 4 (clomiphene and letrozole) and group 5 (clomiphene and low dose gonadotrophins) had the highest ovulation rate which was 31.3 % , 41.3 % respectively and also the highest pregnancy rate which was 33.8 % for each group .

Conclusion: The combination of clomiphene and letrozole and clomiphene and gonadotrophins had proved to be the most effective , low cost infertility treatment in women with PCOS that offers high ovulation and pregnancy rates.

Keywords: Anovulation; PCOS; Clomiphene citrate; Tamoxifen; Metformin; Letrozole; Gonadotrophins; Ovulation ; Induction; Endometrium.

DOI: 10.21608/SVUIJM.2023.194749.1534

***Correspondence**: Yassor@gmail.com

Received: 1 February,2023.

Revised: 23 February,2023..

Accepted: 26 February,2023..

Published: 28 May, 2024

Cite this article as: Mostafa Khodary , Yasser Ahmed Abuelwafa Abdellatif , Mahmoud Ibrahim Almolakab B- Alrashidy , Sayed Ahmed Mohammed Taha (2024). Clomiphene Citrate versus Clomiphene Citrate in combination with other drugs in Ovulation Induction in Patients with Polycystic Ovary Syndrome. *SVU-International Journal of Medical Sciences*. Vol.7, Issue 2, pp: 1-8.

Introduction

One in seven couples struggle with infertility, and ovulation abnormalities account for 25% of all cases **(NICE, 2013)**.The most typical type of anovulatory infertility is called normogonadotrophic anovulation, also known as WHO group II anovulation.The diagnostic criteria for PCOS, which were agreed upon jointly by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, are known as the Rotterdam criteria. PCOS is by far the most common cause of this group **(Legro et al., 2013)**.

Non-steroidal selective oestrogen receptor modulators (SERM) are a safe and efficient method of inducing ovulation **(Brown et al.,2009)**.80% of anovulatory women can stimulate ovulation with clomiphene, however only 40% of them became pregnant **(Witchel, 2019).**Tamoxifen is another anti-estrogen used to induce ovulation; after therapy with either tamoxifen or clomiphene for treating anovulation, there are no discernible differences in ovulation or pregnancy rates **(Witchel, 2019).**

Another option is letrozole, a highly selective aromatase inhibitor that has recently been utilised to induce ovulation in unovulatory infertile patients as an alternative to CC **(Ganesh et al., 2009).**

By lowering insulin levels and altering how insulin affects ovarian androgen production, theca cell proliferation, and endometrial development, metformin also helps improve ovulation induction in women with PCOS **(Welt 2021).**

Following failure therapy with first-line oral ovulation induction drugs, gonadotropins are utilized as second-line ovulation induction agents, this includes women who are resistant to oral therapy or who experience endometrial adverse effects from antioestrogenic drugs **(Bhandari et al., 2016).**

Patients and methods

This was a randomized study that was carried out in the obstetrics and gynaecology department of Qena University Hospital, South Valley University. The study included 400 cases randomly divided into five groups using a computer generated numbers ; each group included 80 patients.

Ethical consideration : The ethics committee of south valley university , Qena, Egypt , has given its approval to this research. Ethical code number : SVU-MED-OBG024-SVU-2-2020-31

Inclusion criteria: Infertile patients less than 35 years with PCOS. The major criteria for the diagnosis of PCOS are oligo- and/or anovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovaries, according to the revised 2003 Rotterdam Criteria **(Legro et al., 2013).**

Exclusion criteria: Other causes of infertility as (male factor , tubal factor , uterine factor).

Samples: This study was conducted on 400 infertile women with PCOS attended outpatient clinics, Qena university hospital and fulfilled inclusion criteria from February 2020 to December 2021.

Study tools

History taking: Full history taking including the duration of infertility, menstrual history , obstetric history, history of previous surgeries, medical problems could be present

Examination: General, abdominal and vaginal examination.

Investigations: Laboratory investigations: Laboratory investigation as Hormonal profile (basal FSH, LH , E2 & TSH & Prolactin). Husband semen analysis . Mid luteal serum progesterone for ovulation. Husband semen analysis .Complete blood count (CBC) ,blood group and Rh typing. Random blood sugar. Liver and kidney functions. **Other investigations:** Transvaginal ultrasound: on day 2-5 for assessment of the uterus and the adnexa for any lesion and to assess antral follicle count (AFC) for ovarian reserve assessment. Hystersalpingogram (HSG) : Mainly for tubal assessment

Ovulation induction : Group I received 100 mg clomiphene every day after lunch for 5 days. Group II received 500 mg of metformin three times a day and 100 mg clomiphene every day after lunch for 5 days. Group III received a dose 40 mg of tamoxifen every night for 5 days and 100 mg clomiphene every day after lunch for 5 days. Group IV received a dose of 5 mg Letrozole every night for 5 days and 100 mg clomiphene every day after lunch for 5 days. Group V received a dose of 75 IU/day of recombinant FSH every night for 5 days and 100 mg clomiphene every day after lunch for 5 days.

Follow up : Transvaginal ultrasound from day 9 to monitor the number and size of developing follicles and endometrial thickness .Pregnancy test

after missed period and follow up of pregnancy outcome.

Research outcome measures: Primary (main); Ovulation rate , no of follicle approaching > 18mm, incidence of ovarian cyst formation.. **Secondary:** Pregnancy rate, multiple pregnancy rate, miscarriage rate

Results

(**Table .1**) shows that there is no statistically significant difference between the studied groups as regard the age, and BMI. (**Table. 2**) shows that there is statistically significant higher LH level in group 1 than other groups while FSH is statistically significant lower in group 4 than other groups

Table 1. Age and BMI of the studied groups

Variables		Mean	SD	Rang		f	P-value	Sig.
				Min.	Max.			
Age (year)	Group 1	25.79	4.19	18	34	0.249	0.910	NS
	Group 2	26.05	4.33	19	34			
	Group 3	26.01	4.38	20	35			
	Group 4	26.34	3.67	20	34			
	Group 5	26.32	4.08	20	33			
BMI	Group 1	26.57	2.70	18	31	0.736	0.568	NS
	Group 2	26.50	3.09	18	30			
	Group 3	26.48	2.40	20	31			
	Group 4	26.05	3.36	18	30			
	Group 5	25.96	3.09	18	30			

	Post hoc analysis									
	G1 vs G2	G1 vs G3	G1 vs G4	G1 vs G5	G2 vs G3	G2 vs G4	G2 vs G5	G3 vs G4	G3 vs G5	G4 vs G5
Age	0.691	0.733	0.402	0.415	0.954	0.661	0.678	0.620	0.637	0.980
BMI	0.884	0.842	0.266	0.192	0.957	0.335	0.249	0.363	0.271	0.852

Table 2. Comparison of FSH and LH between the studied groups

Variables		Mean	SD	Rang		f	P-value	Sig.
				Min.	Max.			
FSH	Group 1	6.74	1.65	3.9	10	**3.764**	**0.005**	**HS**
	Group 2	6.83	1.51	3.8	10.4			
	Group 3	6.82	1.63	3.2	11			
	Group 4	6.06	1.50	3.5	9.5			
	Group 5	6.36	1.52	3.9	10.1			
LH	Group 1	5.13	1.17	2.7	8.7	**5.970**	**<0.0001**	**HS**
	Group 2	4.76	1.44	2	13			
	Group 3	4.42	1.19	1.8	8.5			
	Group 4	4.40	1.11	1.4	6.3			
	Group 5	4.38	1.09	2.1	6.8			

	Post hoc analysis									
	G1 vs G2	G1 vs G3	G1 vs G4	G1 vs G5	G2 vs G3	G2 vs G4	G2 vs G5	G3 vs G4	G3 vs G5	G4 vs G5
FSH	0.725	0.752	**0.006**	0.126	0.972	**0.002**	0.061	**0.002**	0.066	0.218
LH	0.052	**<0.0001**	**<0.0001**	**<0.0001**	0.073	0.057	0.044	0.911	0.829	0.917

(Table. 3) shows that there is statistically significant higher number of dominant follicle in group 4 and 5 than other groups while no statistically significant difference in number of dominant follicle is detected between group 4 and group 5.

Table 3. Comparison of the dominant follicle and antral follicle count (AFC) of the studied groups

		Mean	SD	Rang		f	P-value	Sig.
				Min.	Max.			
AFC	Group 1	17.33	5.49	5	24	0.304	0.876	**NS**
	Group 2	17.86	5.31	6	24			
	Group 3	17.79	5.59	5	24			
	Group 4	18.24	5.31	6	24			
	Group 5	17.99	5.31	6	28			
Dominant Follicle	Group 1	14.43	2.76	10	22	6.955	<0.0001	**HS**
	Group 2	14.19	2.39	10	21			
	Group 3	14.48	2.64	10	21			
	Group 4	15.99	2.86	11	21			
	Group 5	15.68	3.20	11	21			

	Post hoc analysis									
	G1 vs G2	**G1 vs G3**	**G1 vs G4**	**G1 vs G5**	**G2 vs G3**	**G2 vs G4**	**G2 vs G5**	**G3 vs G4**	**G3 vs G5**	**G4 vs G5**
AFC	0.535	0.594	0.289	0.441	0.930	0.661	0.883	0.599	0.814	0.769
Dominant follicle	0.577	0.922	<0.0001	0.005	0.514	<0.0001	0.001	0.001	0.006	0.482

Table 4. Comparison of endometrial thickness of the studied groups

Variables		**Mean**	**SD**	**Rang**		**f**	**P-value**	**Sig.**
				Min.	**Max.**			
Endometrial thickness	**Group 1**	**6.55**	**1.63**	**3.4**	**11**	**22.892**	**<0.0001**	**HS**
	Group 2	**7.00**	**1.61**	**3.4**	**10**			
	Group 3	**8.73**	**1.84**	**4**	**12**			
	Group 4	**8.32**	**1.97**	**3.5**	**12**			
	Group 5	**8.13**	**1.62**	**3.9**	**12**			

	Post hoc analysis									
	G1 vs G2	**G1 vs G3**	**G1 vs G4**	**G1 vs G5**	**G2 vs G3**	**G2 vs G4**	**G2 vs G5**	**G3 vs G4**	**G3 vs G5**	**G4 vs G5**
Endometrial thickness	0.097	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.132	0.029	0.502

(**Table .4**) shows that group 1 has statistically significant lowest endometrial thickness than other groups followed by group 2 while group 3 has statistically significant highest thickness than other groups. There is no statistically significant difference in endometrial thickness between group 4 and 5.

Table 5. Comparison of the clinical data of the studied groups

Variables		Group 1	Group 2	Group 3	Group 4	Group 5	X^2	P-value	Sig.
Follicle number	1	69	68	70	51	58	21.007	<0.0001	HS
		86.3%	85.0%	87.5%	63.8%	72.5%			
	2	11	12	10	29	22			
		13.8%	15.0%	12.5%	36.3%	27.5%			
Ovarian cyst	No	79	77	76	76	72	6.842	0.144	NS
		98.8%	96.3%	95.0%	95.0%	90.0%			
	Yes	1	3	4	4	8			
		1.3%	3.8%	5.0%	5.0%	10.0%			
Ovulation	No	41	59	53	25	33	39.158	<0.0001	HS
		51.3%	73.8%	66.3%	31.3%	41.3%			
	Yes	39	21	27	55	47			
		48.8%	26.3%	33.8%	68.8%	58.8%			
Pregnancy	No	62	68	63	53	53	11.577	0.021	HS
		77.5%	85.0%	78.8%	66.3%	66.3%			
	Yes	18	12	17	27	27			
		22.5%	15.0%	21.3%	33.8%	33.8%			
Miscarriage	No	74	74	76	69	72	4.384	0.357	NS
		92.5%	92.5%	95.0%	86.3%	90.0%			
	Yes	6	6	4	11	8			
		7.5%	7.5%	5.0%	13.8%	10.0%			
Multiple Pregnancy	No	80	80	79	80	78	5.374	0.251	NS
		100.0%	100.0%	98.8%	100.0%	97.5%			
	Yes	0	0	1	0	2			
		0.0%	0.0%	1.3%	0.0%	2.5%			

(**Table. 5**) shows that group 4 and 5 has statistically significant higher number of follicles (1 follicle in 63.8 %, and 72.5 % respectively and 2 follicles in 36.3 % and 27.5 % respectively) and also higher pregnancy rate than other groups (66.3 % for each group) . Ovulation is statistically significant lower in group 2 and 3 than other groups (26.3 % , 33.8 % repectively) .

Discussion

The most frequent reason for anovulatory infertility is polycystic ovarian syndrome (PCOS) (**Mejia et al ., 2019**). Focusing on ovulation induction, PCOS patients' infertility is treated. For a long time, clomiphene citrate has been the medicine of choice. Tamoxifen, however, has also shown to be highly effective and functions similarly to clomiphene, with the exception that it has a favourable effect on the endometrium and cervical mucus (**Legro and Richard ,2016**). Letrozole is another medication that suppresses oestrogen levels in PCOS patients by causing ovulation by blocking the enzyme aromatase. The monovulation benefit of letrozole is its primary benefit in ovulation induction since it lowers the likelihood of multiple pregnancies. (**Mejia et al ., 2019**). Recombinant FSH for injection is another treatment when taking oral medicine does not result in a pregnancy (**Razi et al ., 2014**). Metformin has grown in popularity and is increasingly being administered before to CC in many patients with positive results because it has been demonstrated that insulin resistance is crucial in this syndrome (**Neveu et al ., 2007**).

The primary objective of this study was to assess the clinical outcomes of anovulatory women while comparing the efficacy of clomiphene citrate alone with various combinations (tamoxifen, metformin, letrozole, and low dose gonadotrophins).

This randomized trial was carried out at Obstetrics and Gynecology Department, Qena

University Hospital , South Valley University. 400 PCOS cases were enrolled in the study and were divided into five groups using various induction methods.

As regard socio-demographic data we found that the mean age of clomiphene group was 25.79±4.19 with range (18-34) and mean BMI was 26.57±2.70 with range (18-31) and there was no statistically significant difference between the studied groups as regard the age, and BMI.

According to **Mejia et al., 2019**, a study aimed to determine whether letrozole alone or clomiphene citrate (CC) combined with letrozole results in higher ovulation rates than letrozole alone in infertile women with polycystic ovary syndrome (PCOS) found that mean age of the letrozole group vs letrozole and clomiphene group was 31±3.9 vs 30±4.4 respectively and mean BMI was 33±8.7 vs 34±7.0 respectively and there was no significant differences between both groups.

Additionally, **Elshamy and Khalafallah (2018)** sought to compare the effects of clomiphene citrate, tamoxifen, and letrozole in women with PCOS and discovered that there were no significant differences in the mean ages of the groups under study for any of the drugs (clomiphene, tamoxifen, and letrozole, respectively) which was 26.91 ±2.69 , 27.24 ±2.75 and 27.50 ±2.99 respectively.

Also in the current study there is no statistically significant difference in E2 and level but there is statistically significant higher LH level in clomiphene group than other groups while FSH is statistically significant lower in clomiphene and Letrozole group than other groups.

In contrast **Sagnita et al ., 2021** who compared tamoxifen and clomiphene citrate for ovulation induction on 104 PCOS-afflicted women discovered no statistically significant difference between the 2 groups in terms of basal FSH and LH.

Our study results found that there is statistically significant higher number of dominant follicle in group (clomiphene and letrozole) and (clomiphene and recombinant FSH) than other groups while no statistically significant difference in number of dominant follicle is detected between them.

This is consistent with **Badr 2022**, who compared the effects of clomiphene citrate and letrozole versus letrozole alone in treating PCOS. In this randomized controlled trial, 64 infertile women with PCOS were evaluated, and it was discovered that there was a significant difference in the number of follicles (P value 0.006). The appearance of one follicle was more in group B (clomiphene-letrozole) than group A (letrozole only) , (68.8% in group B versus 37.5% in group A). And 6.3 % of group B had 2 mature follicles which does not happen in group A. The follicular size appeared significance with P value (<0.001) as group B ranges (20.21±1.47) versus group A (17.17±0.94). This was similar to **Hajishafiha et al., 2013** which revealed that when clomiphene and letrozole were combined, PCOS patients developed dominant follicles in 82.9% of cases, achieved pregnancy in 42% of cases, and had improved resistance to the individual drugs.

Moreover, **Rasekhjahromi et al. (2015)** discovered that a good ovulation rate of 20% was achieved when Clomid and Letrozole were used for the induction of ovulation in PCOS patients.

In the current study as regard endometrial thickness, clomiphene group has statistically significant lowest thickness than other groups mean (6.55±1.63) followed by (clomiphene and metformin) while (clomiphene and tamoxifen) has statistically significant highest thickness than other groups. There is no statistically significant difference in endometrial thickness between (clomiphene and letrozole) and (clomiphene and recombinant FSH).

In accordance to **Badr, 2022**, Endometrial thickness exhibits significance with a P value < 0.001 and the range was (10.06±1.6) in (clomiphene-letrozole), which was better than letrozole alone (8.13±1.79).

Also **Najafi et al2020** .'s study, a double-blind, randomized clinical trial study was conducted in Iran to compare letrozole and clomiphene citrate in women with polycystic ovaries. It found a statistically significant association between the type of medication and the endometrial thickness (p=0.001), and the endometrium thickness was lower in the clomiphene group than the letrozole group.

Also in line with **Elshamy and Khalafallah (2018)**, a study that compared the effectiveness of clomiphene citrate, tamoxifen (TMX), and letrozole as a first-line treatment for inducing ovulation in anovulatory women with polycystic ovary syndrome revealed a statistically significant difference between the clomiphene citrate group on one side and both tamoxifen and letrozole on the other side as regards preovulatory endometrial

thickness being thicker in group 2 (letrozole) and group 3 (TMX) than group 1 (clomiphene).

In the current study we found that (clomiphene and letrozole) and (clomiphene and recombinant FSH) had statistically significant higher number of follicles and higher pregnancy rate than other groups. Ovulation is statistically significant lower in (clomiphene and metformin) and (clomiphene and tamoxifen) than other groups.

This is consistent with a study conducted on 150 PCO patients in 2018 by **Abd-Allatif et al.,** which compared the effectiveness of aromatase inhibitors (letrozole), clomiphene citrate, and recombinant (FSH) on inducing ovulation in PCOS. It found that FSH was the most effective for doing so, followed by Letrozole, and the least effective was clomiphene citrate. Additionally in **Badr 2022**, just 6.3% of the group A recipients of letrozole alone got pregnant, compared to 12.5% of group B recipients of the combined therapy (clomiphene and letrozole).

Mejia et al. 2019 stated that Women who received letrozole and clomiphene together had a statistically greater ovulation rate than women who received letrozole alone (27 of 35 women (77%) vs. 15 of 35 women (43%)).Also according to **El Sedeek and El Maghra (2011)**, who studied 124 patients with anovulation and divided them into two groups (CC and letrozole), they discovered that the letrozole group's mean endometrial thickness was higher than the CC group's (8.3 mm compared to 7.2 mm), and the CC group's follicle count was higher than the letrozole group's, pregnancy rate was greater in the letrozole group than the CC group (33% vs. 28% respectively), and ovulation rate was higher in the letrozole group than the CC group (69.5% vs. 4%).

This was also supported by **Weiss et al2019 's** study, which compared the effectiveness and safety of gonadotrophins as a second-line treatment for ovulation induction in women with clomiphene citrate-resistant polycystic ovary syndrome and they discovered that gonadotrophins led to more clinical pregnancies than continued clomiphene.

In contrast to our findings, **Sharma et al., 2021** a study comparing the efficacy of tamoxifen and clomiphene citrate in inducing ovulation in women with PCOS and anovulation found that ovulation induction with tamoxifen resulted in fewer dominant follicles, better endometrial thickness, and comparable ovulation and pregnancy rates when compared to clomiphene.

Conclusion

Combination of clomiphene with either letrozole or recombinant FSH had proved to be the most effective combination in induction of ovulation in PCOS with higher number of follicles and higher pregnancy rate than other combinations.

References

- **Abd-Allatif EM, Mohammed MF, Doweir HM (2018).** A Comparison of efficacy of aromatase inhibitors (Letrozole), clomiphene citrate and recombinant FSH in induction of ovulation in polycystic ovarian syndrome. The Egyptian Journal of Hospital Medicine, 72(8): 4995-5000.
- **Badr FS (2022).** Combined letrozole with clomiphene citrate versus letrozole only in induction of ovulation in polycystic ovary syndrome patients (A randomized controlled trial). The Egyptian Journal of Fertility of Sterility, 26(3): 33-39.
- **Bhandari PY, Gautam N, Akanksha G (2016).** "Chronic Ultra Low-dose Step-up Protocol for Patients with Polycystic Ovary Syndrome." Manual of Ovulation Induction & Ovarian Stimulation Protocols, 1(35): 347-360.
- **Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E(2009).** Clomiphene and anti-estrogens for ovulation induction in PCOS. Cochrane Database of Systematic Reviews, 12(4): 18-20.
- **Edessy M, Nasr AAM., Fouad M, Ali AA, El Batal K, Abd El hamed A, Gamal Y (2016).** Reproductive outcome of Ovulation Induction for Polycystic Ovary Syndrome Patients according To Edessy Ovarian Reserve Score, American Research Journal of Gynecology, 1(1): 31-37.
- **Elsedeek MS, Elmaghraby HAH (2011).** Predictors and characteristics of letrozole induced ovulation in comparison with clomiphene-induced ovulation in ovulatory PCOS women. Middle East Fertility Society Journal.16(2):125–130.
- **Elshamy E, Khalafallah M (2018).** Impact of clomiphene citrate, tamoxifen and letrozole to induce ovulation in anovulatory women with polycystic ovary syndrome on endometrial thickness and clinical pregnancy rates, a two

center cohort study. Obstetrics and Gynecology International Journal, 9(4): 260-264.

- **Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B (2009).** Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. Journal of assisted reproduction and genetics, 26(1): 19-24.
- **Hajishafiha M, Dehghan M, Kiarang N, Sadegh-Asadi N, Shayegh SN, Ghasemi-Rad M (2013).** Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome. Drug design, development and therapy, 3(7): 1427-1431.
- **Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, Welt CK (2013).** Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology and metabolism, 98(12): 4565–4592.
- **Mejia RB, Summers KM, Kresowik JD, Van Voorhis BJ (2019).** A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome. Fertility and sterility, 111(3): 571-578.
- **Najafi PZ, Noghabi SP, Afzali N, Mohammadzadeh S (2020).** Comparing the effect of clomiphene citrate and letrozole on ovulation induction in infertile women with polycystic ovary syndrome. The Journal of the Pakistan Medical Association, 70(2): 268-271.
- **Neveu N, Granger L, St-Michel P, Lavoie HB (2007)**. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome. Fertility and sterility, 87(1): 113-120.
- **Rasekhjahromi A, Maalhagh M, Hosseinpoor M, Farhang H, Alavi F (2015).** A Clomiphene Citrate and Letrozol Varsus Tamoxifen and Letrozole as an Infertility Treatment in Women with Polycystic Ovary Syndrome. Pakistan Journal of Biological Sciences,18(6): 300-303.
- **Razi MH, Mohseni F, Firouzabadi RD, Janati S, Yari N, Etebary S (2014)**: Results from adding recombinant LH for assisted reproductive technology treatment: A randomized control trial. Iran Journal of Reproductive Medicine, 12(2): 111-116.
- **Sharma S, Choudhary M, Swarankar V, Vaishnav V (2021).** Comparison of Tamoxifen and Clomiphene Citrate for Ovulation Induction in Women with Polycystic Ovarian Syndrome: A Prospective Study. Journal of Reproduction & Infertility, 22(4): 274-279.
- **Weiss NS, Kostova E, Nahuis M, Mol BWJ, Van der Veen F, Van Wely M (2019).** Gonadotrophins for ovulation induction in women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews,16(1): 72-73.
- **Welt CK (2021).** Genetics of Polycystic Ovary Syndrome: What is New?. Endocrinology and Metabolism Clinics, 50(1): 71-82.
- **Witchel SF, Oberfield SE, Peña AS (2019**). Polycystic Ovary Syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent Girls. Journal of the Endocrine Society, 3(8):1545–1573.