Comparison between Metformin and Clomiphene Citrate Therapy for Treatment of Anovulatory Infertility in Cases of Polycystic Ovary Syndrome

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Abstract: Background: Polycystic ovary syndrome (PCOS) is characterized by a combination of hormonal and metabolic disturbances, such as insulin resistance, glucose intolerance, anovulation and hyperandrogenism. Clinical phenotypes of PCOS show different patterns of steroid hormones that have been investigated to some extent. **Aim of the Work**: The aim of work is to compare the efficacy of Metformin and Clomiphene citrate therapies in treatment of anovulation in infertile patients with PCOS and to determine which of them is better as a first line medication. **Patients and Methods:** This prospective study was conducted on 300 women with PCOS who were recruited from outpatient clinic of Banha Teaching Hospital. **Results:** Clomiphene citrate achieved a cumulative rate of ovulation of 51.7% while Metformin achieved 48.7%. So, there was no statistically significant difference between both groups as regard cumulative rate of ovulation (P>0.05). **Conclusion:** The results of the present study are comparable to previous reported studies revealed that both CC and Metformin are effective in treatment of infertility in PCOS patients. One limiting step of the present study is the small number of included subjects. **Recommendations:** It is advised to design larger prospective studies to compare the effects of both drugs in the future.
[Mohammad Samir Fouad, Mohammad Mohammad El Khouly, Ahmed Fathi Abd Al-Aziz and Adel Nagah Mohammad. **Comparison between Metformin and Clomiphene Citrate Therapy for Treatment of Anovulatory Infertility in Cases of Polycystic Ovary Syndrome.** *Nat Sci* 2017;15(4):36-42]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 6. doi:10.7537/marsnsj150417.06.

Key words: PCOS, hyperandrogenism, Clomiphene citrate, Metformin, insulin resistance

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility and affects 4-7% of women **(Kim and Choi, 2013)**.

It is by far the most common cause of hyperandrogenicanovulatory infertility and was described more than half a century ago. The underlying cause of this disorder is still uncertain **(El-Gharib et al., 2015).**

The diagnostic criteria for PCOS were revised at a consensus conference jointly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) in Rotterdam, The Netherlands in 2003.

The diagnosis now requires the presence of at least two of the following features:

- Polycystic ovaries.
- Oligo-ovulation or anovulation.
- Clinical and/or biochemical evidence of androgen excess.**(Jayasena and Franks, 2014)**

Metformin is a biguanide currently used as an oral antihyperglycemic agent and is approved by US Food & Drug Administration to manage type 2 DM. The benefits of metformin on insulin sensitivity have been demonstrated in non-DM women with PCOS **(Sinai-Talaulikar et al., 2016).**

The use of metformin in cases of PCOS is associated with increased menstrual cyclisity, improved ovulation and a reduction in circulating androgen levels **(Nestler, 2008a; Lashen, 2010)**.

Clomiphene citrate (CC) this compound has had a remarkably sustained career as the first-line treatment for women with absent or irregular ovulation due to hypothalamic–pituitary dysfunction associated with normal basal levels of endogenous estradiol (WHO group II) **(Katsikis et al., 2006).**

CC was the first medication capable of inducing ovulation and as such created a welcome revolution in the treatment of infertility associated with anovulation **(Roy et al., 2012).**

Aim of the Work

The aim of work is to compare the efficacy of Metformin and Clomiphene citrate therapies in treatment of anovulation in infertile patients with PCOS and to determine which of them is better as a first line medication.

2. Patients and Methods:

1- Patients:

This prospective study was conducted on 300 women with PCOS who were recruited from outpatient clinic of Banha Teaching Hospital.

- **Inclusion Criteria**

1- Primary or secondary infertility.
2- Age between 18 and 39 years.
3- PCOS as diagnosed by at least two out of three of the following (according to the American society of reproductive medicine):

- Clinical or biochemical evidence of androgen excess.
- Oligo and / or anovulation.
- Ultrasound appearance of the ovaries shows more than 12 follicles in each ovary each measures 2: 9 mm.

4- Normal levels of TSH and prolactin.
5- Normal renal functions (assessed by creatinine level).
6- Normal liver functions (assessed ALT and AST).

- **Exclusion Criteria**

1- Impaired renal or liver functions.
2- Contraindication or known allergy to the study medications.
3- Morbid obesity (BMI exceeded 35 kg /m^2).
4- Diabetes mellitus.

2- Methods:

The following was done to all patients after obtaining their informed consents:

1- History taking

a. At the first visit, detailed history was taken. It included age, duration of infertility, menstrual history, symptoms and signs suggestive of endocrine disorders, history of chronic diseases including diabetes mellitus and hypertension, surgical history which includes laparoscopy e.g. (ovarian drilling) and laparotomy.

b. Women were also asked about previous investigations that had been done for infertility and any previous treatment that has been given for induction of ovulation.

2- General, abdominal and pelvic examination were carried out.

3- Pelvic ultrasound was performed to confirm the presence ultrasound picture of polycystic ovaries.

4- Weight and height measurement and body mass index (BMI) calculation (BMI= weight/height in meters²).

5-Venous blood samples were obtained for measurements of:

- Fasting glucose and 2 hours postprandial.
- Mid luteal serum progesterone (normal: more than 3 ng/ml).
- Total testosterone (normal: 15-70 ng/dL), free testosterone (normal: 0.5 – 5 pg/ml).
- FSH (normal: 3-10 mIU/ml), LH (normal: less than 7 mIU/ml).
- AST (normal: 5 to 40 units per liter) and ALT (normal: 7 to 56 units per liter).
- Creatinine (0.5 to 1.0 mg/dL).

The patients are divided into two groups:

➢ **Group A:** included 150 women received metformin, (cidophage; chemical industries development (C I D), Cairo, Egypt), 500mg two times daily then follow up by folliculometry.

➢ **Group B:** included 150 women received clomiphene citrate for induction of ovulation starting from day 2 of the cycle for 5 days with starting dose of 50 mg/day up to 100 mg/day.

The drug administration was continued in six cycles for all women except who got pregnant.

Follow up:

All cases were followed up for 6 cycles by transvaginal ultrasound folliculometry and by progesterone level at day 22nd of the cycle to document ovulation. Each lady has to evacuate the urinary bladder and transvagianalultrasound were done.

Transvaginal ultrasound was performed using the 5-7.5 MHZ

Ultrasound was done starting from the day 10 of the cycle and repeated according to the size of the follicles. Follicles measure more than 18mm were considered mature follicles.

The following measures were done for all patients:

- Endometrial thickness in (mm) at the greatest diameter perpendicular to the midsagittal plane in the fundal region including both layers of the endometrial cavity.
- Diameter of the growing follicle.
- Number of growing follicles.

Evidence of failure to respond to induction was documented by failure of follicular maturation.

TVS was done one week after missed period for diagnosis of pregnancy by detection of gestational sac.

- **Outcome measures:**

The primary outcome was the ovulation rate.

The 2ry outcome was the pregnancy rate.

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.

- Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
- Probability (P-value).
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

3- Results

In the present study, 300 patients were recruited and equally divided into two groups. Each one includes 150 patients. The 1st group is Clomiphene citrate group and the 2nd group is Metformin group.

In the present study, there was no statistically significant difference between CC group and Metformin group as regard pattern of menses, neither before treatment (90 cases 60.0%) had oligomenorrhea in CC group and (80 cases 53.3%) in Metformin group, nor after treatment (35 cases 23.3%) had oligomenorrhea in CC group and (50 cases 33.3%) in Metformin group.

However, there was statistically significant decrease in oligomenorrhea after treatment in comparison to their values before treatment in both groups. These results by Chi Square test means that, both CC and Metformin had nearly equal effect in regulating menstrual cycle.

As regard effect of treatment on ovulation, CC reported 53.3% ovulation at the first cycle after treatment, decreased to 50.3% at the second cycle and decreased to 51.0% at the third cycle, increased to 61.2% at the fourth cycle, decreased to 45.1% at the fifth cycle and increased to 59.6% at the sixth cycle. On the other hand, Metformin reported 43.3% ovulation at first cycle after treatment, which increased to 56.7% at the second cycle, then decreased to 33.8% at the third cycle, then increased to 60.5% at the fourth cycle, then decreased to 44.1% at the fifth cycle and increased to 59.4% at the sixth cycle.

CC achieved a cumulative rate of ovulation of 51.7% while Metformin achieved 48.7%. So, there was no statistically significant difference between both groups as regard cumulative rate of ovulation (P>0.05).

Table (1): Comparison between CC group and Metformin group as regard menses pattern before and after treatment. Data are presented as number (frequency).

Oligomenorrhea	CC	Metformin	x^2	P
Before treatment	90 (60%)	80 (53.3%)	0.656	0.731 NS
After treatment	35 (23.3%)	50 (33.3%)	1.115	0.359 NS
P	**<0.001 HS**	**<0.001 HS**		

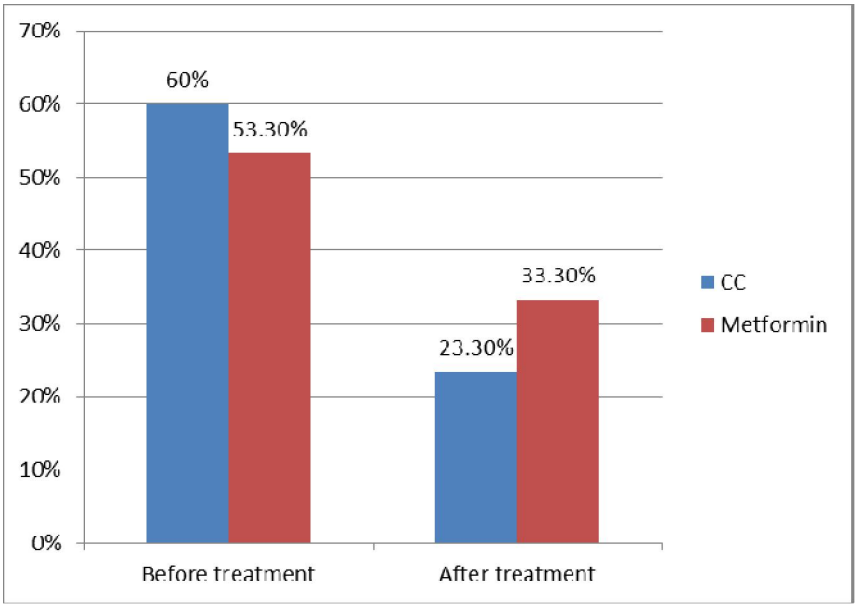

Figure (1): Comparison between CC group and Metformin groupas regard menstrual pattern before and after treatment.

Table (2): Effect of treatment on ovulation in both groups. Data are presented as number (frequency).

Ovulation	CC	Metformin	x^2	p-value
Ovulation after one month treatment	80/150 (53.3%)	65/150 (43.3%)	0.580	0.800 NS
Ovulation after two months treatment	75/149 (50.3%)	85/150 (56.7%)	0.987	0.293 NS
Ovulation after three months treatment	75/147 (51%)	50/148 (33.8%)	0.334	0.591 NS
Ovulation after four months treatment	90/147 (61.2%)	89/147 (60.5%)	0.038	0.842 NS
Ovulation after five months treatment	65/144 (45.1%)	64/145 (44.1%)	1.085	0.295 NS
Ovulation after six months treatment	84/141 (59.6%)	85/143 (59.4%)	0.067	0.733 NS
Cumulative ovulation	465 (51.7%)	438 (48.7%)	0.702	0.678 NS

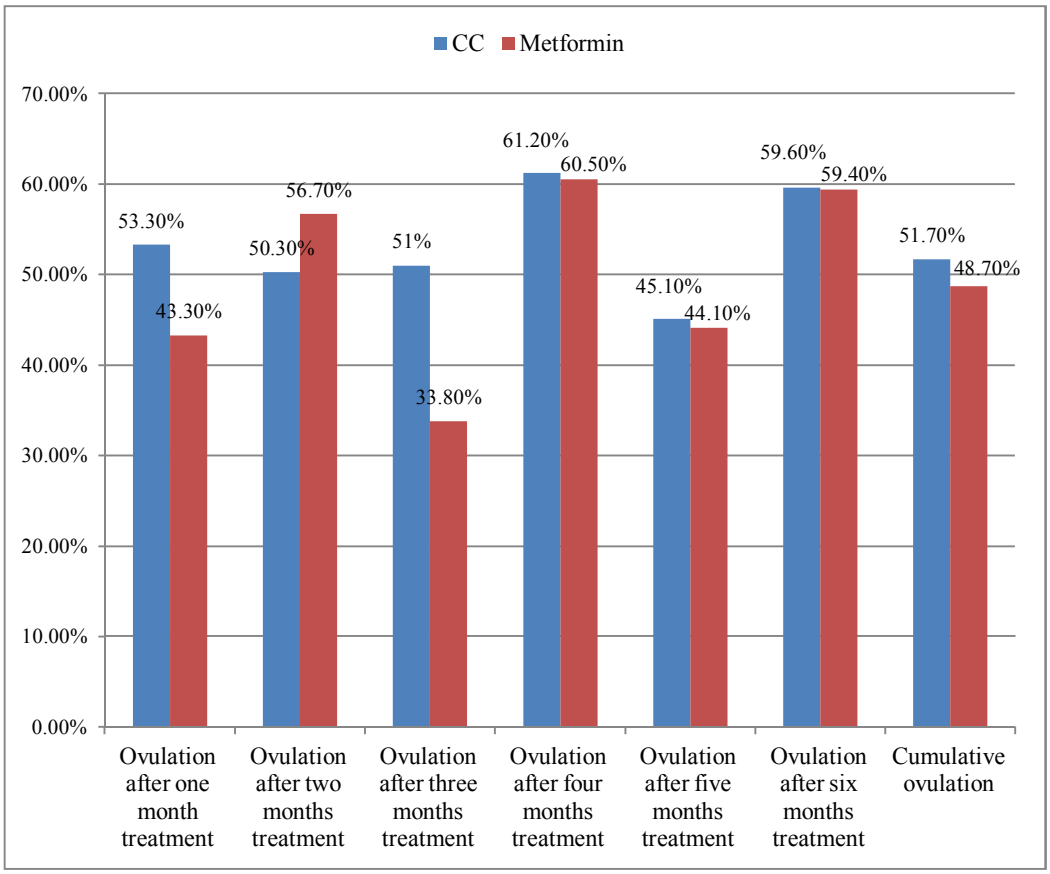

Figure (2): Effect of treatment on ovulation in studied groups

4. Discussion

Polycystic ovary syndrome (PCOS), also called hyperandrogenic anovulation (HA), is one of the most common endocrine disorders among females. PCOS has a diverse range of causes that are not entirely understood, but there is strong evidence that it is largely a genetic disease**(Diedrich et al., 2011).**

The most common immediate symptoms are anovulation, excess androgenic hormones and insulin resistance. Anovulation results in irregular menstruation, amenorrhea and ovulation-related infertility. Hormone imbalance generally causes acne and hirsutism. Insulin resistance is associated with obesity, type 2 diabetes and high cholesterol levels**(Teede et al., 2010).** The symptoms and severity of the syndrome vary greatly among affected women.

Clomiphene citrate is considered first-line therapy for ovulation induction for women with PCOS

and infertility **(The Thessaloniki ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2013).**

Many clinical studies have addressed the impact of metformin treatment on hyperandrogenemia in women with PCOS. Most, but not all, studies have confirmed that metformin treatment since then, for at least 6 months reduces androgen levels in women with PCOS **(Diamanti-Kandarakis, 2008).**

Metformin monotherapy, as compared to placebo, has been shown to improve ovulation rates in women with PCOS in randomized controlled trials (RCTs) and cohort studies. However, only few of them had pregnancy as a defined outcome measure **(Lord et al., 2003).**

The present study was designed to compare the efficacy of Metformin and Clomiphene citrate therapies in treatment of anovulation in infertile patients with PCOS and to determine which of them is better as a first line medication.

The results of the present study revealed that both types of treatment were effective in treatment of PCOS patients, no statistically significant difference was found between CC group and metformin group as regard ovulation rate.

There was statistically significant decrease in oligomenorrhea after treatment in comparison to their values before treatment in both groups. These results by Chi Square test means that, both CC and Metformin had nearly equal effects in regulating menstrual cycle. This result agrees with the study of Vandermolen et al., 2001 which concluded that metformin improves menstrual cyclicity and ovulatory functions and may actually be more effective than clomiphene in inducing ovulation and subsequently pregnancy chances.

Fleming et al. (2003), in a randomized controlled trial demonstrated a significantly increased frequency of ovulation with metformin as compared to placebo in a group of 92 oligomenorrheic women with PCOS. This was achieved without any significant changes in the insulin response to glucose challenge after 14 weeks of metformin treatment in a dose of 850 mg, twice a day.

Another study was carried outto assess pregnancy outcome in anovulatory infertility patients diagnosed with polycystic ovary syndrome (PCOS) who were treated with metformin; which revealed that metformin alone in patients with PCOS results in a substantial number of pregnancies, with 69% (20/29) of those who ovulated conceived in less than 6 months**(Heard et al., 2002).**

In another prospective case control study which was carried out in Tikrit teaching hospital by **Salman et al. (2010),** sixty women with PCOS were included in the study, thirty patients received clomiphene citrate and thirty patients received clomiphene citrate and metformin for inducing ovulation. They concluded that both metformin and clomiphene citrate can be used as agents for induction ovulation in infertile patients. However, combination of clomiphene citrate and metformin can induce ovulation better than clomiphene alone.

A randomized controlled trial of independent cases and controls was conducted in Saudi Arabia by **Ayaz et al. (2013)** in which forty two subjects diagnosed as PCOS were divided into group A and B (21 subjects in each) for the management with CC + metformin and CC alone, respectively for 6 months. Group A achieved a higher rate of regular cycles, ovulation success, and conception than group B (71.4% vs. 38.1%), (76.2% vs. 38.1%) and (66.6% vs. 28.6%), respectively.

Johnson (2014) shows that the therapeutic option with clomiphene and metformin were effective in treating anovulatory infertility in polycystic ovarian syndrome patients more than clomiphene alone.

The capacity of metformin to attenuate both IR and androgen excess, at least in some patients, has rationalized the investigation of metformin's role in the management of reproductive failure in PCOS women. Metformin either alone or in combination with clomiphene citrate (CC) is a pharmaceutical option for ovulation induction in women with PCOS **(Practice Committee of the American Society for Reproductive Medicine, 2004).**

Our study doesn't agree with another clinical trial by **Legro et al. (2008),** in the USA comparing extended release Metformin (once a day) to combined Metformin and Clomiphene. It showed that Metformin was not as effective as originally thought when used as first line treatment in women with PCOS trying to conceive.

Another Systematic review and meta-analysis of the head-to-head randomized controlled trials (RCTs) by **Palomba&Nestler (2008b),** four head-to-head RCTs were identified and qualified for inclusion in the analysis data showed no difference in fertility improvement between the combination treatment and CC monotherapy.

Our study agrees with study by **Misso et al. (2013)** concludedthat there is insufficient evidence to establish a difference between metformin and clomiphene citrate in terms of ovulation, pregnancy and live birth.

Another randomized prospective study of **Khorram et al. (2006),** was done to determine if two weeks of metformin improves clomiphene citrate-induced ovulation and metabolic profiles in women with polycystic ovary syndrome. The study involved 31 subjects with PCOS and infertility. They were treated either with CC or CC+MET for 2 weeks. In the

CC/MET group, a significant increase in day 21 progesterone occurred, with 44% of subjects ovulating in the CC+MET group as compared with 6.7% in the CC group. Five subjects in the CC+MET group and none in the CC group conceived. In obese PCOS patients, 2 weeks of MET significantly reduces serum insulin and insulin resistance and increases SHBG levels, resulting in an improved response to CC. This regimen may be beneficial in noncompliant patients or those with intolerance to the side effects of MET.

In the study by **Moll et al. (2006),** 228 patients were randomized. The primary outcome of this study was the ovulation rate. The ovulation rate in the metformin and C/C group was 64% compared with 72% in the placebo and C/C group which was not statistically significant. There was no difference in the pregnancy rates or the abortion rates of the two groups.

Our study doesn't agree with another study by **Legro et al. (2008)** in which 626 PCOS patients were randomized. They concluded that C/C (22.5%) is superior to metformin (7.2%) but similar to the combination group (26.8%) in achieving live birth rates. They did not observe any difference in the abortion rates between the three groups and observed a significantly better live birth rate if the BMI is less than 30 regardless of the treatment options used.

Palomba et al. (2007) reported that 6-months clomiphene or metformin treatment resulted in cumulative pregnancy rates of 49 and 63%, respectively.

Study of **Zain et al. (2009),** to determine the first-line medication to be used in anovulatory patients with polycystic ovary syndrome (PCOS) for ovulation induction and pregnancy achievement in Asian women. These patients were assigned to three groups: group 1 (38 patients) received 500 mg of metformin three times a day; group 2 (39 patients) received clomiphene citrate (CC) at an incremental dose; group 3 (38 patients) received both medications. The ovulation rate was 23.7% in the metformin group, 59% in the CC group, and 68.4% in the combination treatment group. This was translated into a similar pregnancy rate and live birth rate, which were higher in the CC and combination groups compared to the metformin group, although statistically the differences were not significant.

The previous studies discovered that metformin is effective in inducing ovulation in women with PCOS. A Cochrane review of clinical trials comparing metformin vs. placebo for ovulation induction in women with PCOS reported that metformin is more effective than placebo in achieving ovulation. The studies of the Cochrane review concluded that metformin is an effective treatment for anovulation in women with PCOS, and its choice as a first line agent seems justified **(Fleming et al., 2003).**

So the studies that approved the efficacy of metformin **(Fleming et al., 2003), (Heard et al., 2002) (Khorram O et al., 2006)** demonstrated significantly increase frequency of ovulation with metformin.

In addition to the studies of **Salman et al. (2010), Johnson study (2014)** showed that Combination of clomiphene citrate and metformin can induce ovulation better than clomiphene alone.

Other studies that reported efficacy of clomiphene citrate **(Capelo et al., 2003), (Zainet al., 2009).** The studies that agree with our study **(Palomba S & Nestler, 2008a), (Moll et al., 2006).** Showed no difference in fertility improvement between the combination treatment and CC monotherapy. Also **Misso et al. (2013)** concludedthat there is insufficient evidence to establish a difference between metformin and clomiphene citrate. Another study that doesn't agree with our study, **Legro et al. (2008)** showed that metformin is not effective as originally thought when used as first line treatment. The relative clinical efficacy of clomiphene vs. metformin remains controversial.

The different results among these clinical studies may be explained by patient heterogeneity, including differences in genotype, BMI, and circulating androgen levels may account for some of differences.

Conclusion:

The results of the present study are comparable to previous reported studies revealed that both CC and Metformin are effective in treatment of infertility in PCOS patients. One limiting step of the present study is the small number of included subjects.

Recommendations:

It is advised to design larger prospective studies to compare the effects of both drugs in the future.

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