

The efficacy and safety of clomiphene citrate and metformin on ovulation induction in patients suffering from anovulatory infertility

Hardik Patel*, Prakruti Patel, R. K. Dikshit, Samidh Shah

Department of Pharmacology,
B. J. Medical College,
Ahmedabad, Gujarat, India

Received: 24 October 2015

Accepted: 14 November 2015

***Correspondence to:**

Dr. Hardik Patel,
Email: patelhardik8795@
gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Ovulation disorders are an important cause of infertility. Polycystic ovarian syndrome (PCOS) comprises almost 90% cases of all ovulatory disorders. Clomiphene citrate helps to stimulate ovulation. Recently, use of metformin to treat PCOS due to its insulin sensitizing property is increasing. Hence, this study was undertaken to evaluate efficacy and safety of clomiphene citrate and its combination with metformin on ovulation induction and pregnancy outcome in the treatment of anovulatory infertility.

Methods: This study was done in patients of primary infertility due to anovulatory cycles at Civil Hospital, Ahmedabad. Patients were treated with clomiphene citrate in incremental doses from 50 to 150 mg for a period of maximum 6 menstrual cycle. In patients of anovulatory infertility with PCOS, clomiphene citrate was given along with metformin. At every visit, abdominal and pelvic examination, the size of ovarian follicle, endometrial thickness by ultrasonography was recorded. Urine pregnancy test was done once the menstruation was overdue by 9 days. Adverse drug effects, if any were noted. If patient did not conceive, then whole treatment was repeated from the next menstrual cycle.

Results: Out of 53 patients, five patients were lost to follow-up. The mean age of the enrolled patients in the study was 26.04 ± 7.78 . There were 20 patients (41.67%) with body mass index (BMI) $< 25 \text{ kg/m}^2$ while 28 patients (58.33%) with BMI above 25 kg/m^2 . Among 21 patients who received clomiphene citrate alone in the study, 12 patients were ovulated (57.12%). Among 27 patients (PCOS) who received clomiphene with metformin, 18 patients were ovulated (66.74%). Pregnancy rate was 23.8% with clomiphene citrate alone while in PCOS patients, the pregnancy rate was 25.91%. Both clomiphene citrate and metformin were well tolerated in most of the patients.

Conclusion: Ovulation rate was significantly higher compared to pregnancy rate. We could not find any benefit of adding metformin to the standard treatment with clomiphene citrate.

Keywords: Clomiphene citrate, Infertility, Metformin

INTRODUCTION

Infertility is defined 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 The prevalence of infertility is increasing across the developed world.² Infertility is a medical and social condition that can cause considerable social, emotional, and psychological distress.³

The important etiological causes of male and female infertility are sperm defects, ovulation failure, unexplained infertility, tubal damage, endometriosis, failure or

infrequency of sexual intercourse, cervical mucus defects or dysfunction, and uterine abnormalities.⁴ In female, ovulation disorders, particularly anovulatory cycles are an important cause of infertility and these accounts for 30-40% cases of infertility.⁴ Polycystic ovarian syndrome (PCOS) comprises almost 90% cases of all ovulatory disorders. PCOS affects approximately 5-10% of the female population in developed countries.^{5,6} Women with this syndrome have hyperandrogenism, morphologic changes in the ovary (polycystic), inappropriate gonadotropin secretion (elevated levels of circulating luteinizing hormone), and insulin resistance with accompanying compensatory hyperinsulinemia.⁷

Observational studies report that weight loss is associated with improved spontaneous ovulation rates in women with PCOS.⁸ Drugs used in the treatment of anovulatory infertility are clomiphene citrate, metformin or combination of both. The anti-estrogen clomiphene citrate helps to stimulate ovulation in women who have infrequent or absent ovulation, unexplained infertility, PCOS, and in assisted reproductive technology.³ Recently, there has been interest in the use of metformin to treat PCOS. It has been shown to increase levels of sex hormone binding globulin, thought to be a secondary response of reducing hyperinsulinemia and thus reducing free testosterone levels in circulation. It also reduces luteinizing hormone (LH) concentrations and ovarian sensitivity to LH.⁴

This study was undertaken to evaluate efficacy and safety of clomiphene citrate and its combination with metformin on ovulation induction and pregnancy outcome in the treatment of an ovulatory infertility.

METHODS

This was a continuous, longitudinal, prospective, interventional, single center study which carried out over a period of 16-month between January 2012 and May 2013 in Obstetrics and Gynecology Department at Civil Hospital, B. J. Medical College Ahmedabad. Patients with primary infertility due to anovulatory cycles were included in the study. Patients with secondary infertility, diabetes mellitus or tuberculosis were excluded. Anovulatory cycles were diagnosed by clinical history, ultrasonography (USG), and hysterosalpingography. The male cause of infertility was diagnosed by sperm examination. For PCOS diagnosis, criteria set by Rotterdam was used (Rotterdam, 2003).

An approval was obtained from the Institutional Ethics Committee (IEC). A written informed consent was obtained from all patients enrolled in the study. We enrolled all newly diagnosed patients of primary anovulatory infertility based on inclusion and exclusion criteria as described above. During first visit, a detailed history was taken and general and systemic examination was performed by the Obstetrician-Gynecologist. General information of the patient, presenting complaints, past and family history were recorded. Routine investigations like a complete blood count and hemoglobin level were performed. Renal and liver function tests were performed if required. Additional information about personal habits, personal and family history was also obtained. All the informations were documented in case record form. Patients were treated with clomiphene citrate, 50 mg/day, for 5 days from 3rd to 7th day of menstruation for 1st cycle. If patient did not ovulate, the same dose of clomiphene citrate was given for next cycle. After 2 cycles of clomiphene if ovulation did not take place, a 100 mg dose of clomiphene citrate was given for 3rd and 4th cycles. If ovulation was still not achieved, 150 mg of clomiphene was given for 5th and 6th cycles. In patients of anovulatory infertility with

PCOS, clomiphene citrate was given in same way as above in different cycles along with metformin 500 mg thrice a day throughout the study.

The investigator followed the patient for every menstrual cycle for next 6 cycles. At every subsequent visit, the details of hemoglobin level, abdominal and pelvic examination, the size of ovarian follicle in both ovaries, endometrial thickness in millimeter by ultrasonography was recorded. In each patient, transvaginal follicular monitoring (USG) was started from day 9 of menstrual cycle; then, after every alternate day, USG was done to measure follicle size and endometrial thickness. When follicle reaches an around 15 mm in size, intercourse was advised. Urine pregnancy test was done once the menstruation was overdue by 9 days and later confirmed by transvaginal sonography which shows the presence of gestation sac with cardiac activity at the 7th week of gestation and then the patient was followed every 3 monthly for the first 6 months and then after every monthly until pregnancy termination. At every subsequent visit compliance of the patient and adverse drug effects, if any was noted. If patient did not conceive, then the whole cycle was repeated from the next menstrual cycle. This procedure was repeated for 6 cycles until the patient conceives. If patient did not conceive at the end of 6 cycles, clomiphene citrate was stopped and alternative treatment was suggested (Figure 1).

RESULTS

A total of 53 patients were enrolled during the study period and were followed up at every menstrual cycle for a period of maximum six cycles or until pregnancy terminates. Out of 53 patients, five patients were lost to follow-up by unknown reasons. Clinical profile and demographic details of patients were mentioned in Table 1.

Most of patients were between 20 and 35 years. The mean age of the enrolled patients in the study was

Table 1: Clinical profile and demographic details (n=48).

Characteristics	Number of subjects (%)
Age (years)	
20-25	20 (41.67)
26-30	24 (50)
>31	4 (8.33)
BMI (kg/m ²)	
<25	20 (41.67)
>25	28 (58.33)
Oligomenorrhea	22 (45.83)
Amenorrhea	26 (54.17)
Hirsutism	27 (56.25)
Acne	22 (45.83)

BMI: Body mass index

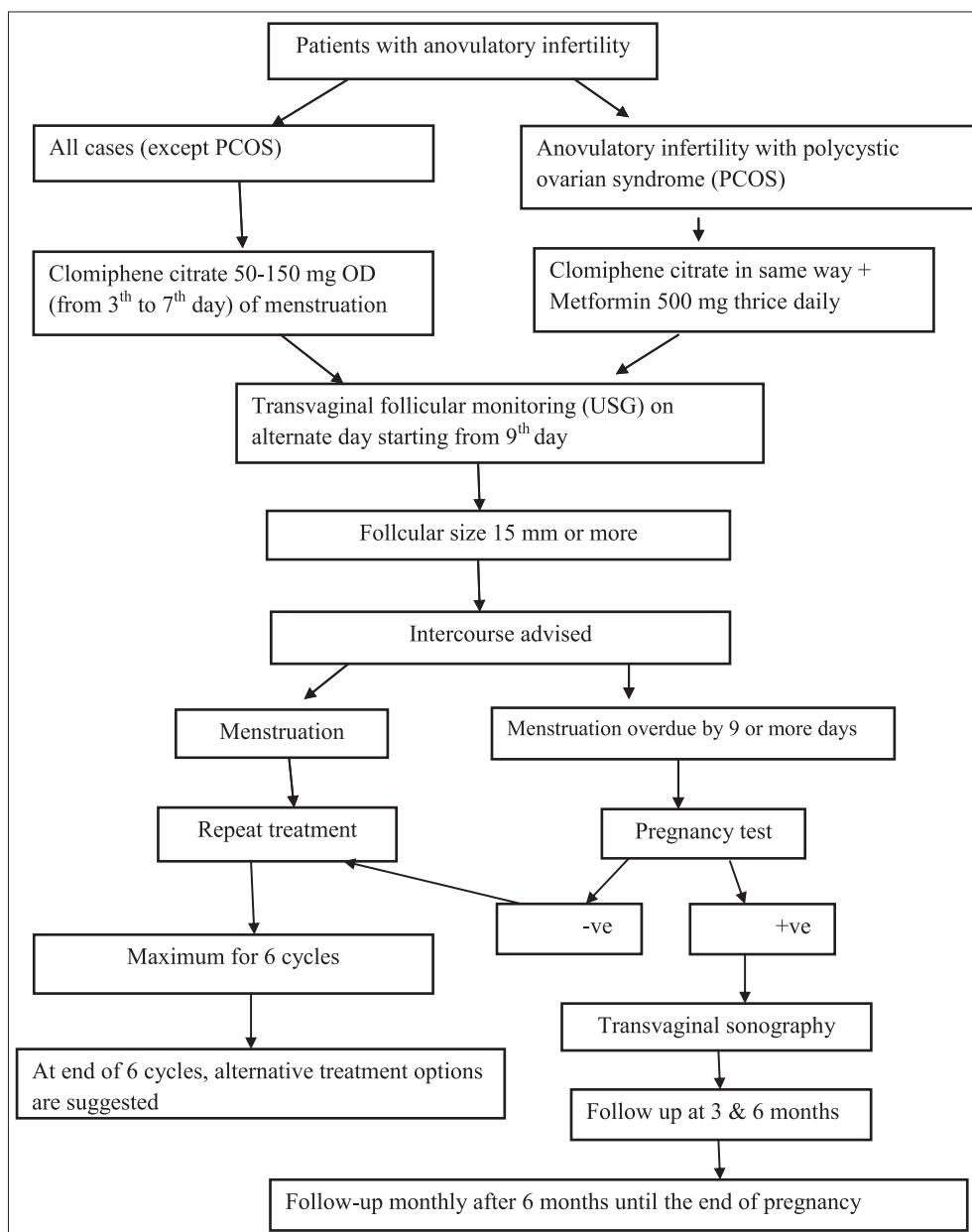


Figure 1: Study design.

26.04±7.78. Only 8.33% were more than 31 years of age. There were 20 patients (41.67%) with body mass index (BMI) <25 kg/m² while 28 patients (58.33%) with BMI above 25 kg/m². Around 50% patients had complained of hirsutism (56.25%) and amenorrhea (54.17). Acne (45.83%) and oligomenorrhea (45.83%) were also common presentation.

Among 48 patients, 27 (56.25%) patients have been diagnosed as polycystic ovary syndrome (PCOS) as per Rotterdam criteria.⁹ According to Rotterdam criteria,⁹ PCOS is defined as “if any 2 out of the following 3 criteria are met in patient (1) Oligoovulation and/or anovulation (2) Excess androgen activity and (3) Polycystic ovaries (by ultrasound). Remaining 21 patients were classified as idiopathic anovulatory infertility.

Patients with PCOS were prescribed clomiphene citrate and metformin while patients with idiopathic infertility were given clomiphene citrate alone. Anatomical therapeutic chemical code and daily defined dose (DDD) of clomiphene citrate and metformin were mentioned in Table 2.

Among 21 patients who received clomiphene citrate alone in the study, 12 patients were ovulated. Total ovulatory rate was 57.12% at end of the study. With 50 mg, 100 mg and 150 mg of clomiphene citrate in different cycles, ovulatory rate was 14.28%, 23.80% and 19.04% respectively. The highest ovulatory rate was 23.80% and that was achieved with 100 mg of clomiphene citrate in the third cycle (Table 3).

In PCOS patients, metformin was added to clomiphene citrate. Among 27 patients, 18 patients were ovulated

successfully. Total ovulatory rate among these patients was 66.74%. With 50 mg, 100 mg and 150 mg of clomiphene citrate in different cycles, ovulatory rate was 14.80%, 37.03% and 14.81%, respectively. The highest ovulatory rate was 37.03% and that was achieved with 100 mg of clomiphene citrate in third and fourth cycles (Table 4).

Endometrial thickness was positively correlated with ovulatory rate. However, in our study, endometrial thickness was varied from 7.1 to 7.8 mm and no significant difference was observed in ovulated and non-ovulated patients.

Among 48 patients, 12 patients became pregnant. Total pregnancy rate was 25% at end of the study. Pregnancy rate was 23.8% with clomiphene citrate alone. In PCOS patients where metformin was added to clomiphene citrate, the pregnancy rate was 25.91%. There was one twin pregnancy occurred with clomiphene citrate and metformin. There were no any loss of early gestation and congenital anomalies seen in the study (Tables 5 and 6).

Table 2: ATC code and DDD of clomiphene citrate and metformin.

ATC code	Name of drug	DDD	Unit	Route of administration
G03GB02	Clomiphene citrate	9	Mg	Oral
A10BA02	Metformin	2	G	Oral

ATC: Anatomical therapeutic chemical, DDD: Daily defined dose

Analysis of adverse drug reactions (ADRs)

Clomiphene citrate was well-tolerated in most of the patients. Two patients complained of abdominal discomfort during the first 2-3 days of therapy. However, it was mild and withdrawal of drug therapy was not required. One patient complained of rashes which gradually resolved. One patient complained of vomiting. Causality assessment of ADRs was done by Naranjo's algorithm. Accordingly to that 3 ADRs were "probable" while 1 was "possible." No case of ovarian hyperstimulation syndrome was observed.

A combination therapy of clomiphene citrate and metformin was also well tolerated in most of the patients. Five patients complained of diarrhea during the first 4-5 days of therapy. However, it was mild and subsided with continued therapy. Six patients complained of vomiting while five patients complained of anorexia. All of the adverse reactions were categorized as "possible" when analyzed according to Naranjo's algorithm. No case of ovarian hyper stimulation syndrome was observed.

DISCUSSION

Prevalence of infertility is increasing across the developed world.² Infertility is a medical and social condition that can cause considerable social, emotional and psychological distress.³ In females, ovulation disorders are an important cause of infertility and these accounts for 30-40% cases of infertility. PCOS comprises almost 90% cases of all

Table 3: Effect of clomiphene citrate alone on ovulation rate.

Cycle	Clomiphene citrate dose (mg)	Number of patients ovulated	Ovulatory rate (%)	Total ovulation rate (%)
1	50	2	9.52	14.28
2	50	1	4.76	
3	100	5	23.80	23.80
4	100	0	0	
5	150	3	14.28	19.04
6	150	1	4.76	
Total	-	12/21	57.12	57.12

Table 4: Effect of clomiphene citrate and metformin on ovulation in PCOS patients.

Cycle	Clomiphene citrate (mg)	Metformin dose (mg)	Number of patients ovulated	Ovulatory rate (%)	Total ovulatory rate (%)
1	50	1500	2	7.40	14.80
2	50	1500	2	7.40	
3	100	1500	6	22.22	37.03
4	100	1500	4	14.81	
5	150	1500	3	11.11	14.81
6	150	1500	1	3.70	
Total	-	-	18/27	66.64	66.64

PCOS: Polycystic ovarian syndrome

Table 5: Effect of clomiphene citrate alone on pregnancy rate.

Clomiphene citrate (mg)	Number of patients became pregnant	Pregnancy rate (%)
50	2	9.52
100	2	9.52
150	1	4.76
Total	5/12	23.8

Table 6: Effect of clomiphene citrate and metformin on pregnancy rate in PCOS patients.

Clomiphene citrate (mg)	Metformin (mg)	Number of patients became pregnant	Pregnancy rate (%)
50	1500	1	3.70
100	1500	2	7.40
150	1500	4	14.81
Total		7/27	25.91

PCOS: Polycystic ovarian syndrome

ovulatory disorders.⁵⁻⁶ Ovulation disorders often respond to simple treatments that can be safely initiated in primary care.⁴

In our study, we evaluated efficacy and safety of clomiphene citrate and its combination with metformin on ovulation induction and pregnancy outcome in the treatment of anovulatory infertility. Ovulatory rate was 57.12% with clomiphene citrate alone while it was 66.64% with clomiphene citrate and metformin combination in PCOS patients. Pregnancy rate was 23.8% with clomiphene citrate alone while it was 25.91% with clomiphene citrate and metformin combination in PCOS patients. Treatment was well-tolerated in most of patients.

In our study, mean age of the women was 26.04±7.78. Same finding was reported in other study by Legro et al., in the USA where mean age of patients was 27.9±4.0.⁷ Weight gain is one of the most common symptoms in patients of PCOS. It was reflected in our study as well as in other study by Moll et al. In our study, 41.67% patients were with BMI <25 kg/m² while 58.33% patients with BMI above 25 kg/m². In other study, 44.13% patients were with BMI <25 kg/m² while 55.87% patients with BMI above 25 kg/m².¹⁰ Other symptoms of PCOS are oligomenorrhea and hirsutism which were also present in our patients (45.83% and 56.25%, respectively).

The pharmacological management of infertility includes clomiphene citrate, metformin, and gonadotropins. In our study, all the patients have received clomiphene citrate in dose range (50-150 mg) and patients with PCOS also received metformin 1500 mg which as per recommended DDD.

In our study, ovulatory rate was 14.28%, 23.8%, and 19.04% with 50 mg, 100 mg, and 150 mg of clomiphene citrate, respectively. Other study reported ovulatory rate of 33.3%, 23%, and 57% with 50 mg, 100 mg, and 150 mg of clomiphene citrate, respectively.^{10,11} Total ovulatory rate in our study was 57.12% while in other study; it was observed 49%.⁷ In our study with a combination of clomiphene citrate and metformin, total ovulation rate achieved was 66.64%. Similar other studies using this combination reported ovulatory rate was 70%.¹¹

In our study, the pregnancy rate was 23.8%. In other studies using clomiphene citrate alone, pregnancy rate was 8%.¹¹ Clomiphene citrate alone was less effective in ovulation induction in patients of PCOS.¹² In above-mentioned study PCOS patients were more which may be reason for lower pregnancy rate compared to our study. In our study, pregnancy rate was 25.91% in patients who received clomiphene citrate and metformin. Other studies using this combination reported pregnancy rate was 24%.¹¹

We could not find any benefit of adding metformin to the standard treatment with clomiphene citrate. We found no significant differences in pregnancy rate and can exclude any substantial improvement in rates of ovulation and pregnancy. Metformin monotherapy induces ovulation through its insulin sensitizing effect. In our study, however, we failed to find an increase in ovulation rate of combined therapy compared with clomiphene citrate alone. The effects of metformin on ovulation may not be sufficiently strong to improve on the already high ovulation rates with clomiphene citrate in these women. Study done by Moll et al., (2006) also demonstrated that adding of metformin to clomiphene citrate was not associated with significant higher ovulation and pregnancy rate. In our study, ovulation rate was significantly higher compared to pregnancy rate. The reasons for the relatively low pregnancy rate are not clear, but may be related to the high LH levels, the anti-estrogenic effects of clomiphene on endometrium and to adverse effects on the oocytes.⁸

Clomiphene citrate, along with other ovulation induction therapies can cause multiple follicular developments, ovarian hyper stimulation and multiple pregnancies.¹⁰ One twin pregnancy was observed with clomiphene citrate and metformin in our study. Same combination also reported one twin pregnancy in other studies.^{11,13}

Clomiphene citrate as well as its combination with metformin was well-tolerated in most of patients in our study. No serious side effect was seen in patients. No case of ovarian hyperstimulation syndrome was observed. The incidence of ADRs as observed by us was significantly less than other study where 80% complained of loss of appetite and 24% had nausea and vomiting.¹¹ Under-reporting due to lack of awareness cannot be ruled out in our study.

Limitation of our study was small sample size which was because that many patients lost to follow-up. We followed

patient only for 6 cycles due to lack of time. A longer duration of study may be helpful to include more number of patients and give better results. Because of lack of the proper laboratory facilities and as most patients were from lower economic class, the follicle stimulating hormone, LH and thyroxin level were not done which would have helped us to correlate the cause of infertility and hence would have helped us to change treatment modality.

Overall, we said that drugs play an important role in the treatment of infertility. Clomiphene and clomiphene plus metformin are commonly used in the treatment of infertility at our center. A longer duration and a larger number of patients can give better results. Though the study has limited patients but this information can be used as a baseline data for further studies.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr Malini Desai, Head of Obstetrics and Gynecology department for her active support in the study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. World Health Organization. Definition of Infertility and other Reproductive Disorders. Available at <http://www.who.int/reproductivehealth/topics/infertility/definitions/en/>. Accessed 09 October 2015.
2. Goossens V, Traeger-Synodinos J, Coonen E, De Rycke M, Moutou C, Pehlivan T, et al. ESHRE PGD Consortium data collection XI: cycles from January to December 2008 with pregnancy follow-up to October 2009. *Hum Reprod* 2012;27(7):1887-911.
3. Women's Health Council. Infertility Treatments for Women.

- A Review of the Bio-medical Evidence Full Report. Dublin: Women's Health Council; 2009.
4. Cahill DJ, Wardle PG. Management of infertility. *BMJ*. 2002;325(7354):28-32.
 5. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med*. 2012;9(12):e1001356.
 6. Xita N, Georgiou I, Lazaros L, Psofaki V, Kolios G, Tsatsoulis A. The role of sex hormone-binding globulin and androgen receptor gene variants in the development of polycystic ovary syndrome. *Hum Reprod*. 2008;23(3):693-8.
 7. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2007;356(6):551-66.
 8. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. *Hum Reprod Update*. 2003;9(4):359-72.
 9. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004;89(6):2745-9.
 10. Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *BMJ*. 2006;332(7556):1485.
 11. Dasari P, Pranahita G. The efficacy of metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS. *J Hum Reprod Sci*. 2009;2(1):18-22.
 12. Homburg R. Clomiphene citrate – end of an era? A mini-review. *Hum Reprod*. 2005;20(8):2043-51.
 13. Batukan C, Baysal B. Metformin improves ovulation and pregnancy rates in patients with polycystic ovary syndrome. *Arch Gynecol Obstet*. 2001;265(3):124-7.

Cite this article as: Patel H, Patel P, Dikshit RK, Shah S. The efficacy and safety of clomiphene citrate and metformin on ovulation induction in patients suffering from an anovulatory infertility. *IntJBasicClinPharmacol*2015;4:1241-6.