Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
2 December 2013
Number of times this article has been viewed

Masomeh Hajishafiha[1]
Meisam Dehghan[2]
Nazila Kiarang[1]
Nahideh Sadegh-Asadi[1]
Seyed Navid Shayegh[3]
Mohammad Ghasemi-Rad[2]

[1]Department of Gynecology, Reproductive Health Research Center, Urmia University of Medical Sciences, [2]Urmia University of Medical Sciences, [3]Gulf Medical University, Ajman, United Arab Emirates

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age (6.8%–18%), is among the most common causes of infertility due to ovulation factors, and accounts for 55%–70% of infertility cases caused by chronic anovulation. In this study, we used a combination of letrozole and clomiphene in patients resistant to both drugs individually, and studied the effects of this combination in ovulation and pregnancy in resistant PCOS patients.

Methods: The study population included infertile couples diagnosed as PCOS in the wife. The women used clomiphene for at least six cycles in order to ovulate after failure to form the dominant follicle, and were then put on letrozole for four cycles. Patients who were unable to form the dominant follicle were enrolled on letrozole and clomiphene combination therapy.

Results: One hundred enrolled patients underwent 257 cycles of a combination of letrozole and clomiphene, in which 213 were able to form the dominant follicle (82.9%) and 44 were unable to do so (17.1%). The number of mature follicles was 2.3±1.1. The mean endometrial thickness in patients on the day of human chorionic gonadotropin administration was 8.17±1.3 mm. The pregnancy rate was 42%.

Conclusion: According to the results of this study, it can be proposed that in PCOS patients resistant to clomiphene and letrozole used as single agents, a combination of the two drugs can be administered before using more aggressive treatment that may have severe complications or surgery. This combination may also be used as a first-line therapy to induce ovulation in severe cases of PCOS in order to save time and expense.

Keywords: letrozole, clomiphene, combination therapy, infertility, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age. Its prevalence, using different diagnostic criteria, has been reported to be 6.8%–18%,[1,2] and it is estimated that a large number of patients are not diagnosed.[1] The first signs of PCOS are diagnosable in the prepubertal period, and given its heterogeneous nature, the beginning of symptoms in the patient can be accompanied by psychologic disorders such as depression and anxiety, along with irregular menstrual periods in adolescence and then infertility.[1,3]

In PCOS patients, excessive androgen secretion results in increased estrogen precursors in granulosa cells. In these patients, luteinizing hormone receptors, in the presence of hyperinsulinemia, appear earlier in granulosa cells, causing activation of aromatase in these cells. This phenomenon results in increased estrogen production,

Correspondence: Mohammad Ghasemi-Rad
Department of Medicine, Brigham and Women's Hospital, Harvard-MIT Division of Health Sciences and Technology, Harvard Medical School, Boston, MA, USA
Email medman11@gmail.com

© 2014 Hajishafiha et al. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution – Non Commercial (unported, v3.0) License. The full terms of the License are available at http://creativecommons.org/licenses/by-nc/3.0/. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. Permissions beyond the scope of the License are administered by Dove Medical Press Limited. Information on how to request permission may be found at: http://www.dovepress.com/permissions.php

with positive feedback on luteinizing hormone and negative feedback on follicle-stimulating hormone (FSH), and ultimately disruption of folliculogenesis.[4]

Hyperandrogenism and insulin resistance cause chronic anovulation and therefore infertility. Even if pregnancy does occur, it is associated with repeated spontaneous miscarraige in the first trimester and with gestational diabetes.[5] In general, clinical signs of PCOS consist of clinical or laboratory evidence of hyperandrogenism, oligoovulation, presence of PCOS, after ruling out other causes such as adrenal hyperplasia and hyperprolactinemia which consist of; 1) clinical or laboratory evidence of hyperandrogenism, 2) oligoovulation, 3) presence of polycystic ovaries in the sonography.

Anovulation or oligoovulation are important characteristics of PCOS. Oligoovulation manifests as irregular menstrual bleeding and is seen in 70% of patients.[6] In PCOS patients with a complaint of infertility, the treatment of choice is induction of ovulation. Different treatment regimens have been used in PCOS patients, but none has had a significant outcome. The reason behind this diversity in treatment options is the multifactorial pathology of PCOS and its different manifestations. Therefore, because of its diverse clinical and endocrine characteristics and unknown pathophysiology, as well as the role of genetics in its pathogenesis, it is difficult to use only one treatment option in PCOS.[3]

Multiple treatments have been recommended for infertility in patients with PCOS, including weight reduction, clomiphene citrate, metformin, gonadotropins, pulsed gonadotropin-releasing hormone, gonadotropin-releasing hormone agonists, ovary cauterization, ovarian wedge resection, letrozole, and assisted reproductive technology, such as in vitro fertilization.[3,7,8]

Clomiphene is still considered first-line therapy for ovarian stimulation in PCOS.[9,10] Due to its structural similarities to estrogen, clomiphene competitively attaches to nuclear estrogen receptors. By lowering the negative feedback of estrogen, it activates mechanisms that change the secretion pattern of gonadotropin-releasing hormone, which in turn result in increased pituitary gonadotropin hormones. This process ultimately causes ovarian follicles to grow.[9] With clomiphene, ovulation occurs in 80% of cases and pregnancy in 40%. It can be used for 6–12 months, but longer periods of administration could potentially increase the risk of malignant and borderline ovarian tumors.[9] Clomiphene resistance is defined as three cycles of failure to ovulate or six cycles of ovulation without pregnancy.[11]

Aromatase is a microsomal enzyme that mediates conversion of androstenedione to estrogen, and testosterone to estradiol. It is present in several tissues, including the ovary, brain, placenta, adipose tissue, muscle, liver, and breast. Aromatase is a good target to control estrogen secretion, because estrogen is the final step in the biosynthetic pathway. Several studies have demonstrated the effectiveness of aromatase inhibitors in induction of ovulation.[3,12–15] Monofollicular ovulation is another example of the advantages of the aromatase inhibitors, especially when PCOS patients have an exaggerated response to gonadotropins. Recently, aromatase inhibitors have become an alternative to clomiphene citrate as first-line therapy for stimulation of ovulation in ovulating and nonovulating infertile women.[16,17] Letrozole, as opposed to clomiphene, is rapidly excreted,[17] and causes ovulation in 60%–80% of patients;[18] in clomiphene-resistant patients, it caused ovulation in 62% of cases, and pregnancy occurred in 14.7% of patients. Letrozole does not have any adverse effects on the fetus and is safe.[7,8,18] Letrozole decreases the secretion of estrogen both in the brain and in the periphery, and causes an increase in gonadotropins, which in turn causes maturation of the ovarian follicles.

Gonadotropins are recommended in the event of resistance to clomiphene and letrozole. In PCOS patients resistant to clomiphene, gonadotropin levels are normal, and luteinizing hormone levels may even be high. Therefore, treatment with exogenous gonadotropins can result in increased levels of luteinizing hormone and FSH. In this situation, using FSH alone is superior to human menopausal gonadotropins, even though its superiority is not known when it comes to adverse effects. Moreover, studies show no difference in ovulation, pregnancy, miscarraige, multiple pregnancy, and ovarian hyperstimulation syndrome rates between them. PCOS patients resistant to clomiphene need a lower dose of gonadotropins to stimulate ovulation. Further, the therapeutic index is very narrow because a suboptimal dose will not cause ovulation, and a small increase in dose can potentially cause ovarian hyperstimulation syndrome. Therefore, treatment with gonadotropins requires precise and continuous monitoring and serial hormonal and sonographic evaluation.[9] PCOS patients have an increased risk of ovarian hyperstimulation syndrome due to formation of numerous follicles. Different methods have been proposed to prevent ovarian hyperstimulation syndrome in PCOS, but none of them can completely prevent it.[9] Even with all these modalities, patients may still develop ovarian hyperstimulation syndrome that could be fatal.[9,19] Multiple pregnancies are another adverse effect of these drugs, and are considered to be an adverse effect of infertility treatments in general.[9,20]

Another treatment option is surgery in the form of wedge resection and ovarian cauterization, which are not

recommended these days due to their adverse effects, including premature ovarian insufficiency and adhesions, and are only used in patients who do not accept the cost and adverse effects of gonadotropins.[4,9]

Considering the side effects of gonadotropins, the need for continuous monitoring, risk of ovarian hyperstimulation syndrome, and even risk of death, in this study we decided to use a combination of letrozole and clomiphene in clomiphene-resistant or letrozole-resistant PCOS patients prior to gonadotropins, to evaluate the effect of this combination on ovulation and pregnancy in such patients.

Materials and methods

The study population consisted of infertile couples, in which the wives had menstrual disturbances such as oligomenorrhea or regular menstrual cycles without ovulation (anovulation was confirmed by progesterone levels on day 21 of their cycles). These patients had other criteria of PCOS, including high luteinizing hormone levels, a luteinizing hormone to FSH ratio of more than 5:2, clinical features of hyperandrogenism like acne, hirsutism, and multicystic ovaries on ultrasound, while having normal thyroid-stimulating hormone and prolactin levels. All patients had normal hysterosalpingograms and spermograms, and the only reason for their infertility was ovulatory dysfunction. These patients had been on clomiphene for at least 6 months, and were then put on letrozole because of inability to form a dominant follicle. They received four cycles of letrozole. Those patients who could not ovulate after that were chosen for combination therapy with clomiphene and letrozole. Over a period of 3 years, 100 PCOS patients who were resistant to clomiphene and letrozole were enrolled into the study. A dose of 5 mg Letrozole every night and 100 mg clomiphene every day after lunch was prescribed for 5 days. In Patients with oligomenorrhea the medication (letrozole and clomiphene) started after induction of bleeding with progesterone, and for those patients with regular cycles the medications (letrozole and clomiphene) were started from day 2 or 3 of cycle. To evaluate the growth of follicles, vaginal ultrasound was performed on day 11 of the cycle, and Gonal-f® (rFSH, Puregon, NV Organon, OSS, the Netherland) was prescribed to complete follicle growth. It is important to note that prior to administration of drugs on day 2 or 3, vaginal ultrasound was performed, and in the event of follicles larger than 2 cm, therapy was not started. After at least one follicle reached 18 mm, the patients were given 5,000 units of human chorionic gonadotropin, and underwent intrauterine insemination 36–38 hours later. The number of Gonal-f doses used, number of mature follicles, endometrial thickness on the day of human chorionic gonadotropin administration, occurrence of pregnancy, multiple pregnancies, and miscarraiges were recorded and evaluated for up to 20 weeks of gestation.

All the steps of the study were explained to the patients, and informed consents were taken from them. All patient information remained confidential. The cost of combination therapy with letrozole and clomiphene was less than that of gonadotropins and surgery, so there were no extra costs to the patients. With regard to potential drug interactions between letrozole and clomiphene, two pharmacologists were consulted and approved the safety of the combination. In addition, the ethics committee of Urmia University approved the study.

Results

One hundred infertile couples, each couple including a wife with PCOS resistant to clomiphene and letrozole were enrolled in the study. The women were evaluated in three cycles. Fourteen patients became pregnant in the first cycle, 15 patients in the second cycle, and 13 patients in the third cycle. In general, 257 cycles of combination therapy with clomiphene and letrozole were carried out, of which 213 cycles resulted in formation of a dominant follicle (82.9%). The mean patient age was 28.36±7.2 (range 19–37) years. The mean duration of infertility was 4.76±3.4 years. Primary infertility was present in 76 cases and secondary infertility in 24 cases. Sixty-three patients with primary infertility formed dominant follicles, as did 20 patients with secondary infertility. With regard to menstrual cycles, 80 patients had oligomenorrhea, four had menometrorrhagia, and 16 had regular cycles. Forty-four patients had hirsutism, and the mean body mass index was 27.3±3.1. There was a history of miscarraige in 23 patients (Table 1). Only one patient had an anatomic problem in the form of a uterine septum, which had been resected with hysteroscopy prior to the study.

Table 1 Demographic and laboratory results of the patients

Mean patient age, years	28.36±7.2
Duration of infertility (years)	4.76±3.4
Oligomenorrhea	80 (80%)
Menometrorrhagia	4 (4%)
Regular menstruation	16 (16%)
Hirsutism	44 (44%)
Mean body mass index	27.3±3.1
History of previous miscarraige	23 (23%)
Mean LH on day 3 of menstruation	10.05±4.19 mIU/mL
Mean FSH on day 3 of menstruation	5.24±1.9 mIU/mL
Mean TSH	1.76±0.9 mIU/mL
Mean estradiol on day 3 of menstruation	90.97±21 *pg/mL*

Note: Data are mean ± standard deviation, or mean (percentage).
Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

On day 3 of the cycle, the mean luteinizing hormone level was 10.05±4.19, the mean FSH level was 5.24±1.9, the mean thyroid-stimulating hormone level was 1.76±0.9, and the mean serum estradiol level was 90.97±21.3 pg/mL. The mean number of dominant follicles after treatment was 2.3±1.1. Mean Gonal-f use was 3.7±0.9 ampoules. The mean endometrial thickness on the day of human chorionic gonadotropin administration was 8.17±1.3 mm (Table 2).

In the 100 patients, 42 pregnancies occurred, comprising 41 cases following intrauterine insemination, and one case following in vitro fertilization (due to number of follicles 13 to 14). Of the 42 pregnancies, ten resulted in miscarraige, in which six had a history of miscarraige and four did not. Thirty-seven pregnancies were single pregnancies and five were twin pregnancies. All twin pregnancies reached term, and the ten miscarraiges occurred in the 37 single pregnancies.

Discussion

PCOS is a common endocrine disorder in women of childbearing age (6.8%),[1,2] and is one of the most common causes of infertility due to ovulation disturbance. In fact, 75% of ovulation disturbances are PCOS-related. Induction of ovulation is an appropriate therapy for PCOS. Several medications and regimens have been used for induction of ovulation in PCOS, but none has had a significant outcome. Examples of such treatments include clomiphene, letrozole, metformin, gonadotropins, gonadotrophin-releasing hormone agonists, cauterization and wedge resection of the ovaries, and assisted reproductive technology.[3,7,8]

Clomiphene is still considered to be a first-line treatment for induction of ovulation in PCOS,[9,10] and can cause ovulation in 73%–80% of cases.[9,21] Failure of clomiphene to cause ovulation is known as clomiphene citrate resistance, and failure of pregnancy to occur within 6–12 months is known as clomiphene citrate failure.[9] Generally, women with a high body mass index, amenorrhea, severe hyperandrogenemia, and insulin-resistance are resistant to clomiphene.[6]

Table 2 Treatment outcome in patients

Formation of dominant follicle	213 (82.9%)
Number of dominant follicles	2.3±1.1
Mean endometrial diameter (mm)	8.17±1.3
Number of recombinant human follicle-stimulating hormone treatments used	3.7±0.9
Occurrence of pregnancy	42 (42%)
Miscarraige	10 (23.8)
Single fetus	37 (88%)
Twin fetus	5 (12%)

Note: Data are mean ± standard deviation, or mean (percentage).

Clomiphene resistance is defined as three cycles of failure to ovulate or six cycles of ovulation without pregnancy.[11]

Recently, letrozole has been proposed as the most effective infertility medication and is being used for induction of ovulation in PCOS.[12–15] This drug has been recommended as a substitute for clomiphene as first-line treatment to induce ovulation in PCOS.[19] In recent practice, letrozole is considered an alternative to clomiphene in ovulatory and nonovulatory infertile women.[16,17] This drug can induce ovulation in 62% of clomiphene-resistant patients, and can result in pregnancy in 14.7% of these cases.[18] Moreover, use of letrozole has been recommended for patients who ovulate with clomiphene but have a thin endometrium.[9]

Considering its low risk of adverse effects and low cost, letrozole is used instead of gonadotropins in patients resistant to clomiphene. Moreover, with letrozole, the risk of multiple pregnancies is reduced. It is excreted from the body quite rapidly and does not have fetotoxicity.[6,7,8,9,18] In a cohort study, the frequency of fetal anomaly after using letrozole was 2.4% and after clomiphene was 3%, which is not significant.[9]

Gonadotropins are also recommended for PCOS patients resistant to clomiphene. Their use requires serial evaluation of hormones and sonographic monitoring, and there is a risk of serious adverse effects including ovarian hyperstimulation syndrome and even death.[9] Multiple pregnancies can also result from these medications.[9,17,20] Suboptimal doses of gonadotropins can result in no response and high doses can cause ovarian hyperstimulation syndrome.[9] Therefore, only physicians who are expert in this field and have adequate experience should prescribe exogenous gonadotropins.

Laparoscopic ovarian drilling can be an effective treatment in clomiphene-resistant patients, but due to its temporary effects, risk of adhesions, and risk of poor ovarian reserve, its use is still a matter of debate. This technique is more appropriate for patients who fail to ovulate after gonadotropins, or do not accept the cost and adverse effects of these drugs.[9]

Considering the extent of adverse effects associated with gonadotropins and surgery, we decided to use a combination of letrozole and clomiphene in our patients, who were resistant to letrozole and clomiphene used alone. It is noteworthy that we did not find any other similar paper with which to compare our results.

The results of our study show that in PCOS patients resistant to clomiphene and letrozole alone, a combination of the two drugs resulted in formation of dominant follicles in 82.9% of cases and pregnancy in 42% of cases. The risk of ovarian hyperstimulation syndrome is very low with this method, and multiple pregnancies occur less frequently than

in patients treated with gonadotropins. Moreover, this strategy does not have the cost and adverse effects of surgery, such as adhesions and premature ovarian failure.

The frequency of miscarraige in our study was 23.8%. Speroff and Fritz reported that the frequency of miscarraige following gonadotropins in their clomiphene-resistant patients was 20%–25%, which is more than that in the general population (15%). They also explained that the reason for this was the older age and number of obese subjects in their study population.[9] Abu Hashim et al reported that 15%–40% of their PCOS patients were resistant to clomiphene.[18] Letrozole causes ovulation in 54.6%–84.4% of clomiphene-resistant patients.[11,13] In our study, a combination of letrozole and clomiphene resulted in ovulation in 82.9% of cases, and pregnancy occurred in 42% after three cycles of combination therapy.

According to the results of this study, it can be advised that, in PCOS patients resistant to clomiphene and letrozole alone, a combination of the two drugs can be tried prior to treatments having more severe adverse effects, or surgery. More studies need to be initiated, to have a better understanding on the effectiveness of the combination of drugs on a larger population of patients. The combination may also be used as first-line therapy to induce ovulation in severe cases of PCOS in order to save time and expense.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med*. 2010;8:41.
2. Saad AK. Amer. Polycystic ovary syndrome: diagnosis and management of related infertility. *Obstetrics, Gynaecology and Reproductive Medicine*. 2009;19(10):263–270.
3. Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphen citrate in women with polycystic ovaries undergoing ovarian stimulation. *J Int Med Res*. 2006;34(1):73–76.
4. Palomba S, Orio F, Zullo F. Ovulation induction in women with polycystic ovary syndrome. *Fertil Steril*. 2006 Jul;86 Suppl 1:S26–S27.
5. Begum MR, Fedrous J, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *Fertil Steril*. 2009;92(3):853–857.
6. Tulandi T, Martin J, Al-Fadhli R, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. *Fertil Steril*. 2006;85(6):1761–1765.
7. Jirege PR, Patill RS. Comparison of endocrine and ultrasound profiles during ovulation induction with clomiphene citrate and letrozole in ovulatory volunteer women. *Fertil Steril*. 2010;93(1):174–183.
8. Rouzi AA, Ardawi MS. A randomized controlled trial of the efficacy of rosiglitazone and clomiphene citrate versus metformin and clomiphene citrate in women with clomiphene citrate-resistant polycystic ovary syndrome. *Fertil Steril*. 2006;85(2):428–435.
9. Fritz M, Speroff L. Clinical Gyneocology endocrinology and infertility. 8th ed. PhiladelphiaL. *Lippincott Williams & Wilkins*. 2011:1305–13.
10. Amer SA, Li TC, Metwally M, Emarh M, Ledger WL. Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome. *Hum Reprod*. 2009 Jan;24(1):219–225.
11. Al-Omari WR, Sulaiman WR, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2004;85(3):289–291.
12. Badawy A, Shokeir T, Allam AF, Abdolhady H. Pregnancy outcome after ovulation induction with aromastase inhibitors or clomiphene citrate in unexplained infertility. *Acta Obstet Gynecol Scand*. 2009;88(2):187–191.
13. Elnashar A, Fouad H, Eldosoky M, Saeid N. Letrozole induction of ovulation in women with clomiphene citrate-resistant polycystic ovary syndrome may not depend on the period of infertility, the body mass index, or the luteinizing hormone/follicle-stimulating hormone ratio. *Fertil Steril*. 2006;85(2):511–530.
14. Badawy A, Mosbah A, Shady M. Anastrozole or letrozole for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome: a prospective randomized trial. *Fertil Steril*. 2008;89(5):1209–1212.
15. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril*. 2004;82(6):1561–1563.
16. Homburg R. Polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol*. 2008;22(2):261–274.
17. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. *Fertil Steril*. 2001;75(2):305–309.
18. Abu Hashim H, Shokeir T, Badawy A. Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. *Fertil Steril*. 2009;94(4):1405–1409.
19. Healey S, Tan SL, Tulandi T, Biljan MM. Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril*. 2003 Dec;80(6):1325–1329.
20. Amer SA,Li TC, Ledger WL. Ovulation induction using laparoscopic ovarian drilling in women with polycystic ovarian syndrome:predictors of success. *Hum Reprod*.2004 Aug; 19(8):1719-24.
21. Siebert TI, Kruger TF, Steyn DW, Nosarka S. Is the addition of metformin efficacious in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome ? A structured literature review. *Fertil Steril*. 2006;86(5):1432–1437.

Drug Design, Development and Therapy Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/drug-design-development-and-therapy-journal