AMJ Australasian Medical Journal [AMJ 2018;11(6):326-330]

The combination of letrozole and metformin has a better therapeutic effect on uterine and ovarian arteries in PCOS patients than the combination of clomiphene citrate and metformin

Nazanin Farshchian, Siavash Teimuri Nezhad, and Parisa Bahrami Kamangar

Department of Radiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

RESEARCH

Please cite this paper as: Farshchian N, Teimuri Nezhad ST, Bahrami Kamangar P. The combination of letrozole and metformin has a better therapeutic effect on uterine and ovarian arteries in PCOS patients than the combination of clomiphene citrate and metformin. AMJ 2018;11(6):326–330. https://doi.org/10.21767/AMJ.2018.3252

Corresponding Author:
Nazanin Farshchian
Department of Radiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
Email: nfarshchian@kums.ac.ir

ABSTRACT

Background

Polycystic ovary syndrome (PCOS) is the most prevalence endocrine disorder in the reproductive age of women. In these patients, medications such as clomiphene citrate, letrozole and metformin are used to induce ovulation and overcome infertility.

Aims

This study was done for comparing the findings of Color Doppler sonography of the uterine and ovarian arteries in women with PCOS under treatment of two drug groups of letrozole-metformin and clomiphene-metformin.

Methods

Intervention-applied study was performed on 108 women with secondary infertility due to PCOS in Imam Reza Hospital of Kermanshah in 2016. Women were divided in two groups of 54 people, for investigating the effect of letrozole-metformin and clomiphene-metformin on ovarian and uterine arteries.

Results

Blood flow in the uterus and ovaries significantly increased after treatment with letrozole-metformin and clomiphene-metformin ($P<0.05$). However, the effect of letrozole-metformin was significantly higher than that of clomiphene-metformin on uterine and ovarian arteries Resistance Index (RI) ($P<0.05$).

Conclusion

Letrozole-metformin as well as clomiphene-metformin have a significant effect on blood flow in the uterus and ovaries. The group which received letrozole-metformin had a better response in this regard.

Key Words

Infertility, Resistance Index (RI), Polycystic Ovary Syndrome (PCOS)

What this study adds:

1. What is known about this subject?

PCOD is one of the most common fertility disorders in women of reproductive age with several treatment methods.

2. What new information is offered in this study?

The reduction of RI in the uterine and ovarian arteries was greater in letrozole-metformin group compared to clomiphene citrate-metformin. Treatment with letrozole-metformin is recommended.

3. What are the implications for research, policy, or practice?

Since polycystic ovary can cause infertility, treatment or control of this disease can help infertile couples in fertility.

Background

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder in women of reproductive age and approximately 5–10 per cent of women in this age

group are affected.[1] Manifestations of this disease include irregular menstrual cycles, anovulation, infertility, obesity and hirsutism. One or all of these symptoms may occur in patients.[2,3] To detect PCOS, the presence of 2 of 3 following criteria is necessary: 1) Oligomenorrhea or anovulation 2): Clinical or laboratory evidence of hyperandrogenism 3): Polycystic ovarian morphology in sonography. The presence of 12 or more follicles with a diameter less than 10mm, and increasing ovarian volume over 10cc in grey scale sonography is diagnostic for this syndrome.[4,5] In a number of studies, symptoms such as changes in vascularization of ovaries with PCOS, increase of blood flow in the affected stroma as well as reduction in Resistance Index and Pulsatility Index (PI) have been reported in the involved ovary.[6] In some studies, uterine artery RI was higher and ovarian artery RI was lower than.[7,8] In these patients, medications such as clomiphene citrate, letrozole and metformin are used to stimulate ovulation and treat infertility. About 75 per cent of women with PCOS are infertile due to anovulation.[9] It has been over 50 years that clomiphene citrate is a major therapy for stimulating the ovulation in PCOS cases (10). However, clomiphene citrate reduces endometrial receptivity by decreasing the endometrial development and uterine blood flow. This can lead to thinning the endometrium in 15–50 per cent of patients with subsequent implantation and early pregnancy failure caused by luteal phase complications.[10,11] In recent years, letrozole emerges as an effective treatment for an ovulatory PCOS women, especially in the cases that clomiphene citrate causes side effects on the thickness of the endometrium in spite of an improving effect on the ovulation. Letrozole even enhances uterine receptivity by increasing the endometrial thickness, trilaminar and blood flow.[12] But these drugs have side effects on the patient. For example, clomiphene citrate causes massive enlargement of the ovaries metformin causes hypoglycaemia and diarrhoea and letrozole can also lead to thromboembolism.[6] In this research we aimed to compare the effect of two common therapeutic strategies, clomiphene citrate-metformin and letrozole-metformin. Metformin was selected here because it is inexpensive and easily available in Iran. We decided to determine the effect of these combinations on blood flow of uterine and ovarian patients that were suffered from the secondary infertility due to PCOS. Resistance index of uterine and ovarian arteries were measured before and after the drug administrations in 108 women and statistically analysed using non-parametric methods.

Method

Patients

This intervention - applied study was individually and randomly performed to investigate the effects of letrozole-metformin and clomiphene-metformin on ovarian and uterine arteries on 108 women with secondary infertility due to PCOS. They were divided to two matched 54-subject groups in Imam Reza Hospital of Kermanshah in 2016. Patients with certain criteria (aged 18-45 years with 12 or more follicles with a diameter less than 10 mm, an increase in ovarian volume more than 10 cc and infertility more than a year) were subjected in this study. Exclusion criteria were having the age of less than 18 years old and more than 45 years, Body Mass Index (BMI) greater than 36 or less than 18, neoplastic disorders or metabolic diseases such as diabetes, impaired thyroid function and adrenal gland disorder, intake of the contraceptive pills over the past year, glucocorticoid, anti-androgens, anti-diabetic drugs or any other hormonal drugs and finally disorders of the pelvic organs and infertility due to tubal reasons. Patients were divided in two categories according to age and parity.

Treatment

The Color Doppler sonography of the uterine and ovarian arteries was performed in the early days of the follicular phase (2–5 days) by Siemens Ultrasound G40. Using grey scale ultrasound, the echogenicity and thickness of the stroma were analysed and, the size of the ovaries as well as the size and number of follicles were measured. Then the patients either consume clomiphene citrate-metformin or letrozole-metformin. Based on previous studies the dosage and the scheme for drug administration were determined as this: 2,000mg metformin in combination with 100mg clomiphene or 5mg letrozole, was given to the patients from the 5th day of menstruation for five days.[4,5]

Data collection and analysis

Sonography was performed on the patients (on the 14th day of the menstrual cycle, subsequently uterine and ovarian artery RI were analysed and compared to the measurements before the administration of the drugs. The normal distribution of data was determined using the Kolmogorov-Smirnov test. Normally distributed data were compared between the two groups using the Student t test and the Mann-Whitney U test was applied for non-normally distributed data. The Chi-square test was used to compare categorical data between the groups.

$P<0.05$ was considered significant. The drugs were produced by the Razi Pharmaceutical Distribution Company located in Iran.

Results

In this study, 108 women with PCOS, with mean age 30.6±6.33 (18-45) and mean BMI 26±3.8(19–36.6kg/m^2) were subjected in two 54-member groups and treated with two drugs, letrozole and clomiphene, in combination with metformin. The demographic and clinical data in two groups are detailed in Table 1.

Based on the results of this study, RI of ovarian arteries before and after receiving the two groups of drugs and difference in RI of uterus and ovary arteries after receiving drugs changes were significant in the two groups of patients (Table 2). The effect of both drug groups on RI in the uterine and ovarian arteries is significant, but this effect in the Letrozole-metformin group is more than clomiphene-metformin (Table 3).

Discussion

The high prevalence of PCOS in women and its consequences in infertility have led to numerous studies aiming new drugs with less or none side-effects. Currently, clomiphene citrate and letrozole are highly-demanded treatments with thoughtful debates on effectiveness and side-effects. The combination of clomiphene citrate + metformin has been an effective therapeutic strategy for the secondary infertility caused by PCOS for many years. However, having random side effects such as Hyperinsulinemia, insulin resistance and even growth in androgen production led to more investigations on new drugs.[13-15] Letrozole-metformin is a widely recommended substitute that can stimulate FSH secretion and ovarian follicular development.[16,17]

This study was performed to investigate the effects of letrozole-metformin and clomiphene-metformin on ovarian and uterine arteries on 108 women with secondary infertility due to Polycystic Ovary Syndrome (PCOS). The results of this study showed that Letrozole-metformin and clomiphene-metformin drugs have a significant effect on blood flow to the uterus and ovaries but letrozole-metformin is most affected in this regard. This observation was in line with many previous studies. Morad et al. concluded from a research on 60 infertile women with PCOS that the letrozole compared to clomiphene citrate has a better therapeutic effect on the arteries of the uterus[12] Similar results were achieved by Mohamed Selim et al. in 2012.[8] Based on Sakhavar et al. investigation, letrozole and clomiphene citrate have no significant effect on the RI and PI in women with unexplained infertility. They showed that letrozole enhances the rate of the pregnancy more than clomiphene citrate, however, the difference between the effect of letrozole and clomiphene citrate statically is not significant.[18]

Abu Hashim's study showed that the effectiveness of letrozole is equal to clomiphene citrate-metformin and both therapies significantly increase the number of mature follicles, ovulation and the pregnancy rate.[19] Baruah et al. in a study on 58 patients with PCOS under treatment with letrozole and 25 PCOS patients under treatment with clomiphene citrate showed that RI in spiral arteries of patients treated with letrozole was lower than those received clomiphene citrate.[6] Su Julian et al. in China concluded that clomiphene citrate and letrozole improve blood flow to the ovaries and uterus in PCOS patients.[20] Our results are also in line with that of SU Jilian et al. Palomba et al. in the study on 32 PCOD women under treatment with clomiphene-metformin. The result of their study has shown that the blood flow in the uterus was increased after treatment with these drugs.[4,5] On the other hand based on our results RI of ovarian arteries after treatment with Letrozole-metformin and clomiphene-metformin was reduced, but this result was not in line with Ozcimen et al.[7] This difference can be due to methodology of research, number of patients and drug producer company.

Conclusion

RI in the uterus and ovarian arteries was reduced after treatment with letrozole-metformin as well as clomiphene citrate-metformin. However, this reduction was greater in the letrozole-metformin group in comparison to clomiphene citrate-metformin treated group.

References

1. Solomon CG. Polycystic ovary syndrome. N Engl J Med. 2016;375:54–64.
2. Miguel D, Newton G, Javier B, et al. Polycystic ovarian syndrome: A ssessment with color Doppler angiography and three – Dimensional Ultra sonography J Ultra sound med. 1999;18:303–13.
3. Resende AV, Mendes MC, Mendonca HC, et al. Doppler study of the uterine arteries and ovarian stroma in paients with polycystic ovary syndrome. Gynecol Obstet Iavest. 2001;52:153–57.
4. Palomba S, Russo T, Orio Jr. F, et al. Uterine effect of clomiphene citrate in women with polycystic ovary syndrome. Human. Reprod. 2006;21(11):2823–29.
5. Palomba S, Russo T, Orio Jr. F, et al. Uterine effects of metformin administration in anovulatory women with polycystic ovary syndrome. Human Reproduction. 2006;21(2):457–65.
6. Baruah J, Roy KK, Rahman SM, et al. Endometrial effects

of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. Archives of Gynecology & Obstetrics. 2008;279(3):311.
7. Ozcimen EE, Uckuyu A, Ciftci Fc, et al. The effect of metformin Treatment on ovarian stromal blood flow in women with polycystic ovary syndrome. Arch Gynecol obstet. 2009;280(2):263.
8. Mohamed F.S, Tamer F.B. Letrozole and clomiphene citrate effect on endometrial and subendometrial vascularity in treating infertility in women with poly cystic ovary syndrome. J Gynecologic Surgery. 2012;28(6):405-401–9.
9. Bellver J, Rodríguez-Tabernero L, Robles A, et al. Polycystic ovary syndrome throughout a woman's life. J Assist Reprod Genet. 2017;10.1007/s10815-017-1047-7.
10. Thessaloniki ESHRE/ASRM-sponsored PCOS Consensus Workshop Group Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod. 2008;23(1):462–477.
11. C.C. Hsu, H.C. Kuo, S.T. Wang, et al. Interference with uterine blood flow by clomiphene citrate in women with unexplained infertility Obstet Gynecol. 866 (1995), p. 917 ArticlePDF (528KB).
12. Morad AWA, Elhadi Farag MA. Impact of letrozole on ultrasonographic markers of endometrial receptivity in polycystic ovary syndrome women with poor endometrial response to clomiphene citrate despite adequate ovulation. Middle East Fertility Society Journal 2015;20(3):182–187.
13. Kocak M, Caliskan E, Simsir C, et al. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate–resistant women with polycystic ovary syndrome. Fertil Steril. 2002;77:101–6.
14. Malkawi HY, Qublan HS. The effect of metformin plus clomiphene citrate on ovulation and pregnancy rates in clomiphene-resistant women with polycystic ovary syndrome. Saudi Med J. 2002;23:663–6.
15. Siebert TI, Kruger TF, Steyn DW, et al. 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;86:1432–7.
16. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006;85:277–84.
17. Homburg R. Oral agents for ovulation induction—clomiphene citrate versus aromatase inhibitors. Hum Fertil (Camb). 2008;11:17–22.
18. Sakhavar N, Kaveh M, Sadegi K. The Impact of Letrozole Versus Clomiphene Citrate on Uterine Blood Flow in Patients with Unexplained Infertility. Journal of Family and Reproductive Health. 2014;8(1):1–5.
19. 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. 2010;94(4):1405–9.
20. SU Jilian, AI Hong, ZHENG Jianhuai, et al. Effect of Letrozole Combined Clomiphene Citrate on the Uterine and Ovarian Blood Flow in Women with Polycystic Ovarian Syndrom al(The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an Shanxi 710061, China) 2008.

ACKNOWLEDGEMENTS

We are thankful to all of the colleagues and patients who made this study possible. The authors are also grateful to the personnel of Radiology Department of Imam Reza Hospital, for their time and valuable contributions to the study and Kums for their financial support. The authors declare that there is no conflict of interest in this article.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

Table 1: The demographic and clinical data in two groups

Properties	Group				value
	Letrozole-metformin		Clomiphene-metformin		
	Mean	Standard Deviation	Mean	Standard Deviation	
Age (Year)	29.81	5.84	31.46	6.72	0.177
Weight (kg)	65.37	10.29	64.13	8.03	0.486
Height (cm)	158.19	4.03	157.83	5.06	0.690
BMI	26.15	4.14	25.81	3.58	0.652
Number of deliveries	0.46	0.82	0.63	0.78	0.282
Number of years of marriage	7.0	5.08	8.04	5.25	0.299
The number of infertility months	54.33	34.95	68.89	44.73	0.062

Table 2: Descriptive characteristics of uterine artery, ovarian artery and ovarian arteries difference before and after drug treatment

Properties	Group				Total		P-value
	Letrozole-metformin		Clomiphene-metformin				
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Before Treatment, Uterine Resistant Index (BURI)	0.725	0.101	0.703	0.114	0.714	0.108	0.286
After Treatment, Uterine Resistant Index (AURI)	0.69	0.11	0.68	0.11	0.68	0.11	0.576
Before Treatment, Ovarian Resistant Index (BORI)	0.653	0.079	0.701	0.096	0.677	0.091	0.005
After Treatment, Ovarian Resistant Index (AORI)	0.61	0.08	0.69	0.1	0.65	0.1	0.001
The difference before and after treatment of uterine artery	0.03	0.03	0.02	0.03	0.03	0.03	0.03
The difference before and after treatment in ovarian artery	0.04	0.04	0.02	0.02	0.03	0.03	0.001

Table 3: Comparing the impact of two pharmaceutical groups on each other

Properties		No.	Mean Rank	Sum of Rank	P-value
Differences in uterine artery RI	Letrozole-metformin	54	60.94	3291	0.03
	Clomiphene-metformin	54	48.06	2595	
Differences in ovarian artery RI	Letrozole-metformin	54	65.73	3549.5	<0.001
	Clomiphene-metformin	54	43.27	2336.5	