

## Artículo de investigación

## Comparing the effects of letrozole and the effects of routine treatment of polycystic ovary syndrome in improving symptoms of hyperandrogenism

Comparación de los efectos de la letrozole y los efectos del tratamiento del síndrome de ovario poliquístico en los síntomas de hiperandrogenismo

Comparando os efeitos do letrozol e os efeitos do tratamento de rotina da síndrome dos ovários policísticos na melhora dos sintomas de hiperandrogenismo

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### Abstract

Polycystic ovary syndrome (PCOS) is one of the common forms of chronic anovulation associated with an increase in androgens. This disorder is associated with important morbidities during reproductive years. The objective of this research was to compare the effects of letrozole and routine treatment (oral Ethinylestradiol, cyproterone acetate and metformin) of polycystic ovary syndrome in improving symptoms of hyperandrogenism (hirsutism, acne).

This is an applied-experimental study in which, 80 patients diagnosed with PCOS (polycystic ovary syndrome) were randomly divided into two groups. The first group was treated with 2.5 mg of Letrozole daily and the second group was treated with 500 mg of metformin once per day, 100 mg of cyproterone acetate once per day since 5-15 days of menstruation and oral Ethinylestradiol daily since 5 -25 days of menstrual cycles and they were followed-up regularly and periodically in the endocrinology clinic. After collecting data, they were analyzed using spss Software.

### Resumen

El síndrome de ovario poliquístico (SOP) es una de las formas comunes de anovulación crónica asociada con un aumento de los andrógenos. Este trastorno se asocia con importantes morbilidades durante los años reproductivos. El objetivo de esta investigación fue comparar los efectos del letrozol y el tratamiento de rutina (etinilestradiol oral, acetato de ciproterona y metformina) del síndrome de ovario poliquístico para mejorar los síntomas de hiperandrogenismo (hirsutismo, acné).

Este es un estudio experimental aplicado en el que 80 pacientes diagnosticados con SOP (síndrome de ovario poliquístico) se dividieron aleatoriamente en dos grupos. El primer grupo se trató con 2,5 mg de letrozol al día y el segundo grupo se trató con 500 mg de metformina una vez al día, 100 mg de acetato de ciproterona una vez al día desde los 5 a 15 días de menstruación y etinilestradiol oral diariamente de 5 a 25 días de ciclos menstruales y fueron seguidos regularmente y periódicamente en la clínica de endocrinología.

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No significant difference was found between two groups in the improvement of the hirsutism ( $p = 0.27$ ). No significant difference was found between two groups in the improvement of acne ( $p = 0.54$ ). In addition, the results of this study did not show any significant difference between the two groups in terms of acne and hirsutism improvement in the 6-month follow up.

Based on the results of this study, two groups did not differ significantly. However, given the reduction in Ferriman-Gallwey score, letrozole can be a suitable drug for treating the symptoms of hyperandrogenism. Extensive studies are required in this regard to prove this assumption.

**Keyword:** letrozole, polycystic ovary syndrome, metformin, cyproterone acetate, oral Ethinylestradiol

Después de recopilar los datos, se analizaron utilizando el software 21 de spss.

No se encontraron diferencias significativas entre los dos grupos en la mejora del hirsutismo ( $p = 0,27$ ). No se encontraron diferencias significativas entre los dos grupos en la mejora del acné ( $p = 0.54$ ). Además, los resultados de este estudio no mostraron diferencias significativas entre los dos grupos en cuanto a la mejoría del acné y el hirsutismo en el seguimiento de 6 meses.

Sobre la base de los resultados de este estudio, dos grupos no difirieron significativamente. Sin embargo, dada la reducción en la puntuación de Ferriman-Gallwey, el letrozol puede ser un fármaco adecuado para tratar los síntomas de hiperandrogenismo. Se requieren estudios extensos a este respecto para probar este supuesto.

**Palabra clave:** letrozol, síndrome de ovario poliquístico, metformina, acetato de ciproterona, etinilestradiol oral

## Resumo

A síndrome do ovário policístico (SOP) é uma das formas mais comuns de anovulação crônica associada a um aumento de andrógenos. Este distúrbio está associado a importantes morbidades durante os anos reprodutivos. O objetivo desta pesquisa foi comparar os efeitos do tratamento com letrozol e rotina (Ethinilestradiol oral, acetato de ciproterona e metformina) da síndrome dos ovários policísticos na melhora dos sintomas de hiperandrogenismo (hirsutismo, acne).

Este é um estudo experimental-aplicado no qual 80 pacientes diagnosticados com SOP (síndrome do ovário policístico) foram divididos aleatoriamente em dois grupos. O primeiro grupo foi tratado com 2,5 mg de Letrozole diariamente e o segundo grupo foi tratado com 500 mg de metformina uma vez por dia, 100 mg de acetato de ciproterona uma vez por dia desde 5-15 dias da menstruação e Ethinilestradiol oral diariamente desde 5 -25 dias de ciclos menstruais e eles foram acompanhados regularmente e periodicamente na clínica de endocrinologia. Depois de coletar os dados, eles foram analisados usando o spss 21 Software.

Nenhuma diferença significativa foi encontrada entre os dois grupos na melhora do hirsutismo ( $p = 0,27$ ). Nenhuma diferença significativa foi encontrada entre os dois grupos na melhora da acne ( $p = 0,54$ ). Além disso, os resultados deste estudo não mostraram diferença significativa entre os dois grupos em termos de melhora da acne e do hirsutismo no seguimento de 6 meses.

Com base nos resultados deste estudo, dois grupos não diferiram significativamente. No entanto, dada a redução no escore de Ferriman-Gallwey, o letrozol pode ser um medicamento adequado para tratar os sintomas do hiperandrogenismo. Estudos extensos são necessários a esse respeito para provar essa suposição.

**Palavras-chave:** letrozol, síndrome dos ovários policísticos, metformina, acetato de ciproterona, Ethinilestradiol oral

## Introduction

Polycystic ovary syndrome (PCOS) is an endocrine, metabolic and systemic reproduction disease. It is very common and affects 6-8% of women in their reproductive age (Lee et al., 2018; Sylus et al., 2018). Patients with PCOS are usually women who are at their reproductive age (Lee et al., 2018). A study conducted in India reported that the prevalence of PCOS in young girls aged 15 to 24 was 22.5% (Joshi et al., 2014). PCOS is associated with the clinical conditions of increased androgen. Increased androgen is responsible for these clinical signs and complications of this syndrome. One of these conditions is hirsutism (Longo et al., 2012). Hirsutism involves excessive hair growth as a male pattern and affects about 10% of women (Farr et al., 2010). Excessive increase in androgens in women leads to increased hair growth in most androgen-sensitive areas. However, it is followed by an increase in hair loss in the head area. Important points in evaluation of hirsutism include the onset age and the speed of progression and associated symptoms, such as acne (Boivin et al., 2007). A simple and common method to grade the hirsutism is to use Ferriman-Gallwey scale. In this grading, nine areas of the body are examined in terms of hirsutism and score of 1 to 4 is given to each area. A total of higher than 8 indicates overgrowth due to androgens (Balasubramanian et al., 2010). Hyperandrogenism is a key factor in PCOS. After activating the activity of the aromatase enzyme, androgen is accumulated, leading to endocrine imbalance. Letrozole is a non-steroidal aromatase inhibitor. It contributes to androgen non-accumulation and prevention of hyperandrogenism (Daneasa et al., 2016). Chronic infection and infertility are considered among the most common complications of PCOS (Duleba & Dokras, 2012).

It has been reported that patients with PCOS are hospitalized twice more than to healthy subjects (Hart & Doherty, 2015). Thus, accurate and early diagnosis of PCOS and effective therapies on it seems to be necessary to reduce costs and improve the function (Kamangar et al., 2015). Nitrogen oxide (NO) indicates endothelial function, increases naturally during ovarian folliculogenesis and it contributes in maintaining the pregnancy. Previous studies reported that NO level decreases in infertile women with PCOS (Mahran et al., 2016). As letrozole is widely used nowadays to treat infertility and as it has been approved by the FDA for the treatment of breast cancer and its long-term use in women with breast cancer and

women with infertility caused by Polycystic ovary syndrome has not been associated with important complications (Craigle, 2007), the objective of this study is to compare the effects of common and routine treatments (combination of oral Ethinylestradiol, cyproterone acetate and metformin) and modern treatments through letrozole aromatase inhibitor.

### Methodology

This study is an applied-experimental study in which 80 patients diagnosed with PCOS (Polycystic ovary syndrome) were randomly divided into two groups based on Roterrandom criteria. One number was assigned for each person diagnosed with PCOS and the patients were assigned into case and control groups alternately. The first group was treated with 2.5 mg of Letrozole daily and the second group was treated with 500 mg of metformin once per day, 100 mg of cyproterone acetate once per day since 5-15 days of menstruation and oral Ethinylestradiol daily since 5 -25 days of menstrual cycles and they were followed-up regularly and periodically in the endocrinology clinic and the information derived from improvement or non-improvement of the symptoms was carefully and separately recorded by one person for each case. At the end of a 6-month period, data were analyzed. Exclusion criteria included kidney failure, metabolic acidosis, and history of thromboembolic disease, liver disorders, liver tumors, meningioma, severe and chronic depression, history of thromboembolic disease, pregnancy, and breastfeeding. After data collection, they were analyzed using spss 21 software.

### Results

In this research, 80 women at their reproductive age (between 18 and 38) with polycystic ovary syndrome who admitted to Endocrinology clinic of Imam Khomeini Hospital in Urmia due to symptoms of hyperandrogenism (hirsutism, acne) were studied. These patients were divided into two groups (each contained 40 patients). Among all patients studied, 4 patients were finally excluded from the study due to lack of meeting the inclusion criteria and the study continued with 76 patients. The mean age of patients was  $28.47 \pm 6.06$  years in the control group and  $27.29 \pm 5.60$  years in the case group. The mean BMI was  $27.29 \pm 2.83$  kg / m<sup>2</sup> in the control group and  $25.91 \pm 3.84$  kg / m<sup>2</sup> in the case group. Based on the T-test, no significant

difference was found between age and BMI of the two groups. Comparing the hirsutism improvement in the two groups showed that the baseline mean Ferriman-Gallwey score was  $20.80 \pm 2.69$  in the control group and  $20.80 \pm 3.33$  in the case group, which no significant difference was not found between the two groups in Ferriman-Gallwey scores based on the T-test, when they referred to clinic ( $p=0.27$ ).

After follow up of patients for 6 months, the mean Ferriman-Gallwey score was  $16.32 \pm 2.83$  in the control group and  $16.44 \pm 2.75$  in the case group. Based on the T – TEST, no significant

difference was found between two groups in the Ferriman-Gallwey scores after the treatment and during the follow up period. In the study of acne improvement, the results showed that in 40 patients in the control group, acne improved significantly in 24 patients (60%) and it improved partially in 16 (40%) patients. In case group, out of 36 patients, acne improved significantly in 24 patients (66.7%), while improvement was partial in 12 patients (33.3%). Based on the Chi-square test, there was no significant difference between the two groups in terms of acne improvement during the second visit ( $P=0.54$ ) (Table 1).

Table 1: Distribution of absolute and relative acne improvement in second visit of patients

Group	Acne improvement in second visit (after two months)		Total
	improvement	Non-improvement or partial improvement	
Control	(%60)24	(%40)16	(%100)40
Case	(%66.7)24	(%33.3)12	(%100)36
Total	(%63.2)48	(%36.8)28	(%100)76
p.value	Chi- exact test= 0.54		

In 6-month follow, out of 40 patients in the control group, 30 patients (75%) showed significant acne improvement and 10 patients (25%) had partial improvement. Out of the 36 patients in the case group, 32 patients (88.9%) showed significant acne improvement and 4 patients (11.1%) showed partial improvement. Based on Chi-square test, no significant difference was found between the two groups and acne improvement in 6-month follow up ( $P = 0.11$ ) (Table 2).

Table 2: absolute and relative distribution of acne improvement in 6-month follow up patients studied

Group	Acne improvement status		Total
	improvement	Non-improvement or partial improvement	
control	(%75)30	(%25)10	(%100)40
Case	(%88.9)32	(%11.1)4	(%100)36
Total	(%81.6)62	(%18.4)14	(%100)76
p.value	Chi- square= 0.11		

## Dissuasion

Ovulation disorders are common causes of infertility and Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting women in their reproductive age (Mehdinejadani et al., 2018). The prevalence of PCOS varies in different populations and its prevalence has been reported to be between 5% and 15% according to phenotype and ethnicity (Bozdag et al., 2016). It has been well recognized that steroid hormones have a good effect on endometrial proliferation and folliculogenesis in ovarian of the fertile women (Gifford, 2015). Letrozole is a non-steroidal aromatase inhibitor with a short half-

life. It is among the drug used widely in the treatment of infertility and it is used as ovulation-inducing drug, especially in patients with PCOS (Mehdinejadani et al., 2018; Franik et al., 2015). The present study was conducted to compare the effects of two different treatments on PCOS. Combination of oral Ethinylestradiol, cyproterone acetate and metformin was used in the first treatment, while letrozole aromatase inhibitor was used in the second treatment.

Comparing the hirsutism improvement of patients of two groups showed that the mean Ferriman-Gallwey score at the time of admission to clinic was  $20.05 \pm 2.69$  in the control group

and  $20.80 \pm 3.33$  in the case group. These results suggest lack of difference between two drugs used by patients in terms of Ferriman-Gallwey score when patients admitted to the clinic. The results revealed that Ferriman-Gallwey score decreased to  $16.32 \pm 2.83$  in the control group subjects and it decreased to  $16.44 \pm 2.75$  in patients treated with the aromatase letrozole inhibitor after 6 months of follow-up. Although no significant difference was seen in this study, the Ferriman-Gallwey score was significantly reduced compared to combined treatment. With regard to acne improvement, the results of our study showed that letrozole aromatase inhibitor had a better effect than combined treatment. In studies conducted by Saha et al. (2012), Atay et al. (2006) Roy et al. (2012), letrozole had better effect on fertility than clomiphene citrate. These results are in line with the results of our study with regard to the effect of letrozole (Although we did not examine the fertility of women, but we observed the effect of letrozole on inducing fertility and improvement of acne and hirsutism according to the results).

In another study conducted by Mehdinejadani et al (2018), it was reported that the use of letrozole compared to clomiphene citrate had a better effect on the mean of estrogen and progesterone, an increase in the appropriate endometrial protein and a more acceptable activation of the Wnt / B- catenin pathway. In a systematic study conducted by Escobar et al. (2012) on hirsutism, their results focused on epidemiology, pathology, diagnosis and treatment of hirsutism. Their study on the relationship between androgens and hair growth revealed that growth of hair in the sexual areas was clearly associated with androgenic hormones. The results of the study carried out by Escobar et al. (2012) and the results of our study on the effects of letrozole in comparison with effects of conventional treatment, no significant relationship was found, but acne and hirsutism improved significantly after treatment. Our study proves that due to objective and double-blind evaluations of the effects of treatment, small size of available samples, short duration of interventional studies and specific physiology of hair growth, each person's response to treatment may vary. There is also limitation in scoring system on the comparative investigation of the effects of various existing treatments. The only side effects observed in this study included dizziness and nausea.

### Conclusion

Based on the research results, it seems that letrozole to be suitable drug for the treatment of symptoms of hyperandrogenism. However, extensive studies are required to prove this assumption .

### Reference

Atay, V., Cam, C., Muhcu, M., Cam, M., & Karateke, A. (2006). Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *Journal of international medical research*, 34(1), 73-76.

Balasubramanian, R., Dwyer, A., Seminara, S. B., Pitteloud, N., Kaiser, U. B., & Crowley Jr, W. F. (2010). Human GnRH deficiency: a unique disease model to unravel the ontogeny of GnRH neurons. *Neuroendocrinology*, 92(2), 81-99.

Boivin, J., Bunting, L., Collins, J. A., & Nygren, K. G. (2007). International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human reproduction*, 22(6), 1506-1512.

Bozdog, G., Mumusoglu, S., Zengin, D., Karabulut, E., & Yildiz, B. O. (2016). The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. *Human Reproduction*, 31(12), 2841-2855.

Craigle, V. (2007). MedWatch: the FDA safety information and adverse event reporting program. *Journal of the Medical Library Association*, 95(2), 224.

Dăneasă, A., Cucolaș, C., Lenghel, L. M., Olteanu, D., Orăsan, R., & Filip, G. A. (2016). Letrozole vs estradiol valerate induced PCOS in rats: glycemic, oxidative and inflammatory status assessment. *Reproduction*, 151(4), 401-409.

Duleba, A. J., & Dokras, A. (2012). Is PCOS an inflammatory process? *Fertility and sterility*, 97(1), 7-12.

Escobar-Morreale, H. F., Carmina, E., Dewailly, D., Gambineri, A., Kelestimur, F., Moghetti, P., ... & Norman, R. J. (2011). Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. *Human reproduction update*, 18(2), 146-170.

Farr, S., Folger, S. G., Paulen, M., Tepper, N., Whiteman, M., Zapata, L., ... & Cansino, C. (2010). U S. medical eligibility criteria for contraceptive use, 2010: adapted from the World Health Organization medical eligibility criteria for contraceptive use. *MMWR. Recommendations and reports: Morbidity and*

mortality weekly report. Recommendations and reports/Centers for Disease Control, 59(RR-4), 1-86.

Franik, S., Kremer, J. A., Nelen, W. L., Farquhar, C., & Marjoribanks, J. (2015). Aromatase inhibitors for subfertile women with polycystic ovary syndrome: summary of a Cochrane review. *Fertility and sterility*, 103(2), 353-355.

Gifford, J. H. (2015). The role of WNT signaling in adult ovarian folliculogenesis. *Reproduction*, 150(4), R137-R148.

Hart, R., & Doherty, D. A. (2015). The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. *The Journal of Clinical Endocrinology & Metabolism*, 100(3), 911-919.

Joshi, B., Mukherjee, S., Patil, A., Purandare, A., Chauhan, S., & Vaidya, R. (2014). A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. *Indian journal of endocrinology and metabolism*, 18(3), 317.

Kamangar, F., Okhovat, J. P., Schmidt, T., Beshay, A., Pasch, L., Cedars, M. I. ... & Shinkai, K. (2015). Polycystic ovary syndrome: special diagnostic and therapeutic considerations for children. *Pediatric dermatology*, 32(5), 571-578.

Lee, Y., Yang, H., Lee, S., Kwon, S., Hong, E. J., & Lee, H. (2018). Welsh onion root (*Allium fistulosum*) restores ovarian functions from letrozole induced-polycystic ovary syndrome. *Nutrients*, 10(10), 1430.

Longo, D. L., Fauci, A. S., Kasper, D. L., Hauser, S. L., Jameson, J. L., & Loscalzo, J. (2012). *Harrison's principles of internal medicine 18E Vol 2 EB*. McGraw Hill Professional.

Mahran, A., Abdelmeged, A., Shawki, H., Moheyelden, A., & Ahmed, A. M. (2016). Nitric oxide donors improve the ovulation and pregnancy rates in anovulatory women with polycystic ovary syndrome treated with clomiphene citrate: A RCT. *International Journal of Reproductive BioMedicine*, 14(1), 9.

Mehdinejadani, S., Amidi, F., Mehdizadeh, M., Barati, M., Pazhohan, A., Alyasin, A. ... & Sobhani, A. (2018). Effects of letrozole and clomiphene citrate on Wnt signaling pathway in endometrium of polycystic ovarian syndrome and healthy women. *Biology of reproduction*.

Mehdinejadani, S., Amidi, F., Mehdizadeh, M., Barati, M., Safdarian, L., Aflatoonian, R. ... & Mohammadzadeh kazorgah, F. (2018). The effects of letrozole and clomiphene citrate on ligands expression of Wnt3, Wnt7a, and Wnt8b in proliferative endometrium of women with polycystic ovarian syndrome. *Gynecological Endocrinology*, 1-6.

Roy, K. K., Baruah, J., Singla, S., Sharma, J. B., Singh, N., Jain, S. K., & Goyal, M. (2012). A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *Journal of human reproductive sciences*, 5(1), 20.

Saha, L., Kaur, S., & Saha, P. K. (2012). Pharmacotherapy of polycystic ovary syndrome—an update. *Fundamental & clinical pharmacology*, 26(1), 54-62.

Sylus, A. M., Nandeesha, H., Sridhar, M. G., Chitra, T., & Sreenivasulu, K. (2018). Clomiphene Citrate increases Nitric oxide, Interleukin-10 and reduces Matrix metalloproteinase-9 in women with Polycystic Ovary Syndrome. *European Journal of Obstetrics & Gynecology and Reproductive Biology*.