

International Journal of Health Science

Acceptance date: 09/05/2025

TREATMENTS FOR OVULATION IN CASES OF POLYCYSTIC OVARY SYNDROME

Julia Nespoli Dal-Ry

University of Vassouras Vassouras - RJ

<http://lattes.cnpq.br/1041370840890685>

Leonardo Ferraz Filho

University of Vassouras Vassouras - RJ

<http://lattes.cnpq.br/8634515936376398>

Isabella Nascentes Coelho Tanizaki

University of Vassouras Vassouras - RJ

<https://lattes.cnpq.br/7403774782279825>

Caroline Manfrenati Francesconi Bulcão

University of Vassouras Vassouras - RJ

<https://lattes.cnpq.br/1780697184500608>

Bruna Silva Viana

University of Vassouras Vassouras - RJ

<https://lattes.cnpq.br/8530404891333018>

Lohayne Marins Teixeira Rossi Coutinho

University of Vassouras Vassouras - RJ

<http://lattes.cnpq.br/0677319834161280>



All content in this magazine is licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

Abstract: This study addresses Polycystic Ovarian Syndrome (PCOS), a complex endocrine-metabolic condition that affects women of reproductive age, representing a significant challenge for reproductive and metabolic health. It is characterized by dysfunctions such as menstrual irregularity, anovulation, hyperandrogenism and metabolic disorders, notably insulin resistance, increasing the risk of long-term complications. This is a qualitative, retrospective and cross-sectional integrative literature review, which analyzed scientific articles from the PubMed and Virtual Health Library databases, obtaining a total of 11 articles for analysis. The review explores the multifactoriality of anovulation in PCOS and various therapeutic approaches to associated infertility. It highlights studies comparing the efficacy of ovulation inducers such as Letrozole and Clomiphene Citrate, their combinations, the impact of different doses and stimulation protocols, as well as the role of insulin sensitizers such as Metformin and Inositols (Myo-inositol and D-chiro-inositol), evaluating their benefits and the importance of specific proportions. Predictive factors such as Anti-Müllerian Hormone (AMH) levels and the need to update diagnostic criteria for a more integrated approach are also discussed. The study highlights the complexity of PCOS management, underlining the importance of individualized therapeutic approaches and ongoing research to optimize treatments and diagnostic criteria in order to improve reproductive and metabolic outcomes for patients.

Keywords: SOP; Treatments; Management.

INTRODUCTION

Its main characteristics include reproductive dysfunctions, such as irregular or absent menstrual cycles (anovulation or oligo-ovulation), infertility and hyperandrogenism, causing acne, increased hair growth or hair loss.

In addition, PCOS is intrinsically linked to metabolic disorders, with insulin resistance being the most common, leading to hyperinsulinemia and an increased risk of obesity, pre-diabetes, type 2 diabetes mellitus, dyslipidemia and cardiovascular disease in the long term (Liao et al. 2024).

Its characterization goes beyond the visual appearance of the ovaries: although an excess of antral follicles on ultrasound is one of the diagnostic criteria, the syndrome is fundamentally defined by the combination of this finding with menstrual irregularity and/or signs of hyperandrogenism, reflecting a broader hormonal and ovarian dysfunction (Mumford et al. 2016). Excess androgens are a central element linking dysfunctions in brain-ovary communication. The overproduction of these androgens is complex and varies individually. The effect of this is that, although more initial follicles develop in the ovaries, none manage to become dominant and mature to ovulate, due to problems in the function of the granulosa cells induced by the androgens themselves (Agrawal et al. 2019).

METHODOLOGY

This qualitative, retrospective and cross-sectional study consisted of an integrative literature review carried out in the PubMed and Virtual Health Library (VHL) databases, using the descriptors “pcos ovulation” and “treatments” combined by the Boolean operator “AND”. Inclusion criteria were established to ensure the relevance of the articles, selecting those that directly addressed the research themes and met the following eligibility parameters: publication between 2016 and 2025, English, Portuguese or Spanish language, and availability of free access. Articles whose topic did not correspond directly to the research proposal, those that did not meet the defined inclusion criteria, and duplicate publications were excluded. The ini-

tial search process returned a total of 3,920 papers, of which 2,683 were located in the PubMed database and 1,237 in the BVS.

RESULTS AND DISCUSSION

After addressing the selection criteria, 75 articles were screened in the two databases, of which, after reading and careful selection, 11 journals were chosen for analysis. After applying the inclusion and exclusion criteria, 10 articles were selected from the PubMed database and 1 from the BVS, as shown in Figure 1.

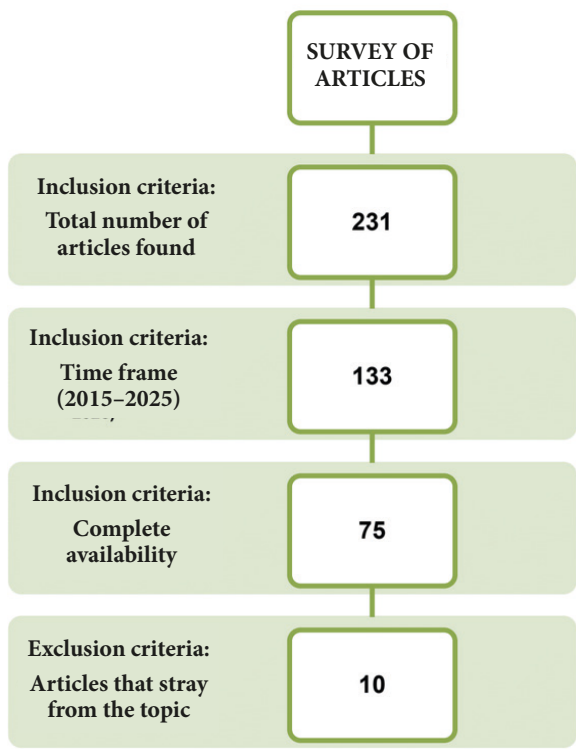


Figure 1. Flowchart for identifying and selecting the selected articles

Source: Authors (2024)

The analysis of the 11 selected studies revealed pertinent results on the various therapeutic approaches for cases of Polycystic Ovary Syndrome (PCOS). The evaluation of these strategies demonstrated a significant clinical impact on the management of the condition, addressing both infertility and associated metabolic disorders.

Table 1 below shows the locations of case studies and randomized studies.

Considering the multifaceted nature of Polycystic Ovary Syndrome, treatment takes on a crucial relevance that transcends the issue of infertility. Although it is the most common cause of anovulatory infertility, significantly impacting reproductive desire, PCOS also entails manifestations of hyperandrogenism that affect quality of life and self-esteem, as well as metabolic disorders with serious long-term implications.

The study by Nordio; Basciani; Camajani (2019), found that DCI (D-chiro-inositol) shows greater benefit when administered in a specific ratio with MI (Mio-inositol) (40:1). Increasing the amount of DCI compromises the positive reproductive results. These findings in humans corroborate a previous pre-clinical study that used different MI/DCI ratios in mice with induced PCOS.

As for Carriero et al. (2025), the study concludes that the diagnostic criteria for PCOS need to be updated to better integrate both endocrine and metabolic factors. This is aimed at more accurate diagnosis, effective treatment and improved patient confidence and communication with specialists.

Al-Thuwaynee; Swadi (2023) compared the efficacy and safety of letrozole versus clomiphene citrate for inducing ovulation in 100 Iraqi women with polycystic ovary syndrome (PCOS) and infertility. The participants were randomly divided into two groups, receiving increasing doses of one of the drugs for up to three cycles. Although letrozole showed slightly higher ovulation (86% vs 72%) and pregnancy (22% vs 18%) rates, these differences were not statistically significant. However, the average time to ovulation was significantly shorter in the letrozole group (approx. 17 days) compared to clomiphene (approx. 24 days).

Author	Year	Type of study	Main conclusions
Nordio; Basciani; Camajani	2019	Clinical Trial (n=56)	The results indicated that the ratio of 40:1 myo-inositol (MI) and D-chiro-inositol (DCI) was the most effective in restoring ovulation and normalizing other important parameters in patients.
Carriero et al.	2025	Case Series (n=769)	Treatments have included lifestyle changes (diet, exercise), metformin, hormonal contraceptives and inositols. Many women rely on unofficial sources such as the internet for information, rather than their doctors.
Al-Thuwaynee; Swadi	2023	Randomized study (n=100)	The study suggests that letrozole is as safe as clomiphene and acts more quickly to induce ovulation, but further studies are needed to validate these results.
Yahyaie; Vesali; Ghaffari	2023	Randomized Clinical Trial (n=120)	Minimal stimulation with u-HMG may be a preferable approach for PCOS patients, offering a good balance between medication dose, number of eggs/embryos, pregnancy rate and lower risk of Ovarian Hyperstimulation Syndrome.
Agrawal et al.	2019	Randomized Clinical Trial (n=120)	The combination of Metformin and Myo-inositol improved regularity of menstrual cycles and, crucially, more than doubled the live birth rate, so it appears to offer a substantial benefit in increasing the chances of successful pregnancy in infertile women with PCOS.
Rajasekaran et al.	2022	Randomized Study (n=102)	The study suggests that Myo-inositol is superior to Metformin for improving IVF outcomes (pregnancy and embryo quality) in PCOS patients.
Nguyen et al.	2020	Case series (n=80)	Research has shown that women with PCOS have insulin resistance. Letrozole is therefore important as it acts on this insulin resistance
Mumford et al.	2016	Case series (n=748)	The high level of anti-Müllerian hormone (AMH) in women with PCOS may indicate a weaker response to ovulation induction, suggesting the need for higher doses of medication.
Thabet et al.	2024	Case series (n=300)	This study evaluated whether adding low-dose HCG to Clomiphene Citrate (CC) appears to be an effective treatment to improve the chances of pregnancy in women with CC-resistant PCOS.
Chen et al.	2024	Case series (n=220)	Using 2.5 mg of letrozole followed by follicle stimulating hormone (FSH) seems to be more effective in achieving pregnancy in women with PCOS than using 5 mg of letrozole followed by FSH.
Prabhakar et al.	2021	Randomized Study (n=116)	The combination with Metformin caused more gastrointestinal side effects. Therefore, Myo-inositol alone seems to be an effective and better tolerated option as an insulin sensitizer for infertile women with PCOS.
Mejia et al.	2019	Randomized Study (n=70)	The combination of letrozole and clomiphene has helped more women with PCOS to ovulate, but it remains to be seen whether this also increases the chances of getting pregnant.

Table 1. Characterization of articles according to year of publication, type of study and main conclusions
Source: Authors (2025)

The research by Yahyaie; Vesali; Ghaffari (2023) compared the effectiveness of “minimal” versus “mild” OE protocols, using two types of gonadotrophins (recombinant FSH (r-FSH) or urinary human menopausal gonadotrophin (u-HMG)) in cycles with a GnRH antagonist. Analyses showed significant differences between the groups in the duration of stimulation, number of eggs retrieved, number of embryos obtained, clinical pregnancy and live birth rates and the need to freeze all embryos to prevent Ovarian Hyperstimulation Syndrome.

For women with PCOS and difficulty getting pregnant, the study compared the effectiveness of two treatments: Metformin alone versus Metformin combined with Myo-inositol, attempting spontaneous conception, ovulation induction and insemination if necessary. The results showed that although both treatments had similar positive effects on some laboratory tests after 3 months, the combination of Metformin and Mio-inositol was superior (Agrawal et al. 2019).

Rajasekaran et al. (2022), in a randomized trial comparing 3 months of treatment with Myo-inositol (Myo) versus Metformin (Met),

although the difference in OSH rate was not statistically significant, the Myo group had significantly higher clinical and cumulative pregnancy rates. In addition, Myo resulted in better fertilization and more good quality embryos, and improved markers of insulin resistance.

The researchers, Nguyen et al. (2020), wanted to analyze whether letrozole helped women with PCOS get pregnant as well as women without PCOS. The drug worked in the same way in both groups: promoting a similar number of eggs and the percentage of women who became pregnant was the same (around 2 in 10).

Mumford et al. (2016), found that women with lower anti-Müllerian hormone (AMH) levels were more likely to ovulate during treatment. In contrast, women with higher AMH levels generally needed higher doses of medication to be able to ovulate.

Thabet et al (2024), evaluated that adding a small dose of HCG to Clomiphene Citrate (CC) benefits women with PCOS who do not respond well to CC alone (CC resistant). The group that received HCG had significantly better results: fewer canceled cycles, more mature eggs (>18mm), better uterine lining thickness, higher ovulation rate and higher clinical pregnancy rate (7.2% vs 2.3%).

Chen et al (2024), when comparing two different doses of letrozole (2.5 mg vs 5 mg), noted that surprisingly, the group receiving the *lower* dose of letrozole (2.5 mg) had a significantly *higher* cumulative pregnancy rate (72.7%) compared to the group receiving the higher dose (59.1%).

REFERENCES

AL-THUWAYNEE, S.; SWADI, A. A. J. **Comparing efficacy and safety of stair step protocols for clomiphene citrate and letrozole in ovulation induction for women with polycystic ovary syndrome (PCOS): a randomized controlled clinical trial.** J Med Life., v. 16, n. 5, p. 725-730, mai. 2023. DOI: 10.25122/jml-2023-0069. Disponível em: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10375350/>. Acesso em: 17 abr. 2025.

CARRIERO, V. C.; FORTE, G.; DINICOLA, S.; OLIVA, M. M.; MUDARRIS, G. A.; UNFER, V. **Insights from the EGOI-PCOS patient survey: Diagnosis, treatment, and quality of life according to Italian PCOS patients.** Eur J Obstet Gynecol Reprod Biol., v. 310, p. 113947, mar. 2025. DOI: 10.1016/j.ejogrb.2025.113947. Disponível em: [https://www.ejog.org/article/S0301-2115\(25\)00212-X/abstract](https://www.ejog.org/article/S0301-2115(25)00212-X/abstract). Acesso em: 17 abr. 2025.

Prabhakar et al. (2021), evaluated whether the combination of Metformin (1500mg) and Myo-inositol (4g) was superior to Myo-inositol (4g) alone for achieving pregnancy and improving metabolic/hormonal parameters. After 6 months (including spontaneous attempt and ovulation induction), there was no significant difference in the clinical pregnancy rate between the groups (42.0% vs 45.5%).

For Mejia et al. (2019), when evaluating the isolated drug letrozole or applying letrozole together with clomiphene (CC), they observed that the combination of the two drugs worked much better: 77% of women who took both ovulated, compared to 43% of those who took letrozole alone.

FINAL CONSIDERATIONS

This integrative review of 11 articles (2016-2025) on Polycystic Ovary Syndrome (PCOS) highlights the complexity of managing the associated infertility, confirming the multifaceted nature of the condition which impacts both reproductive function and long-term metabolic health. The analysis reveals a variety of effective therapeutic approaches, such as ovulation inducers and insulin sensitizers alone or in combination, the results of which vary significantly with the protocol, dose and individual characteristics. This reinforces the need for individualized treatment and the updating of diagnostic criteria for a more integrated approach, aimed not only at conception, but also at managing metabolic risks and improving women's overall health.

CHEN, L. J.; LIU, Y.; ZHANG, L.; LI, J. Y.; XIONG, W. Q.; LI, T.; DING, H.; LI, B. J. **Sequential 2.5 mg letrozole/FSH therapy is more effective for promoting pregnancy in infertile women with PCOS: a pragmatic randomized controlled trial.** *Front Endocrinol (Lausanne)*, v. 14, p. 1294339, jan. 2024. DOI: 10.3389/fendo.2023.1294339. Disponível em: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10811237/>. Acesso em: 15 abr. 2025.

LIAO, M.; LI, X.; ZHANG, H.; ZHOU, L.; SHI, L.; LI, W.; SHEN, R.; PENG, G.; ZHAO, H.; SHAO, J.; WANG, X.; SUN, Z.; ZHENG, H.; LONG, M. **Effects and plasma proteomic analysis of GLP-1RA versus CPA/EE, in combination with metformin, on overweight PCOS women: a randomized controlled trial.** *Endocrine*, v. 83, n. 1, p. 227-241, jan. 2024. DOI: 10.1007/s12020-023-03487-4. Disponível em: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10806039/>. Acesso em: 16 abr. 2025.

MEJIA, R. B.; SUMMERS, K. M.; KRESOWIK, J. D.; VAN VOORHIS, B. J. **A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome.** *Fertil Steril*, v. 111, n. 3, p. 571-578.e1, mar. 2019. DOI: 10.1016/j.fertnstert.2018.11.030. Disponível em: [https://linkinghub.elsevier.com/retrieve/pii/S0015-0282\(18\)32225-8](https://linkinghub.elsevier.com/retrieve/pii/S0015-0282(18)32225-8). Acesso em: 19 abr. 2025.

MUMFORD, S. L.; LEGRO, R. S.; DIAMOND, M. P.; COUTIFARIS, C.; STEINER, A. Z.; SCHLAFF, W. D.; ALVERO, R.; CHRISTMAN, G. M.; CASSON, P. R.; HUANG, H.; SANTORO, N.; EISENBERG, E.; ZHANG, H.; CEDARS, M. I. **Baseline AMH Level Associated With Ovulation Following Ovulation Induction in Women With Polycystic Ovary Syndrome.** *J Clin Endocrinol Metab*, v. 101, n. 9, p. 3288-96, set. 2016. DOI: 10.1210/jc.2016-1340. Disponível em: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5010565/>. Acesso em: 19 abr. 2025.

NGUYEN, T. T.; DOAN, H. T.; QUAN, L. H.; LAM, N. M. **Effect of letrozole for ovulation induction combined with intrauterine insemination on women with polycystic ovary syndrome.** *Gynecol Endocrinol*, v. 36, n. 10, p. 860-863, out. 2020. DOI: 10.1080/09513590.2020.1744556. Disponível em: [https://www.tandfonline.com/doi/10.1080/09513590.2020.1744556](https://www.tandfonline.com/doi/10.1080/09513590.2020.1744556?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed). Acesso em: 15 abr. 2025.

NORDIO, M.; BASCIANI, S.; CAMAJANI, E. **The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios.** *Eur Rev Med Pharmacol Sci*, v. 23, n. 12, p. 5512-5521, jun. 2019. DOI: 10.26355/eurrev_201906_18223. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/31298405/>. Acesso em: 15 abr. 2025.

PRABHAKAR, P.; MAHEY, R.; GUPTA, M.; KHADGAWAT, R.; KACHHAWA, G.; SHARMA, J. B.; VANAMAIL, P.; KUMARI, R.; BHATLA, N. **Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles - randomized controlled trial.** *Gynecol Endocrinol*, v. 37, n. 4, p. 332-336, abr. 2021. DOI: 10.1080/09513590.2020.1810657. Disponível em: [https://www.tandfonline.com/doi/10.1080/09513590.2020.1810657](https://www.tandfonline.com/doi/10.1080/09513590.2020.1810657?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed). Acesso em: 16 abr. 2025.

RAJASEKARAN, K.; MALHOTRA, N.; MAHEY, R.; KHADGAWAT, R.; KALAIVANI, M. **Myoinositol versus metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study.** *Gynecol Endocrinol*, v. 38, n. 2, p. 140-147, fev. 2022. DOI: 10.1080/09513590.2021.1981282. Disponível em: [https://www.tandfonline.com/doi/10.1080/09513590.2021.1981282](https://www.tandfonline.com/doi/10.1080/09513590.2021.1981282?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed). Acesso em: 17 abr. 2025.

THABET, M.; ABDELHAFEZ, M. S.; ELSHAMY, M. R.; ALBAHLOL, I. A.; FAYALA, E.; WAGEEH, A.; EL-ZAYADI, A. A.; BAHGAT, N. A.; MOHAMMED, S. M.; MOHAMED, A. A.; AWAD, M. M.; EL-MENAYYER, A.; EL-SHERBINY, M.; ELSHERBINI, D. M. A.; ALBARAKATI, R. G.; ALSHAIKH, A. B. A.; EDRIS, F. E.; BUSHAQER, N. J.; SALAMA, Y. G. M.; ABDEL-RAZIK, M. M. **Competence of Combined Low Dose of Human Chorionic Gonadotropin (HCG) and Clomiphene Citrate (CC) Versus Continued CC during Ovulation Induction in Women with CC-Resistant Polycystic Ovarian Syndrome: A Randomized Controlled Trial.** *Medicina (Kaunas)*, v. 60, n. 8, p. 1300, ago. 2024. DOI: 10.3390/medicina60081300. Disponível em: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11356540/>. Acesso em: 19 abr. 2025.

YAHYAEI, A.; VESALI, S.; GHAFARI, F. **Introduce an optimal method of ovarian stimulation in the polycystic ovarian syndrome affected: a randomized controlled trial.** *BMC Womens Health*, v. 23, n. 1, p. 323, jun. 2023. DOI: 10.1186/s12905-023-02473-2. Disponível em: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10283261/>. Acesso em: 15 abr. 2025.