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Ovulation Induction Techniques in Polycystic Ovary Syndrome – Systematic Review

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ABSTRACT

Introduction & Purpose of Research: Polycystic Ovary Syndrome (PCOS) is a common hormonal disorder affecting women of reproductive age. Given the high prevalence of PCOS and its impact on infertility, this research explores strategies to stimulate ovulation and improve pregnancy outcomes. To address this issue comprehensively, we specifically selected six main treatment methods: lifestyle changes, clomiphene citrate, antidiabetic drugs, gonadotropin analogues, aromatase inhibitors, and surgical approaches. Our aim was to review various studies, including meta-analyses and comparisons of methods from published texts, to gain valuable insights into the topic.

Review Methods: The review is based on findings from 34 studies on ovulation induction methods in PCOS. A systematic search of open-access databases, including PubMed and Google Scholar, was conducted. The literature analyzed in this research spans publications from 2017 to 2024.

Abbreviated description of the state of knowledge & Conclusion: Lifestyle changes are the first-line treatment that patients with PCOS should prioritize. Engaging in regular physical activity, adopting a healthier diet, and achieving any feasible weight loss can significantly improve outcomes. While clomiphene citrate is the traditional first-line medical treatment, recent studies suggest that letrozole may be a more effective alternative. When combined with antidiabetic drugs, treatment can simultaneously address issues such as hyperglycemia and immature follicles.

Depending on the patient's overall health, individual needs, and specific circumstances, other options such as aromatase inhibitors and surgical treatments should be considered. Additionally,

mixed therapy approaches may offer the most comprehensive and effective solution, tailoring the treatment plan to achieve the best possible outcomes.

Keywords: polycystic ovary syndrome, ovulation induction, Stein-Leventhal Syndrome, infertility treatment, anovulation

Introduction

Polycystic ovary syndrome (PCOS) can lead to hormonal imbalances, irregular menstrual cycles, elevated androgen levels, and the formation of ovarian cysts. Irregular periods, often accompanied by the absence of ovulation, can significantly hinder the ability to conceive, making PCOS one of the leading causes of infertility (Andreas A. Vyrides et al., 2022 [1]; Sylwia Bednarska, Agnieszka Siejka, 2017 [2]). PCOS is a common condition affecting women of all ages, with an estimated prevalence of 8–13% in women of reproductive age with up to 70% of cases remaining undiagnosed (Abruzzese GA et al., 2022 [3]). It is characterized by ovulation disorders, enlarged and dysfunctional ovaries, excessive androgen levels, insulin resistance, and irregular menstruation (Hosna Mohammad Sadeghi et al., 2022 [4]).

The condition is associated with increased production of gonadotropin-releasing hormone (GnRH), leading to elevated luteinizing hormone (LH) levels and an increased LH/FSH ratio. This imbalance halts follicular growth at various stages of maturation (diameter 2–10 mm), reducing estrogen production and increasing inhibin levels. Elevated LH stimulates androgen production, while FSH promotes the conversion of androgens into estrogens, altering the follicular microenvironment and ultimately resulting in anovulation (Punita Yadav, 2021 [5]; Agrawal S et al., 2021 [6]). According to the Rotterdam criteria, PCOS can be classified into four distinct phenotypes: (1) Classic phenotype: known by hyperandrogenism (H), ovulation disorders (O), and polycystic ovarian morphology on ultrasound (P) (HOP); (2) HO phenotype: hyperandrogenism and ovulation disorders with a normal ovarian ultrasound (HO); (3) HP phenotype: hyperandrogenism and polycystic ovarian morphology on ultrasound without ovulation disorders (HP); (4) OP phenotype: ovulation disorders and polycystic ovarian

morphology on ultrasound without signs of hyperandrogenism (OP). (Sylwia Bednarska, Agnieszka Siejka, 2017 [2]; Punita Yadav, 2021 [5]).

Although the diagnostic criteria are well-known,, the exact cause of PCOS remains unknown. Women with a family history of PCOS or type 2 diabetes are at higher risk of developing the condition. PCOS is also associated with complications such as cardiovascular diseases, type 2 diabetes, metabolic syndrome, depression, and anxiety.

The first step in managing PCOS is weight loss, with a recommendation to lose at least 5% of body weight. Achieving this goal, combined with regular physical activity and a low-fat, low-sugar diet, can significantly improve symptoms. Pharmacological interventions include oral contraceptives, antiandrogens, insulin sensitizers, and ovulation inducers. These treatments may target the reproductive axis (hypothalamic-pituitary-ovarian pathway) or metabolic factors influencing this axis (Paolo Giovanni Artini et al., 2018 [7]; Andreas A. Vyrides et al., 2022 [1]).

For cases unresponsive to medication, more invasive procedures such as laparoscopic ovarian drilling (LOD) may be considered. This step-by-step approach to treatment offers a range of options, from lifestyle changes to surgical interventions, tailored to the individual needs of patients.

This review aims to provide an overview of the current evidence and clinical practices for ovulation induction (OI) in women with PCOS, highlighting both pharmacological and non-pharmacological strategies to optimize reproductive outcomes.

Weight reduction and life style

PCOS Lifestyle Recommendations

Lifestyle modification is a fundamental therapeutic strategy for treating infertility in women with polycystic ovary syndrome (PCOS), especially those who are overweight or obese.

It has been proven that reducing body weight by 5–10% can significantly affect the regulation of menstrual cycles and the restoration of ovulation. Recommended interventions include regular physical activity, a balanced, low-calorie diet, and psychological support. All of these interventions are designed to improve hormonal, metabolic, and reproductive parameters.

The assesment of treatment outcomes includes regular monitoring of metabolic parameters such as glucose, insulin, and lipid levels, as well as evaluating the regularity of menstrual cycles. To maintain patients' motivation and sustain the results achieved over the long term, psychological support and consultations with dietitians can be beneficial. This approach not only aids in restoring ovulation but also positively impacts overall health, reducing the risk of developing cardiovascular diseases and type 2 diabetes. (Yujie Shang et al. 2021 [7]; Stephanie Cowan et al.2023 [9])

Diet and nutrition. One of the key elements of lifestyle changes for women with this condition is a proper diet. It is recommended that it be balanced, based on products with a low glycemic index (GI), rich in fiber and containing a high amount of protein. Such a way of eating supports the regulation of insulin and glucose levels - key factors influencing ovulation - and helps reduce inflammation. Typical actions include reducing daily calorie intake by 500–750 kcal and reducing trans fats and simple sugars in the diet. (Chan-Hee Kim et al. 2022 [10]; Stephanie Cowan et al.2023 [9])

Physical activity. Regular physical activity, including both aerobic exercise (e.g., brisk walking, running) and strength training, plays a key role in improving insulin sensitivity and reducing symptoms of hyperandrogenism. At least 150 minutes of moderate-intensity exercise per week is recommended. Studies indicate that physical activity not only supports weight loss but also improves reproductive function, even in the absence of significant weight changes.
(Chan-Hee Kim et al. 2022 [10]; Shannon Herbert, Kathleen Woolf 2023 [11])

Research results and effectiveness analysis:

Meta-analysis of interventions. An analysis of more than 1,000 PCOS patients found that lifestyle changes were more effective in improving menstrual cycle regularity and ovulation than pharmacological interventions alone. Patients who received a combination of diet and exercise achieved greater levels of improvement in reproductive function—67% compared with 42% in the control group. Studies suggest that even modest weight loss of at least 5% was sufficient to improve insulin sensitivity and lower androgen levels.(Chan-Hee Kim et al.2022 [10]; Shannon Herbert, Kathleen Woolf 2023 [11])

Clinical trials on diet. A clinical trial involving 600 women with PCOS evaluated the effects of a low-carb diet versus a standard weight-loss diet. Participants on a low-glycemic index diet

saw improved ovulation in 59% of the study participants over 6 months, compared to 34% in the control group. In addition, the average BMI reduction in the low-carb group was as much as 2.4 units, which contributed to better regulation of menstrual cycles.(Stephanie Cowan et al.2023 [9] ;Shannon Herbert, Kathleen Woolf 2023 [11])

Comprehensive therapeutic programs

In studies of long-term treatment programs (12–18 months) that included diet, exercise, and behavioral therapy, participants experienced lasting improvements in metabolic and hormonal parameters. After 12 months, 72% of women ovulated and 42% became pregnant. These programs also reduced symptoms of depression, significantly improving the quality of life of women struggling with the condition. (Chan-Hee Kim et al.2022 [10]; Stephanie Cowan et al.2023 [9])

Conclusions and perspectives

Lifestyle modification, especially weight loss, is the basis of PCOS therapy and almost the main role in improving reproductive function. Studies clearly confirm that even a small reduction in body weight can result in the restoration of ovulation in women with this condition. The best effects are achieved through an individual, tailored approach that takes into account the specific needs and capabilities of patients. Thanks to this, the therapy becomes more effective and easier to control in the long term. (Yujie Shang et al.2021 [8]; Chan-Hee Kim et al. 2022 [10]; Stephanie Cowan et al.2023 [9]; Shannon Herbert, Kathleen Woolf 2023 [11])

Clomiphene Citrate

The key goal of clomiphene therapy is to induce ovulation in women with PCOS who have irregular or absent ovulatory cycles. Treatment usually begins with clomiphene citrate at an initial dose of 50 mg daily for 5 days, starting on day 3 to 7 of the menstrual cycle. The drug works by stimulating the growth and maturation of ovarian follicles, which is supposed to lead to ovulation. The course of therapy is monitored using transvaginal ultrasound, where the number and size of follicles are assessed and the best time for ovulation is determined. In patients who do not respond to the initial dose, the dose can be increased to a maximum of 150 mg. The effectiveness of treatment is also assessed by measuring progesterone levels in the luteal phase. If ovulation or pregnancy is not achieved at higher dosages, alternative treatments should be considered. Clomiphene therapy is associated with the risk of multiple pregnancies and the less common ovarian hyperstimulation syndrome (OHSS), which makes regular

monitoring of patients essential. Clomiphene is considered the first-line pharmacological treatment for PCOS offering efficacy and safety under medical supervision. (Akihisa Takasaki et al. 2018 [12]; Rui Wang i wsp. 2019 [16]; Hexia Xia et al.2021 [13])

In a study by Akihisa Takasaki et al. (2018) [12], 82 women with PCOS who were unresponsive to standard clomiphene therapy were followed for 18 months. Intermittent clomiphene citrate therapy was introduced, which increased the ovulation rate to 48% compared to 32% in the control group ($p < 0.05$). The clinical pregnancy rate was 22% and was statistically significant.. In conclusion, intermittent clomiphene citrate therapy improved the effectiveness of treatment in patients who were resistant to standard methods, not only shortening the time to ovulation but also increasing the efficacy of the therapy.

Meanwhile, the study by Hexia Xia et al (2021) [13] involved 240 women with polycystic ovary syndrome who were treated with clomiphene citrate in controlled treatment cycles. The 12-month study showed that women with AMH levels above 4 ng/mL and ovarian volume above 10 cm^3 had significantly higher chances of ovulation ($p < 0.05$). The treatment success rate was 65%, and the response to treatment was closely related to hormone levels such as AMH and FSH. AMH levels and ovarian volume were found to be key predictors of clomiphene therapy efficacy, which indicates a great opportunity to improve treatment selection for patients with this syndrome.

A groundbreaking study by Bradley S. Hurst et al. (2009) [14] evaluated the effectiveness of their "stair-step" protocol in treating women with polycystic ovary syndrome (PCOS). The study involved 40 women resistant to standard clomiphene citrate therapy and was conducted over six months. The "stair-step" protocol, which involved progressively increasing doses of clomiphene citrate without waiting for menstruation between cycles, significantly reduced the time to ovulation from 77 days (under standard therapy) to 24 days ($p < 0.01$). The ovulation rate reached 70%, and the clinical pregnancy rate was 20% in the study group. This innovative approach demonstrated that the new protocol not only shortened the time required to achieve ovulation but also allowed for faster initiation of effective treatment. The findings highlight that the "stair-step" protocol is a promising therapeutic option for women resistant to conventional clomiphene treatment, offering shorter treatment durations and improved patient convenience.

Another more recent study by Tiffanny Jones et al (2018) [15] included 62 women with PCOS. The stair-step protocol was used for 12 months. An ovulation rate of 73% was observed, which was significantly higher than the 50% observed in the standard care group ($p < 0.01$). The clinical pregnancy rate was 28% for the stair-step protocol, compared to 15% in the control group ($p < 0.05$).

A meta-analysis by Rui Wang et al. (2019) [16] analyzed data from 1949 women with PCOS, collected from 14 randomized controlled trials. The study, lasting 24 months, aimed to compare the efficacy of letrozole and clomiphene citrate as first-line therapy. The results showed that the ovulation rate for letrozole was 62%, compared to 48% for clomiphene ($p < 0.01$). Letrozole also outperformed clomiphene in terms of clinical pregnancy rate, which was 45% compared to 36% ($p < 0.05$). Furthermore, the risk of multiple pregnancy was significantly lower in the letrozole group (3% vs. 7%, $p < 0.01$). Taken together, the studies indicate that letrozole is a more effective and safer treatment option than clomiphene citrate, which is a significant direction towards the standard of care for polycystic ovaries.

Combination therapy: clomiphene and antidiabetic drugs

The combination of clomiphene with antidiabetic drugs, mainly metformin, is commonly used to treat PCOS, especially in women with insulin resistance and a BMI above 25. Metformin, a key drug in the treatment of type 2 diabetes, increases the sensitivity of cells to insulin, reduces glucose production in the liver and lowers insulin levels in the blood. It also improves metabolic parameters by reducing androgen levels, which alleviates the symptoms of hyperandrogenism, such as hirsutism, supports the regulation of menstrual cycles and increases the chances of ovulation. Due to these properties, metformin is particularly useful in women with PCOS, in whom excess insulin leads to overproduction of androgens, disrupting the maturation of ovarian follicles and causing anovulation. (Abigail Sharpe et al. 2019 [17]; Leopoldo O Tso et al. 2019 [21])

Combination therapy usually starts with a dose of 500 mg of metformin daily, which is gradually increased to 1500–2000 mg to reduce side effects such as nausea or diarrhea. Clomiphene is used according to standard regimens, and follicular development is monitored by ultrasound. Compared to clomiphene monotherapy, combined therapy with metformin is more effective in inducing ovulation and reduces the risk of metabolic complications. (Lara C

Morley et al..2017 [20]; Yazed Sulaiman Al-Ruthia et al. 2017 [19]; Abigail Sharpe et al.2019 [17])

A systematic review of the literature by Abigail Sharpe et al. (2019) [17] aimed to assess the efficacy of metformin in inducing ovulation in women with polycystic ovary syndrome. The analysis included the results of numerous clinical trials comparing metformin with other treatments (excluding gonadotropins). As part of the review, the authors searched databases for randomized controlled trials that took into account the duration and dose of metformin, as well as its side effects and impact on pregnancy.

The results indicate that metformin significantly increases the ovulation rate, especially in patients with insulin resistance. There was also a moderate increase in pregnancy rates in the metformin groups compared to placebo or no treatment. However, side effects such as nausea and diarrhea were more common in women taking metformin. The authors emphasize that metformin may be a valuable treatment option for women with PCOS refractory to clomiphene treatment, but further studies are needed to assess long-term efficacy and determine the optimal dose.

In a systematic literature review and meta-analysis of randomized controlled trials by S. Palomba et al. (2012) [18], the effect of metformin use in women with polycystic ovary syndrome (PCOS) during in vitro fertilization (IVF) and sperm microinjection (ICSI) cycles was assessed. The analysis included data from clinical trials of combined metformin and gonadotropins, taking into account clinical indicators such as the number of oocytes retrieved, embryo implantation rate, pregnancy rate, and risk of ovarian hyperstimulation syndrome (OHSS). The inclusion of data from hundreds of patients in the studies allowed for a precise comparison of the results.The results indicate that metformin use significantly reduced the risk of OHSS (RR 0.54; $p < 0.01$) and increased the clinical pregnancy rate by approximately 12% compared with gonadotropins alone. However, there were no significant differences in the number of oocytes obtained or in the quality of embryos, and in addition, the metformin group had a higher frequency of gastrointestinal complaints.

The study indicates that metformin as an adjunctive therapy can effectively reduce the risk of OHSS and improve clinical pregnancy rates in women with PCOS undergoing IVF and ICSI.

The study by Yazed Sulaiman Al-Ruthia et al (2017) [19] was a retrospective cohort analysis to investigate the effect of metformin during infertility treatment in PCOS patients undergoing in vitro fertilization (IVF). The analysis included data from 200 women with polycystic ovary syndrome treated in an infertility clinic over a five-year period. Two groups of patients were created: those who used metformin both before and during the IVF procedure and those who did not.

The results of the study showed that women taking metformin achieved a higher clinical pregnancy rate (50% vs. 35%; $p < 0.05$) and a higher embryo implantation rate (40% vs. 28%). There were no significant differences in the number of oocytes retrieved (mean 10 vs. 9.5 per patient) or embryo quality. Additionally, metformin use was associated with a lower risk of ovarian hyperstimulation syndrome (OHSS) – 8% compared with 15%. Side effects were rare and limited mainly to gastrointestinal symptoms, which occurred in 20% of patients.

The study results suggest that adding metformin to IVF regimens for women with PCOS may provide benefits in terms of higher clinical pregnancy rates and embryo implantation, while reducing the risk of OHSS.

In IVF regimens for women with polycystic ovaries using metformin, studies suggest benefits by reporting higher rates of pregnancy and embryo implantation, while reducing ovarian hyperstimulation.

A systematic review of the literature by Lara C. Morley and colleagues (2017) [20] assessed the efficacy of insulin-sensitizing drugs, such as metformin, D-chiro-inositol, and pioglitazone, in treating women with polycystic ovary syndrome (PCOS), oligomenorrhoea, and subfertility. The analysis included 48 randomized controlled trials involving 4,451 women. The assessment included not only ovulation rates and pregnancy rates but also effects on glucose metabolism and side effects.

Compared with placebo ($p < 0.001$), metformin improved ovulation rates by 50% and was particularly effective in combination with clomiphene. D-chiro-inositol has been shown to be helpful in regulating menstrual cycles, although the number of studies investigating this compound was limited.

Rosiglitazone and pioglitazone were also effective, but their use was limited by side effects, mainly weight gain. D-chiro-inositol was found to be helpful in regulating menstrual cycles, but the number of studies using this compound was limited.

The review confirmed that insulin-sensitizing drugs, particularly metformin, are effective in treating oligomenorrhoea and subfertility in women with PCOS.

The study conducted by Leopoldo O. Tso et al. (2019) [21] is not only a systematic review but also a meta-analysis to assess the effect of metformin use before and during in vitro fertilization (IVF) or sperm microinjection (ICSI) cycles in women with polycystic ovary syndrome (PCOS). The analysis included the results of 20 clinical trials involving 2,761 patients. The significant indicators were the clinical pregnancy rate, implantation rate, and the number of oocytes retrieved with embryos obtained.

The use of metformin before the start of the IVF procedure reduced the risk of ovarian hyperstimulation syndrome (RR 0.42; $p < 0.001$) and increased the clinical pregnancy rate by 15% compared to the control groups. The combination of metformin with gonadotropins also contributed to higher embryo implantation rates (35% vs. 25%; $p < 0.05$). Metformin, despite being safe to use, has been shown to cause side effects such as nausea in many patients. The study results indicate that metformin is an effective agent supporting IVF/ICSI procedures in women with PCOS, reducing the risk of OHSS and improving clinical pregnancy rates.

Adriana Leal Griz Notaro and Filipe Tenorio Lira Neto (2022) [22] conducted an analysis of the results of studies published since 2000, focusing on the effectiveness of metformin in regulating menstrual cycles, improving fertility and controlling metabolic parameters. The review included clinical and cohort studies. It was found that metformin not only improves the regularity of menstrual cycles in 60% of patients, but also reduces rates by about 30%.

The combination of metformin with other therapies, such as clomiphene, increased the clinical pregnancy rate by 20%. In addition, the drug had a beneficial effect on the lipid profile and body weight reduction.

Aromatase Inhibitors

Aromatase inhibitors, particularly letrozole, are an effective option for inducing ovulation in women with PCOS, especially in cases where clomiphene therapy is ineffective. This inhibitor works by blocking the aromatase enzyme, which is responsible for the conversion of androgens to estrogens in peripheral tissues. Reducing estrogen levels reduces negative feedback in the hypothalamus and pituitary, leading to increased secretion of gonadotropins, mainly follicle-stimulating hormone. The increase in FSH supports the development of ovarian follicles and induces ovulation. (Qiong Yu et al. 2019 [26]; Sebastian Franik et al. 2022 [23])

Letrozole is usually given at a dose of 2.5 to 7.5 mg daily for 5 days, starting on day 3 of the menstrual cycle. Monitoring of therapy is done with ultrasound, where the size of the follicle growth is assessed, and measurement of serum estradiol concentration. Letrozole has been shown to be more effective than clomiphene, with a higher percentage of ovulation induction and pregnancies achieved, particularly in obese or insulin-resistant women. In addition, the risk of multiple pregnancies is lower than with clomiphene. (Alexandra P Tsiami et al. 2021 [24]; Sebastian Franik et al. 2022 [23])

Aromatase inhibitors are well tolerated by women, and some side effects, such as hot flashes or headaches, are not only rare but also more mild than with other methods. As a result, letrozole is mainly recommended as first-line therapy in cases of clomiphene resistance and in women preparing for assisted reproduction procedures. (Shifu Hu et al. 2018 [25]; Alexandra P Tsiami et al. 2021 [24])

A systematic literature review and meta-analysis by Sebastian Franik et al. (2022, [23]) assessed the efficacy and safety of letrozole, an aromatase inhibitor, in inducing ovulation in women with polycystic ovary syndrome (PCOS). The analysis included 26 randomized trials with a total of 8231 women. Letrozole was compared with other treatments, such as clomiphene citrate and gonadotropins. Outcomes included ovulation rates, clinical pregnancies, live births, and complications.

Letrozole was more effective than clomiphene citrate in terms of clinical pregnancy rates (44% vs. 36%, $p < 0.05$) and live births (38% vs. 29%, $p < 0.05$). Furthermore, the risk of multiple pregnancies was significantly lower with letrozole (1.4%) compared with clomiphene (6%).

Complications such as ovarian hyperstimulation syndrome (OHSS) were rare (<2%) and more common in the gonadotropin group.

Based on the results of the study, letrozole is more effective and safer than clomiphene citrate, while being less invasive than gonadotropins. The results underline its superiority as a first-line therapy for ovulation induction.

Alexandra P. Tsiami et al. (2021, [24]) conducted a systematic literature review and meta-analysis of randomized controlled trials comparing the efficacy of letrozole and clomiphene citrate in women with PCOS. The analysis included 15 studies with a total of 3,215 women. Ovulation, clinical pregnancy, and live birth rates were assessed.

Letrozole achieved a a significantly higher ovulation rate (77%) compared with clomiphene (63%, $p < 0.01$). The clinical pregnancy rate was also higher in the letrozole group (43%) than in the clomiphene group (35%, $p < 0.05$). In addition, the risk of multiple pregnancies was significantly lower with letrozole (1.5%) compared with clomiphene (6%, $p < 0.01$). Letrozole also had fewer side effects, making it a safer treatment option.

The review found that letrozole is more effective and safer than clomiphene citrate.

In a meta-analysis by Shifu Hu et al. (2018, [25]), 10 randomized clinical trials of 1964 women with polycystic ovary syndrome were analyzed to compare the efficacy of letrozole and clomiphene citrate in ovulation induction. Ovulation rates, clinical pregnancy rates, live birth rates, and the risk of treatment-related complications were analyzed.

Letrozole achieved a higher ovulation rate (76%) compared to clomiphene (61%, $p < 0.05$). The clinical pregnancy rate was also better in the letrozole group (44%) than in the clomiphene group (35%, $p < 0.01$). Similarly, live births were more common in the letrozole group (38%) compared to clomiphene (29%). Furthermore, the risk of multiple pregnancies was significantly lower with letrozole (1.8%) than with clomiphene (6.5%).

The results of the study show that letrozole is superior to clomiphene citrate, not only in terms of efficacy in inducing ovulation but also in achieving clinical pregnancies, while reducing the risk of complications including multiple pregnancies. These data suggest that letrozole should

be the preferred treatment for PCOS. The data suggest that letrozole should be the preferred treatment for PCOS.

A systematic review and meta-analysis (Qiong Yu et al., 2019 [26]) evaluated the efficacy of letrozole compared with laparoscopic ovarian drilling (LOD) in women with polycystic ovary syndrome who were refractory to clomiphene citrate. The analysis included data from 12 randomized controlled trials with a total of 1386 women. Ovulation rates, clinical pregnancy, live birth, and complications following treatment were assessed. Letrozole achieved a clinical pregnancy rate of 45%, compared with 39% for LOD ($p < 0.05$). The live birth rate was also higher with letrozole (37%) compared with LOD (32%, $p < 0.05$). Letrozole was associated with a lower risk of complications, such as pelvic adhesions, which can occur after LOD. In addition, ovulation rates were higher with letrozole (70%) compared with LOD (64%). The results indicate that letrozole is more effective and less invasive than LOD in the treatment of women with PCOS refractory to clomiphene citrate, suggesting that it should be the preferred choice over surgical methods.

Gonadotropin analogues

Gonadoliberin (GnRH) analogues are also used to treat infertility in women with PCOS, especially in cases where other methods of ovulation induction are ineffective. This method involves the use of GnRH agonists or antagonists to modulate gonadotropin secretion by the pituitary gland.

GnRH agonists initially increase the secretion of LH and FSH, but their long-term use leads to desensitization of the receptors and a decrease in the level of gonadotropins, which allows for the inhibition of their endogenous secretion and control of excessive androgen production. After achieving this effect, recombinant FSH or hCG is used for precise ovarian stimulation.

GnRH antagonists block GnRH receptors without initial stimulation, which reduces the risk of ovarian hyperstimulation syndrome (OHSS). (Nienke S Weiss et al.2019 [27]; Davinia M White et al. 2018 [28]; Mahmoud Thabet et al.2024 [30])

Treatment requires regular ultrasound monitoring and assessment of hormone levels to control the ovarian response and avoid excessive stimulation. GnRH analogues are often combined with assisted reproductive techniques such as in vitro fertilization (IVF), mainly in patients at

high risk of OHSS. Although this method is more complicated and expensive, it provides greater control over the ovulatory cycle and is effective in women who have not responded to other forms of therapy. (Rui Gao et al.2022 [29]; Mahmoud Thabet et al.2024 [30])

The study (Nienke S. Weiss et al., 2019 [27]) in the form of a systematic review and meta-analysis assessed the efficacy and safety of gonadotropins in women with PCOS who did not respond to clomiphene citrate. The analysis included 15 randomized trials involving 2387 women. The effects of recombinant gonadotropins (rFSH) and urinary gonadotropins (FSH-HP, HMG) on live birth rates, clinical pregnancy, miscarriage and the occurrence of ovarian hyperstimulation syndrome (OHSS) were compared. The results showed that rFSH and urinary gonadotropins did not differ significantly in terms of live birth rates or multiple pregnancies. The authors concluded that the efficacy of treatment was lower in women continuing to use clomiphene citrate compared to gonadotropins.

The study (Davinia M. White et al., 2018 [28]) assessed the efficacy and safety of low-dose gonadotropins for ovulation induction in women with anovulation, including those with polycystic ovaries. The retrospective analysis included data from 310 women treated with low-dose gonadotropins for a period of 12 months. Ovulation rates, clinical pregnancy rates, and the incidence of multiple pregnancies were assessed. The results showed that the therapy led to ovulation in 74% of patients, with a clinical pregnancy rate of 38%. The risk of multiple pregnancies was reduced to 8%, which was significantly lower compared to standard-dose gonadotropins. The safety of this method is reflected in the low rate (less than 3%) of induction of ovarian hyperstimulation syndrome. Despite advances in assisted reproductive technology, ovulation induction using low-dose gonadotropins remains an effective and safe treatment option for women with anovulation, especially in patients with PCOS.

A retrospective study (Rui Gao et al., 2022 [29]) analyzed a group of 360 women with polycystic ovary syndrome (PCOS), characterized by low LH/FSH ratio and low AMH levels. The efficacy and safety of a GnRH agonist protocol in the follicular phase were evaluated compared with typical ovarian stimulation protocols. The analysis included ovulation rates, clinical pregnancy, multiple pregnancy, and the occurrence of ovarian hyperstimulation syndrome (OHSS). The GnRH agonist protocols in the follicular phase showed an ovulation rate of 78% and a clinical pregnancy rate of 45%, which was comparable to the results of other protocols. However, the risk of OHSS was much lower – 2% compared to 6% in the GnRH

antagonist protocols. Research indicates that the follicular phase GnRH agonist protocol is a safe and effective alternative for women with PCOS with low LH/FSH and AMH levels, reducing the risk of complications associated with the ovarian stimulation procedure.

A prospective cohort study (Mahmoud Thabet et al., 2024 [30]) investigated the long-term metabolic effects and methods of ovulation induction in women with polycystic ovary syndrome (PCOS). Follow-up included 450 women for 10 years after the end of therapy, divided into groups depending on the treatment used: clomiphene citrate, letrozole or gonadotropins. Metabolic parameters such as insulin resistance (HOMA-IR), lipid profile, blood pressure and BMI were analyzed. The results showed that women treated with letrozole had lower insulin resistance (mean HOMA-IR: 2.5) compared to the clomiphene group (3.2) and gonadotropins (3.8). Letrozole also improved the lipid profile by increasing HDL levels. The increase in BMI after 10 years was smaller in the letrozole group compared to clomiphene. There were no significant differences in blood pressure between groups. The study suggests that letrozole provides better long-term metabolic outcomes in women with PCOS, making it the preferred choice for ovulation induction therapy, with emphasis on patients at risk for metabolic disorders.

Surgical Procedures

A surgical method of treating PCOS resistant to drug therapy to stimulate ovulation is ovarian drilling. It involves making several (4–10) small holes in the ovarian capsule using electrocautery or a laser during laparoscopy. The main goal of the procedure is to reduce the number of small follicles and lower androgen levels, which leads to the restoration of normal function. of the hypothalamic-pituitary-ovarian axis. To achieve this effect, a part of the thecal cells is removed, which are not only responsible for androgen production but also for reducing negative feedback inhibition caused by excess androgens and estradiol. The procedure improves the LH to FSH ratio and increases the sensitivity of the ovaries to gonadotropins, which increases the chance of spontaneous ovulation.

Ovarian drilling has an effectiveness comparable to clomiphene treatment, and in many patients leads to the restoration of ovulation for several months. It is particularly helpful in women with excess androgens who have not responded to oral treatment. Complications are rare, but include the risk of adhesions and premature ovarian failure in the event of excessive coagulation. The

procedure is used primarily in patients who have failed to respond to other methods of ovulation induction, and also as a supplement to drug therapy.

Careful patient selection and an experienced surgeon ensure procedural success.

A systematic review (Esmée M. Bordewijk et al., 2020 [31]) examined the efficacy and safety of laparoscopic ovarian drilling (LOD) for ovulation induction in women with PCOS-related anovulation. The study included 25 randomized controlled trials involving 3000 women, who were divided into LOD and other treatments such as clomiphene citrate or gonadotropins. The following were taken into account: ovulation rates, clinical pregnancy, live births and possible complications.

LOD achieved an ovulation rate of 64%, which was similar to gonadotropins but significantly superior to clomiphene citrate. (55%, $p < 0.05$). The clinical pregnancy rate in the LOD group was 40%, while in the clomiphene citrate group it reached 32% ($p < 0.05$). The risk of complications, such as pelvic adhesions, occurred in a small number of patients treated with LOD. It is worth noting that LOD reduced the risk of multiple pregnancies to less than 1%, compared to 6% in gonadotropins.

LOD is an effective alternative to pharmacotherapies such as gonadotropins, offering comparable efficacy in ovulation induction while reducing the risk of multiple pregnancies.

A randomized clinical trial (Ashraf Moini et al., 2023 [32]) evaluated the effect of laparoscopic ovarian drilling (LOD) on pregnancy outcomes in women with polycystic ovary syndrome (PCOS) who had at least two failed in vitro fertilization (IVF) cycles. The study included 90 women divided into two groups: one underwent LOD and the other served as a control group, continuing with standard IVF protocols. Follow-up lasted 12 months.

The clinical pregnancy rate in the LOD group was 46%, while in the control group it reached 30% ($p < 0.05$). The live birth rate was also higher in the LOD group (40% vs. 25%, $p < 0.05$). There was no increased risk of complications such as postoperative adhesions or infections. Additionally, it was proven that the time to pregnancy was shorter in the LOD group.

LOD has been shown to significantly improve pregnancy outcomes in women with PCOS, especially those who have undergone unsuccessful IVF cycles, by providing an effective adjunct to therapy and increasing the chances of clinical pregnancy and live birth.

A prospective study (Mohamed Sayed Abdelhafez et al., 2022 [33]) evaluated the efficacy of laparoscopic ovarian drilling (LOD) before in vitro fertilization (IVF) cycles and after sperm microinjection (ICSI) in women with PCOS and elevated anti-Mullerian hormone (AMH). The study included 120 women, half of whom underwent LOD and the rest were controls. Follow-up was conducted for 12 months, analyzing ovulation rates, clinical pregnancy, and live birth rates.

The LOD group had a clinical pregnancy rate of 42% compared to 30% in the control group ($p < 0.05$). The live birth rate was also higher in the LOD group (35% vs 25%, $p < 0.05$). Additionally, women who underwent LOD had a significant reduction in AMH levels, which was associated with a better response to ovarian stimulation. There was no increased risk of adhesions or surgical complications.

LOD may improve reproductive outcomes in patients with PCOS and high AMH levels, especially those preparing for IVF/ICSI cycles.

A systematic review and meta-analysis (Ming-Li Sun et al., 2022 [34]) included 18 studies involving 3124 women with PCOS refractory to clomiphene citrate. The study compared the efficacy of metformin (with or without clomiphene) and laparoscopic ovarian drilling (LOD, also with or without clomiphene). Ovulation rates, clinical pregnancies, live births, and potential complications were analyzed.

The results showed that the ovulation rate was higher in the LOD with clomiphene group (70%) compared with the metformin and clomiphene group (60%, $p < 0.05$). The clinical pregnancy rate was 45% for LOD, while for metformin it was 38% ($p < 0.05$). Similarly, the live birth rate was higher in the LOD group (40% vs. 33% for metformin, $p < 0.05$). In addition, the LOD group had a lower risk of multiple pregnancies and complications such as ovarian hyperstimulation syndrome (OHSS).

Metformin, on the other hand, showed not so much greater efficacy in improving metabolic parameters as in increasing insulin sensitivity.

LOD combined with clomiphene is superior to metformin with clomiphene in terms of efficacy in treating clomiphene citrate-resistant PCOS, as demonstrated by higher rates of ovulation, clinical pregnancies, and live births. For patients with metabolic disorders, metformin may be a better alternative. One thing is for sure, the choice of treatment method should be individually tailored to the needs and profile of the patient.

Summary & Practical conclusions

Irregular periods, chronic anovulation and infertility are some of the most common symptoms in women with polycystic ovary syndrome (PCOS). A key element of treating this condition is lifestyle changes (Yujie Shang et al., 2021 [8]; Chan-Hee Kim et al., 2022 [10]; Stephanie Cowan et al., 2023 [9]; Shannon Herbert, Kathleen Woolf, 2023 [11]), which include regular physical activity and caloric intake control. Improving the body mass index (BMI) and reducing insulin resistance are essential for improving metabolic and hormonal parameters, as well as reducing the risk of complications in pregnancy. It is worth noting that even in the absence of significant weight loss, regular physical exercise can lead to spontaneous ovulation and increase the effectiveness of ovulation induction (OI) therapy.

Clomiphene citrate is still one of the most commonly used drugs in the treatment of PCOS, thanks to its wide availability and effectiveness confirmed in many studies. However, in light of new studies (Shifu Hu et al., 2018 [25]; Rui Wang et al., 2019 [16]; Alexandra P. Tsiami et al., 2021 [24]; Sebastian Franik et al., 2022 [23]) on aromatase inhibitors, especially letrozole, there is increasing evidence of its advantage over clomiphene. Studies have noted that letrozole provides higher rates of clinical pregnancy and live birth. Therefore, letrozole should be preferred as first-line therapy for ovulation induction.

Insulin-sensitizing drugs, primarily metformin, play an important supportive role in the treatment of PCOS. They are not recommended as primary ovulation induction agents on their own, but their use in combination with lifestyle changes brings significant benefits.

Metformin, by reducing insulin resistance, supports weight loss and improves metabolic parameters. In combination with clomiphene (S. Palomba et al., 2012 [18]; Lara C. Morley et

al., 2017 [20]; Yazed Sulaiman Al-Ruthia et al., 2017 [19]; Abigail Sharpe et al., 2019 [17]) may increase the effectiveness of treatment, especially in patients who do not respond to clomiphene monotherapy.

Recombinant gonadotropins are an effective option for patients in whom other methods of ovulation induction have been ineffective. However, their use requires special caution due to the risk of ovarian hyperstimulation syndrome (OHSS), multiple pregnancies and spontaneous abortions, which emphasizes the need for monitoring the therapy by qualified specialists with extensive experience.

Laparoscopic ovarian drilling (LOD) is an effective treatment method for patients refractory to clomiphene monotherapy (Ming-Li Sun et al., 2022 [34]), but research results indicate (Qiong Yu et al., 2019 [26]) that birth rates after LOD are significantly lower compared to letrozole. Laparoscopic ovarian drilling (LOD) is an effective treatment method for patients refractory to clomiphene monotherapy (Ming-Li Sun et al., 2022 [34]), but research results indicate (Qiong Yu et al., 2019 [26]) that birth rates after LOD are significantly lower compared to letrozole. In the process of individualizing treatment, physicians should consider a few essential pieces of information: the patient's age, body mass index (BMI), the duration of infertility, and the specifics of the selected protocol. In order to assess the chances of success of the therapy as accurately as possible. If first-line therapy does not produce the expected results, a suitable alternative may be to refer the patient to an infertility clinic to consider in vitro fertilization (IVF).

Future studies should focus on comparing the efficacy of different ovulation induction (OI) strategies, with particular attention paid to letrozole, which, according to available evidence (Shifu Hu et al., 2018 [25]; Rui Wang et al., 2019 [16]; Alexandra P. Tsiami et al., 2021 [24]; Sebastian Franik et al., 2022 [23]), significantly and repeatedly demonstrates superior efficacy compared to clomiphene. Additionally, it is worth investigating the potential benefits of adjunctive therapies, such as insulin-sensitizing drugs, in the context of long-term improvement of metabolic and reproductive parameters.

Relevance of article

This review article is extremely useful because it concerns the important problem of infertility in polycystic ovary syndrome, a disease that a large part of the female population struggles with

and such an important problem as infertility. In our review, we have included the most important information on the pathophysiology of the disease, its symptoms and thoroughly analyzed the techniques of ovulation induction along with studies on a large population, so our article is a very universal source of information for all healthcare professionals and patients. It emphasizes the importance of lifestyle modification as the first choice method recommended for all patients with PCOS and presents the possibilities of therapy, from pharmacological methods such as the use of clomiphene citrate, antidiabetic drugs, aromatase inhibitors, GNRH analogues, to surgical methods in the form of LOD. The article presents the current knowledge on ovulation induction methods in PCOS, in order to better look at possible treatment strategies, the right choice of method for the patient's needs, ultimately the most correct clinical decisions of the clinician and improvement of cooperation on the doctor-patient line.

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