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Letrozole-Assisted Ovulation Induction Combined with Lifestyle Modification in Women with PCOS: A Review

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Introduction. Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory infertility. Lifestyle modification remains the foundation of treatment, yet many women require pharmacological ovulation induction. Letrozole, an aromatase inhibitor originally developed for breast cancer therapy, has emerged as a promising first-line agent for women with PCOS.

Aim. The aim of this article is to assess whether it is clinically appropriate to use letrozole in addition to physical activity and nutrition to achieve better ovulation outcomes in women with PCOS trying to improve infertility.

Review methods. A thorough examination of research articles on PubMed and Google Scholar was conducted using search phrases that included the following keywords: letrozole/ off-label use/

ovulation induction/ female infertility/ polycystic ovary syndrome/ aromatase inhibitors/ diet/ lifestyle modification/ stimulated cyclear

Keywords: letrozole, off-label use, ovulation induction, female infertility, polycystic ovary syndrome/ aromatase inhibitors, diet, lifestyle modification/ stimulated cyclea

1. Polycystic Ovary Syndrome (PCOS)

I. Definition and General Characteristics of Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age, characterized by a heterogeneous clinical presentation and a complex, multifactorial etiology. It represents a chronic condition involving reproductive, metabolic and psychological components, and is associated with significant short- and long-term health consequences [1,3,5,41]. The syndrome is defined by a constellation of symptoms that largely revolve around hyperandrogenism, ovulatory dysfunction, and characteristic ovarian morphology, although the dominance and combination of these features vary considerably among affected individuals [1,7,42]..

PCOS is recognized as a multisystem disorder. Beyond reproductive manifestations, it exerts profound effects on metabolic health, including insulin resistance, obesity, dyslipidemia, and increased risk of type 2 diabetes mellitus, which may occur even in women with normal body weight [1,5,41]. These metabolic alterations interact with neuroendocrine dysregulation, contributing to the diverse phenotypic presentations of PCOS. The condition is therefore not confined to the ovaries but reflects a broader interplay between the hypothalamic–pituitary–ovarian axis, insulin signaling pathways, adipose tissue function and inflammatory responses [1,5,41].

International health organizations, including the World Health Organization, consistently highlight PCOS as a major global health concern due to its high prevalence and multidimensional burden on women's health, fertility, and quality of life [3,42]. The syndrome often presents from adolescence, though its features evolve with age and vary depending on hormonal, metabolic, and environmental factors [1,42]. Because of its clinical heterogeneity, PCOS requires a comprehensive diagnostic

approach that includes assessment of reproductive function, androgen status, metabolic risk factors, and exclusion of other conditions presenting with similar symptoms [1,7,42].

Overall, PCOS constitutes a significant endocrine disorder with wide-ranging implications for women's reproductive and metabolic health. Understanding its definition and systemic nature provides the foundation for further discussion on diagnostic criteria, epidemiology, and therapeutic strategies.

II. Diagnostic Criteria for PCOS

The diagnosis of PCOS relies on clinical, biochemical, and ultrasonographic features, but the specific criteria used to establish the diagnosis vary across professional organizations and have evolved over time. Three major diagnostic systems are widely referenced in clinical practice and research: the NIH 1990 criteria, the Rotterdam 2003 criteria, and the AES 2006 criteria. Differences among these frameworks significantly influence the identification of PCOS phenotypes and reported prevalence rates [6,7,40,42].

Although the NIH 1990 criteria were foundational in shaping the early understanding of PCOS, they are now regarded primarily as historical and are not the recommended diagnostic standard. These criteria required the presence of both chronic anovulation and clinical or biochemical hyperandrogenism, therefore capturing only the "classic" and most severe phenotypes of PCOS. Their narrow scope excludes milder presentations and no longer reflects the recognized clinical heterogeneity of the syndrome [7,40,42].

A major shift occurred with the development of the Rotterdam criteria in 2003, which expanded the diagnostic framework and remain the internationally endorsed and most widely used standard in contemporary clinical practice [42]. According to this consensus, PCOS can be diagnosed when two of the following three features are present, after excluding related disorders:

1. Clinical or biochemical hyperandrogenism
2. Oligo- or anovulation
3. Polycystic ovarian morphology on ultrasound

The adoption of these criteria broadened the definition of PCOS and led to recognition of four phenotypes (A–D), ranging from classic hyperandrogenic presentations to non-hyperandrogenic but ovulatory variants. This expanded framework explains the substantial variation in prevalence estimates reported across studies [6,40].

The Androgen Excess and PCOS Society (AES) 2006 criteria proposed a more restrictive definition, requiring hyperandrogenism as an essential feature, combined with ovarian dysfunction (oligo-

anovulation and/or polycystic ovarian morphology). Although cited in research — particularly in studies focusing on metabolic and androgen-excess phenotypes — the AES criteria are not the dominant standard in clinical practice and are used less frequently than the Rotterdam system.

In summary, while multiple diagnostic frameworks exist, the Rotterdam criteria constitute the contemporary, evidence-based diagnostic standard, whereas the NIH criteria have primarily historical value, and the AES criteria serve as an alternative system used mainly in specific research contexts.

III. Pathophysiology of PCOS

The pathophysiology of polycystic ovary syndrome is complex and multifactorial, resulting from interactions between ovarian, metabolic, neuroendocrine, genetic and environmental factors [1,5,41]. Current evidence supports a model in which ovarian dysfunction (particularly excess androgen production), insulin resistance with compensatory hyperinsulinemia, and neuroendocrine abnormalities act together to produce the characteristic reproductive and metabolic manifestations of the syndrome [1,5,41].

A central feature is ovarian androgen excess. Theca cells in affected women often show increased steroidogenic activity, leading to elevated androgen synthesis which disrupts normal follicular development and contributes to anovulation and polycystic ovarian morphology [1,5,41]. Excess androgens also contribute to clinical signs such as hirsutism and acne, and they may interact with metabolic pathways to amplify disease expression [1,41].

Insulin resistance and compensatory hyperinsulinemia are key metabolic drivers in many women with PCOS. Insulin directly stimulates ovarian androgen production and reduces hepatic synthesis of sex hormone–binding globulin, thereby increasing circulating bioavailable androgens. Importantly, insulin resistance occurs across BMI categories — both lean and obese women with PCOS may exhibit impaired insulin sensitivity — although obesity commonly exacerbates metabolic and reproductive abnormalities [1,2,5,41].

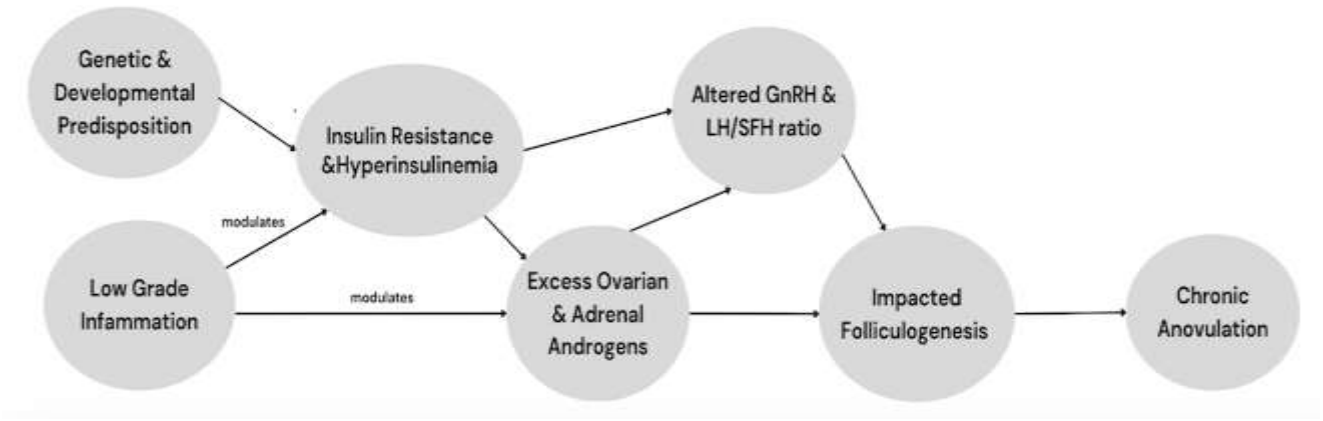
Neuroendocrine dysfunction also contributes: many women with PCOS demonstrate altered hypothalamic–pituitary regulation, including increased GnRH pulse frequency and a relative elevation of luteinizing hormone (LH) secretion compared with follicle-stimulating hormone (FSH). Elevated LH favors ovarian androgen production and, together with impaired FSH-driven follicular maturation, leads to arrested follicle development and anovulation [1,5,41].

Genetic and familial patterns further support a heritable component of PCOS, although the condition is considered polygenic and influenced by environmental modifiers. Emerging evidence highlights

roles for intrauterine androgen exposure, adipose tissue dysfunction, inflammatory pathways, and alterations in gut–hormonal interactions, although the precise contribution of these mechanisms is not yet fully understood [5,41].

Taken together, these interconnected mechanisms explain the heterogeneity of PCOS phenotypes, ranging from classic hyperandrogenic anovulatory forms to milder presentations in which metabolic features may predominate. International guidelines emphasize this multifactorial pathogenesis and recommend that assessment and management consider both reproductive and metabolic axes of the disorder [42].

Figure 1. Multifactorial pathophysiology of polycystic ovary syndrome (PCOS) leading to chronic anovulation [1,5,7,41,42].



IV. Clinical Manifestations of PCOS

The clinical presentation of polycystic ovary syndrome is heterogeneous and varies significantly among affected women. The disorder encompasses reproductive, dermatologic, metabolic, and psychological features, reflecting the multifactorial nature of its underlying pathophysiology [1,5,41,42]. International health agencies, including the World Health Organization, emphasize that PCOS represents a major global cause of anovulatory infertility and metabolic morbidity, with symptoms that may evolve across the lifespan [3].

A hallmark reproductive feature is menstrual irregularity, most commonly presenting as oligomenorrhea or amenorrhea, which reflects chronic or infrequent ovulation [1,5,42]. As a consequence of ovulatory dysfunction, many women experience challenges in achieving pregnancy, although the severity of reproductive impairment varies across PCOS phenotypes [1,5]. Ultrasound

examination may show polycystic ovarian morphology, yet this feature is not universal and is influenced by age, hormonal milieu, and differences in imaging criteria [42].

Clinical or biochemical hyperandrogenism is another key manifestation. Clinically, this includes hirsutism, acne, and androgenic alopecia, although the severity and combination of symptoms differ among phenotypes and ethnic groups [1,5,41]. Elevated circulating androgens—such as total or free testosterone—support the diagnosis of biochemical hyperandrogenism, yet their levels may show considerable interindividual variability [42].

Metabolic disturbances are frequent and constitute a major component of the clinical spectrum. Many women with PCOS exhibit insulin resistance, impaired glucose homeostasis, dyslipidemia, and increased central adiposity, with risk further amplified by coexisting overweight or obesity [1,2,5,41]. These abnormalities contribute to an elevated likelihood of developing type 2 diabetes and other cardiometabolic complications across the life course, underscoring the need for metabolic assessment at diagnosis and during follow-up [42].

Beyond reproductive and metabolic symptoms, PCOS is associated with a range of additional clinical manifestations. Women may experience weight gain or difficulty losing weight, although PCOS also occurs in lean individuals. Evidence indicates that psychological symptoms—including anxiety, depressive symptoms, and reduced quality of life—are more prevalent among women with PCOS, likely reflecting interactions between hormonal, metabolic, and psychosocial factors [41]. Sleep disturbances and obstructive sleep apnea have also been reported with increased frequency, particularly among women with obesity and metabolic dysfunction [41].

Overall, the clinical picture of PCOS is diverse, reflecting the interplay of hyperandrogenism, ovulatory dysfunction, and metabolic abnormalities. International guidelines highlight that assessment should encompass all these domains to ensure accurate diagnosis and comprehensive management [42].

2. Epidemiology and Statistics of PCOS

Polycystic ovary syndrome is one of the most common endocrine and metabolic disorders affecting women of reproductive age, yet its reported prevalence varies widely due to differences in diagnostic criteria, study designs, and population characteristics [6,40,42]. Epidemiological estimates indicate that PCOS affects approximately 8–13% of women globally when contemporary diagnostic frameworks such as the Rotterdam criteria are applied, making it a major public health concern [3,40,42]. However, prevalence may fall to 4–6% when more restrictive definitions—such

as the original NIH 1990 criteria—are used, illustrating how methodological differences significantly shape epidemiological outcomes [6,42].

Global analyses show considerable geographical variation in PCOS prevalence, although part of this heterogeneity reflects diagnostic inconsistencies rather than true biological differences between populations [6,40]. A comprehensive systematic review encompassing diverse regions found prevalence estimates ranging from below 5% in certain East Asian cohorts to above 15% in some Middle Eastern and South Asian populations when assessed using Rotterdam criteria [40]. Factors contributing to these disparities include genetic diversity, environmental influences, lifestyle patterns, and varying levels of awareness and access to diagnostic services [40,42].

Epidemiological studies consistently highlight that PCOS is strongly associated with a high burden of metabolic comorbidities, including insulin resistance, obesity, dyslipidemia, and impaired glucose tolerance, which occur at higher rates compared with women without the syndrome [1,5,42]. As a result, populations with rising rates of obesity and metabolic syndrome tend to show correspondingly higher prevalence of PCOS, further amplifying its public health impact [1,5].

From a demographic perspective, PCOS is primarily diagnosed in women aged 18–44 years, but epidemiological evidence suggests that its manifestations begin much earlier, with adolescent features often emerging around menarche [1,42]. Moreover, symptoms and phenotypes evolve across the lifespan. In adulthood, hyperandrogenic and metabolic phenotypes are more prevalent, whereas ovarian morphology can change with aging, contributing to different phenotype distributions in older cohorts [42]. Such age-related variation complicates prevalence estimates and emphasizes the need for population-specific diagnostic strategies.

3. Infertility

I. Millions of people [11] suffer from infertility, which is defined as the inability to conceive after a year of persistent, unprotected sexual activity [12]. The frequency of infertility is constant across all socioeconomic levels. [12] A variety of anomalies of the ovaries, uterus, fallopian tubes, and endocrine system can lead to infertility in the female reproductive system. [11] A thorough medical history and a physical, gynecological, and endocrine evaluation are necessary for the management of female infertility. [8] There are two types of infertility: primary and secondary. A person is considered primary infertile if they have never conceived, and secondary infertile if they have conceived at least once. The inability to conceive after 12 months or more of consistent, unprotected sexual activity is known as

infertility. [11] An effective test for assessing infertility is anti-müllerian hormone (AMH). It aids in assessing the ovarian reserve and is generated by granulosa cells of early follicles. [8]

II. An essential component of PCOS fertility problems are often linked to ovulation failure. [10] It is the most common cause of infertility and a common syndrome. [8] Compared to their contemporaries without PCOS, women with PCOS have smaller families and are more likely to need fertility therapy to become pregnant. [13]

    To address infertility in women with PCOS, preconception interventions and pharmacological methods to stimulate ovulation are recommended. [9]

4. Letrozole

I. Mechanism and method of operation

It is a highly selective, non-steroidal oral aromatase inhibitor (AI) that inhibits the conversion of androstenedione to estrone and testosterone to estradiol by reversibly binding to the rate-limiting enzyme P450 aromatase in the estrogen biosynthesis pathway. [27] Letrozole may increase how responsive ovarian follicles are to FSH. Research on primates shows that temporarily higher levels of androgens in the ovaries, caused by inhibiting aromatase, encourage follicle growth and estrogen production. This effect is due to stronger FSH activity. Additionally, more androgens in the ovaries can boost levels of IGF-1, a growth factor that works together with FSH to help follicles develop. One theory suggests that letrozole's initial suppression of estrogen synthesis increases the number of estrogen receptors in the endometrium. This heightened sensitivity to estrogen leads to rapid growth of the endometrial lining, along with more estrogen being produced in the following follicular phase. This quick thickening of the endometrium is often seen during transvaginal ultrasound. As a result, the endometrium plays a role in shaping the environment for embryo implantation. [28] Letrozole is quickly and fully absorbed (mean absolute bioavailability of 99.9%) and widely disseminated to tissues after oral treatment. Letrozole is mostly eliminated by CYP-450 isoenzymes, which convert it into an inert carbinol metabolite. As a result, systemic exposure to metabolites is minimal. [26] They have significantly fewer negative effects on peripheral organs including the endometrium and cervix because they are not linked to down-regulation of the hypothalamic-pituitary oestrogen receptors during the late follicular phase. [22]

When used for ovulation induction or superovulation, mild headaches and joint or muscular aches are the most common side effects, which, because of variations in treatment duration, are more common in patients with breast cancer than in women receiving ovulation induction. [21,31]

For postmenopausal women with breast cancer, it is utilized as a hormonal therapy. Oestrogen is known to promote the proliferation of cancer cells in certain forms of breast cancer (hormone receptor positive or hormone-dependent). The medication slows or stops the cancer's growth and spread by inhibiting aromatase activity, which lowers the quantity of oestrogen produced. [29] Letrozole has been shown to be beneficial in a variety of breast cancer scenarios, which is now its sole approved indication. [27]

II. Inducing ovulation with letrozole

In patients with anovulatory infertility, letrozole has been widely used to stimulate ovulation. [27] On cycle days three to five, traditional letrozole or clomiphene medication is started after either progestin-induced bleeding or spontaneous menstruation. The dose is increased after progestin-induced bleeding if ovulation does not occur. If ovulation does not happen in the alternative stair-step technique, a higher dose is given without causing withdrawal bleeding. This compares the classic letrozole protocol with the so-called "stair-step" approach, which involves a rapid increase in potency within the same cycle without waiting until the end if ovulation has not occurred. Two hundred PCOS-afflicted women began taking 5 mg daily. Those who did not reply were randomized to either the standard group (with a gap between cycles) or the stair-step group. The stair-step group experienced a considerably shorter time to ovulation (25 vs. 41 days) due to the growth of dominant follicles. Compared to the conventional technique, the stair-step protocol may reduce treatment duration without sacrificing safety or effectiveness. If the patient does not respond to the initial dose of letrozole, using the stair-step method can save time and lead to ovulation more quickly, which in practice speeds up the infertility treatment process. [17]

A study on PCOS patients unresponsive to standard treatment tested if a longer letrozole regimen (7 vs. 10 days) affected outcomes. Researchers found no major group differences in hormone levels, follicle size, endometrial thickness, or complications. Both regimens induced ovulation, and pregnancy rates were similar, suggesting that a shorter course may be just as effective and useful for personalizing therapy.[18] Another study showed that the standard, most “classic” regimen (2.5 mg for 5 days) may be suboptimal—using 5 mg or extending it to 10 days results in faster and more frequent ovulation, without increasing the side effects (e.g., polyfollicularity). The results of this study are presented in the table below. [19,35]

Figure 2. [19.]

Letrozole regimens	Ovulation frequency	Time to ovulation	Conclusion
2.5 mg x 5 days	The lowest	The longest	The least effective
2.5 mg x 10 days	Much higher (OR 9.12)	Shorter	Extending the time increases the effectiveness
5 mg x 5 days	Higher (OR 3.4)	Shorter	A higher dose improves effectiveness
5 mg x 10 days	High (OR 5.94)	The shortest	The most effective

Letrozole is also useful in the broader context of fertility treatment for PCOS. In PCOS patients undergoing frozen embryo transfer (FET), letrozole may be a reasonable alternative to endometrial preparation without compromising pregnancy outcomes. [16,36] The results indicate that letrozole (in the context of endometrial/cycle preparation) may improve the chances of pregnancy and delivery. There was no increase in congenital anomalies or significant adverse neonatal outcomes. However, the evidence is still limited, and more well-designed RCTs are necessary before letrozole can be regarded as the gold standard in all situations. [25]

Based on the available evidence, letrozole—although originally intended for cancer treatment—is a good option for ovulation induction in women with PCOS. Through its mechanism of aromatase inhibition and restoration of normal hormonal stimulation, letrozole promotes follicular growth and ovulation. It increases the chance of pregnancy and delivery, with a low risk of multiple gestation and relatively good tolerability. [24]

III. Letrozole

a. vs clomiphene in women with PCOS

Letrozole is more effective than clomiphe- selective oestrogen receptor modulator. Letrozole might be a preferable option as a first-line drug, according to this. [23,27] Results indicate that letrozole is more effective than clomiphene citrate in treating subfertility in PCOS women who are resistant to clomiphene citrate or have never received therapy for ovulation induction. [20] Studies indicate that, compared to clomiphene, letrozole results in lower estrogen stimulation while still preserving sufficient endometrial thickness.[34]

When compared to clomiphene citrate, letrozole was linked to higher rates of ovulation, pregnancy, and live births. [33]

b. safety of using

Letrozole has a half-life of approximately 45 hours and a terminal elimination half-life of approximately two days, while clomiphene citrate has a half-life of five days. Letrozole is taken during the first seven days of the menstrual cycle and is gone after five half-lives, or around ten days after the last dose, on Day 17. Therefore, there is very little chance that letrozole will be present in the plasma during embryo implantation. Plasma concentrations of the drug must be found during organogenesis for the ovulation induction agent to have a teratogenic impact. [30] Studies on letrozole's safety as an ovulation-inducing medication and contributed to its reinstatement as a low-risk medication, [39] there is no reason to be concerned about the potential teratogenic effects of taking letrozole to promote ovulation. [37] Letrozole has less detrimental effects on mood and endometrial thickness because, unlike clomiphene, it does not have an anti-estrogenic effect on central estrogen receptors. Researchers have noted that letrozole avoids the long-lasting estrogen receptor blockage that clomiphene causes by giving the endometrium a "more physiologic" hormonal milieu. In fact, there aren't many documented letrozole-related endometrial side effects in the literature, and letrozole users typically don't have the anti-estrogenic side effects (such thin endometrium or noticeable menopausal symptoms) that are frequently associated with clomiphene. [4]

According to the findings, among women receiving ART, letrozole stimulation lowers the chance of miscarriage without increasing the risk of serious congenital defects or unfavorable pregnancy or neonatal outcomes when compared to spontaneous cycles.

For modest ovarian stimulation, letrozole might be a safe choice. [32, 38]

5. Lifestyle modification

Recent evidence-based guidelines for women with PCOS highlight the substantial advantages of losing weight by healthy lifestyle modifications, such as diet and exercise [14] which are the main treatments for PCOS-related infertility. [15] Losing weight also makes the ovulation-inducing substances more effective. In addition to the established metabolic advantages, weight loss increases the pregnancy rate in obese women with PCOS. For overweight and obese women, losing 5 to 10% of their body weight may be enough to get regular menstruation and ovulation back. [8]

Conclusions:

Evidence consistently demonstrates that letrozole is superior to clomiphene citrate in inducing ovulation, achieving pregnancy, and increasing live birth rates in women with PCOS, with fewer anti-estrogenic side effects. Various dosing regimens, including higher doses or extended protocols,

may further improve ovulation outcomes. Letrozole also appears safe, with no increase in congenital anomalies or adverse neonatal outcomes. Lifestyle modification—including weight reduction, dietary improvement, and physical activity—remains essential and significantly enhances ovulatory response and fertility outcomes, especially when combined with pharmacological therapy.

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Software: not applicable;

Verification: Jagoda Węgrzyn, Magdalena Wiernek

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