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THE ROLE OF AROMATASE INHIBITORS IN POLYCYSTIC OVARY SYNDROME

Azimova Bahtigul Jovli kizi
Tashkent Pharmaceutical Institute

Abstract
Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age and represents a major cause of anovulatory infertility. The syndrome is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, often accompanied by metabolic disturbances such as insulin resistance and obesity. Ovulation induction remains a central component in the management of infertility associated with PCOS.

Keywords: Polycystic ovary syndrome; aromatase inhibitors; letrozole; ovulation induction; infertility.

Introduction

Polycystic Ovary Syndrome (PCOS) is a complex and heterogeneous endocrine disorder that affects approximately 6–15% of women of reproductive age, depending on the diagnostic criteria used. It is a leading cause of anovulatory infertility and is associated with significant reproductive, metabolic, and psychological complications. The diagnostic framework most widely accepted today is based on the Rotterdam criteria, which require the presence of at least two of the following features: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovarian morphology on ultrasound examination.

The pathophysiology of PCOS is multifactorial and not yet fully understood. Central features include dysregulation of the hypothalamic–pituitary–ovarian axis, excessive androgen production by the ovaries, insulin resistance, and altered folliculogenesis. Elevated luteinizing hormone (LH) secretion and relatively low or normal follicle-stimulating hormone (FSH) levels contribute to impaired follicular maturation, resulting in chronic anovulation. Increased androgen levels further disrupt follicular development and exacerbate clinical manifestations such as hirsutism, acne, and menstrual irregularities. Infertility management in PCOS primarily focuses on restoring ovulation. For several decades, clomiphene citrate has been the first-line pharmacological agent for ovulation induction. While clomiphene is effective in inducing ovulation in many patients, approximately 15–40% of women with PCOS exhibit clomiphene resistance, defined as failure to ovulate despite adequate dosing. Additionally, clomiphene's anti-estrogenic effects on the endometrium and cervical mucus may negatively influence pregnancy outcomes.

Aromatase inhibitors have gained increasing attention as an alternative therapeutic option for ovulation induction in PCOS. These agents inhibit the aromatase enzyme, which is responsible for the conversion of androgens to estrogens in peripheral tissues and the ovaries. By reducing estrogen levels, aromatase inhibitors remove negative feedback on the hypothalamus and pituitary gland, leading to increased secretion of FSH and stimulation of follicular development. Unlike clomiphene,

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aromatase inhibitors do not deplete estrogen receptors, allowing for a more physiologic endocrine environment.

Among aromatase inhibitors, letrozole has been the most extensively studied in the context of PCOS-related infertility. Accumulating evidence suggests that letrozole may result in higher ovulation, pregnancy, and live birth rates compared to clomiphene citrate, with a lower risk of multiple pregnancies. As a result, several international guidelines now recommend letrozole as a first-line treatment for ovulation induction in women with PCOS.This article aims to critically examine the role of aromatase inhibitors in the management of PCOS. By reviewing current evidence on their mechanisms of action, clinical effectiveness, and safety, this study seeks to highlight the therapeutic potential of aromatase inhibitors and their place in contemporary PCOS treatment protocols.

Materials and Methods

This review is based on an analysis of peer-reviewed scientific literature published in international medical journals. Electronic databases including PubMed, Scopus, and Google Scholar were searched using keywords such as PCOS, aromatase inhibitors, letrozole, ovulation induction, and infertility. Randomized controlled trials, meta-analyses, systematic reviews, and clinical guidelines published in English were included. Studies focusing on ovulation outcomes, pregnancy rates, live birth rates, and adverse effects were prioritized.

Results

Pathophysiology of PCOS and Role of Aromatase

PCOS is characterized by excessive androgen production from the ovaries and adrenal glands. One of the underlying mechanisms involves impaired aromatase activity in granulosa cells, leading to reduced conversion of androgens to estrogens. This results in hyperandrogenism, follicular arrest, and anovulation.

Aromatase inhibitors work by blocking the aromatase enzyme, reducing estrogen synthesis in peripheral tissues and ovaries. The decrease in estrogen levels removes negative feedback on the hypothalamic-pituitary axis, leading to increased secretion of gonadotropin-releasing hormone (GnRH) and FSH, which stimulates follicular development and ovulation.

Aromatase Inhibitors Used in PCOS

The most commonly used aromatase inhibitor in PCOS is letrozole, a third-generation non-steroidal AI. It has a short half-life and minimal anti-estrogenic effects on the endometrium.

Other AIs such as anastrozole have been studied, but letrozole remains the preferred agent due to better clinical outcomes and safety profile.

Clinical Efficacy

Multiple randomized controlled trials have demonstrated that letrozole is superior to clomiphene citrate in inducing ovulation and achieving live births in women with PCOS. Letrozole has been shown to result in:

- Higher ovulation rates
- Improved endometrial thickness

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- Higher pregnancy and live birth rates
- Lower risk of multiple pregnancies

The Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial reported significantly higher live birth rates in women treated with letrozole compared to clomiphene citrate.

Safety and Adverse Effects

Aromatase inhibitors are generally well tolerated. Common side effects include fatigue, dizziness, and mild gastrointestinal symptoms. Unlike clomiphene citrate, letrozole does not adversely affect cervical mucus or endometrial receptivity.

Concerns regarding teratogenicity have been largely disproven, as letrozole is administered early in the follicular phase and cleared from the body before implantation occurs. Large studies have shown no increase in congenital anomalies associated with letrozole use.

Discussion

The introduction of aromatase inhibitors has significantly changed the landscape of infertility treatment in PCOS. Letrozole's targeted mechanism allows for more physiological ovulation induction compared to clomiphene citrate. Its lack of estrogen receptor depletion contributes to better endometrial development and improved implantation rates.

Furthermore, aromatase inhibitors are effective in clomiphene-resistant patients, making them a valuable option in second-line therapy. The lower incidence of multiple pregnancies also enhances their safety profile.

Despite these advantages, individual patient characteristics such as body mass index, insulin resistance, and metabolic profile should be considered when selecting ovulation induction therapy. Combination therapy with lifestyle modification and insulin-sensitizing agents may further improve outcomes.

Conclusion

Aromatase inhibitors, particularly letrozole, play a crucial role in the management of infertility associated with Polycystic Ovary Syndrome. Evidence supports their superiority over traditional ovulation induction agents in terms of ovulation, pregnancy, and live birth rates, with fewer adverse effects. As a result, letrozole is now recommended as a first-line treatment for ovulation induction in women with PCOS by several international guidelines.

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