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RESTORATION OF OVULATION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: CURRENT APPROACHES TO DIAGNOSIS AND TREATMENT

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Abstract: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age and represents the leading cause of anovulatory infertility worldwide. Ovulatory dysfunction in PCOS results from complex interactions among hormonal, metabolic, genetic, and environmental factors. Hyperandrogenism, insulin resistance, and disturbances of the hypothalamic–pituitary–ovarian axis contribute to impaired folliculogenesis and chronic anovulation. Recent advances in reproductive endocrinology have led to significant changes in the management of infertility associated with PCOS, emphasizing individualized treatment strategies. The present review summarizes the current understanding of the mechanisms underlying ovulatory dysfunction in PCOS and discusses evidence-based approaches to ovulation restoration, including lifestyle modification, pharmacological treatment, surgical interventions, and assisted reproductive technologies.
Keywords: polycystic ovary syndrome, PCOS, anovulation, infertility, ovulation induction, letrozole, metformin, hyperandrogenism, insulin resistance.

Introduction

Polycystic ovary syndrome is a heterogeneous endocrine and metabolic disorder affecting approximately 8–13% of women of reproductive age. According to the international evidence-based guidelines, the diagnosis of PCOS is established when at least two of the following criteria are present: ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology, after excluding other endocrine disorders.

Ovulatory dysfunction remains one of the most clinically significant manifestations of PCOS and accounts for nearly 80% of cases of anovulatory infertility. Women with PCOS frequently experience irregular menstrual cycles, oligo-ovulation, or complete absence of ovulation, resulting in reduced fertility and impaired reproductive outcomes.

Beyond reproductive consequences, chronic anovulation is associated with long-term health risks, including endometrial hyperplasia, endometrial carcinoma, type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease, and psychological disorders. Therefore, restoration of

ovulation is not only essential for achieving pregnancy but also for improving overall reproductive and metabolic health.

The objective of this review is to analyze contemporary strategies for restoring ovulation in women with PCOS and to evaluate current evidence regarding their effectiveness.

Pathophysiology of Ovulatory Dysfunction in PCOS

The pathogenesis of anovulation in PCOS is multifactorial and involves dysregulation of the hypothalamic–pituitary–ovarian axis. One of the characteristic hormonal abnormalities is increased pulsatile secretion of gonadotropin-releasing hormone (GnRH), leading to preferential secretion of luteinizing hormone (LH) over follicle-stimulating hormone (FSH).

Elevated LH concentrations stimulate ovarian theca cells to produce excessive amounts of androgens, including testosterone and androstenedione. Hyperandrogenism disrupts normal follicular maturation, preventing the selection and development of a dominant follicle.

Insulin resistance represents another fundamental component of PCOS pathophysiology. Approximately 50–80% of women with PCOS exhibit varying degrees of insulin resistance regardless of body mass index. Compensatory hyperinsulinemia further enhances ovarian androgen production and suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), increasing circulating free androgen levels.

The combined effects of hyperandrogenism and hyperinsulinemia result in arrested follicular development. Numerous small antral follicles accumulate within the ovarian cortex, creating the characteristic polycystic ovarian morphology observed on ultrasound examination. Consequently, ovulation fails to occur, leading to chronic anovulation and infertility.

Lifestyle Modification as the First-Line Intervention

Lifestyle modification is considered the cornerstone of treatment for overweight and obese women with PCOS. Weight reduction has been consistently associated with improvements in reproductive, metabolic, and endocrine parameters.

A modest weight loss of 5–10% has been shown to:

Improve insulin sensitivity;
Reduce circulating insulin levels;
Decrease androgen production;
Restore menstrual cyclicity;
Increase spontaneous ovulation rates;
Enhance fertility outcomes.

Nutritional interventions focusing on caloric restriction, reduction of refined carbohydrates, and increased intake of fiber-rich foods contribute significantly to metabolic improvement. Regular physical activity enhances insulin sensitivity and promotes weight loss.

Several studies have demonstrated that lifestyle intervention alone may restore spontaneous ovulation in a substantial proportion of women, particularly those with obesity-related PCOS.

Pharmacological Approaches to Ovulation Induction

Letrozole

Letrozole is currently recommended as the first-line pharmacological treatment for ovulation induction in infertile women with PCOS.

As a third-generation aromatase inhibitor, letrozole suppresses estrogen synthesis, thereby reducing negative feedback at the hypothalamic and pituitary levels. This results in increased FSH secretion, promoting follicular growth and maturation.

Compared with clomiphene citrate, letrozole has demonstrated:

Higher ovulation rates;
Increased clinical pregnancy rates;
Improved live birth rates;
Lower risk of multiple pregnancy;
Minimal adverse effects on endometrial receptivity.

The superior efficacy of letrozole has been confirmed in multiple randomized clinical trials and meta-analyses, establishing its role as the preferred first-line ovulation induction agent.

Clomiphene Citrate

For several decades, clomiphene citrate was considered the standard treatment for anovulatory infertility associated with PCOS.

Clomiphene acts as a selective estrogen receptor modulator that blocks estrogen receptors in the hypothalamus. This interruption of negative feedback stimulates gonadotropin release and follicular development.

Although ovulation occurs in approximately 70–80% of treated women, pregnancy rates are considerably lower. Furthermore, approximately 15–40% of patients exhibit clomiphene resistance.

The anti-estrogenic effects of clomiphene on the endometrium and cervical mucus may negatively influence implantation and fertility outcomes. Nevertheless, clomiphene remains a valuable therapeutic option where letrozole is unavailable or contraindicated.

Metformin

Metformin is an insulin-sensitizing agent widely used in the management of PCOS, particularly in women with obesity, insulin resistance, impaired glucose tolerance, or type 2 diabetes mellitus.

The mechanisms by which metformin improves reproductive function include:

Reduction of hepatic glucose production;

Improvement of peripheral insulin sensitivity;
Decrease in circulating insulin levels;
Reduction of ovarian androgen synthesis;
Restoration of normal follicular development.

Metformin alone may restore ovulation in some women; however, its greatest benefit is often observed when combined with ovulation induction agents such as letrozole or clomiphene citrate.

Combination therapy is particularly effective in women who previously failed to respond to first-line treatment.

Second-Line Therapeutic Options

Gonadotropin Therapy

Women who do not respond to oral ovulation induction agents may require treatment with exogenous gonadotropins.

Administration of recombinant or urinary FSH directly stimulates follicular development and ovulation. Gonadotropin therapy is associated with high ovulation and pregnancy rates but requires intensive ultrasound monitoring.

Potential complications include:

Ovarian hyperstimulation syndrome (OHSS);
Multiple pregnancy;
Increased treatment costs;
Need for specialized reproductive care.

Careful dose adjustment and individualized stimulation protocols are essential to minimize adverse outcomes.

Laparoscopic Ovarian Drilling

Laparoscopic ovarian drilling (LOD) is a surgical procedure performed in selected women with clomiphene-resistant PCOS.

The procedure involves creating multiple punctures in the ovarian cortex using electrocautery or laser energy. Reduction of androgen-producing ovarian tissue leads to hormonal normalization and restoration of ovulatory cycles.

Potential benefits include:

Reduction of serum androgen levels;
Decreased LH concentrations;
Restoration of spontaneous ovulation;
Reduced need for gonadotropin therapy.

However, concerns regarding postoperative adhesions and diminished ovarian reserve have limited the widespread use of this procedure.

Assisted Reproductive Technologies

When ovulation induction fails or additional infertility factors are present, assisted reproductive technologies (ART) become necessary.

In vitro fertilization (IVF) remains the most effective treatment option for many infertile women with PCOS. Advances in controlled ovarian stimulation protocols have significantly reduced the risk of OHSS, previously one of the major concerns in this population.

Modern approaches include:

GnRH antagonist protocols;
GnRH agonist trigger strategies;
Freeze-all embryo policies;
Individualized ovarian stimulation regimens.
These strategies improve safety while maintaining excellent reproductive outcomes.

Emerging Therapeutic Perspectives

Recent research has focused on novel approaches aimed at improving ovulatory function in women with PCOS.

Promising therapeutic options include:

Inositol Supplementation

Myo-inositol and D-chiro-inositol play important roles in insulin signaling pathways. Supplementation has been associated with improved insulin sensitivity, reduced androgen levels, and enhanced ovulatory function.

Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 receptor agonists have demonstrated beneficial effects on weight reduction, metabolic health, and reproductive function. Their role in fertility management continues to be investigated.

Personalized Medicine

Advances in molecular biology and genetics may enable individualized treatment strategies based on specific phenotypic and genetic characteristics of women with PCOS, thereby improving therapeutic efficacy and reproductive outcomes.

Conclusion

Polycystic ovary syndrome remains the leading cause of anovulatory infertility among reproductive-aged women. Restoration of ovulation requires a comprehensive and individualized approach addressing both reproductive and metabolic abnormalities.

Lifestyle modification remains the foundation of therapy, particularly in overweight and obese patients. Letrozole is currently recognized as the first-line pharmacological agent for ovulation induction due to its superior efficacy and favorable safety profile. Metformin serves as an important adjunctive treatment in women with insulin resistance and metabolic dysfunction. Gonadotropins, laparoscopic ovarian drilling, and assisted reproductive technologies provide effective alternatives for women who fail first-line interventions.

Future advances in reproductive endocrinology and personalized medicine are expected to further optimize ovulation restoration strategies and improve fertility outcomes in women with PCOS.